Zoledronic acid: clinical potential beyond the prevention of skeletal complications in patients with cancer

Adam Brufsky
University of Pittsburgh Cancer Institute, Division of Hematology/Oncology, 200 Lothrop Street MUH N755, Pittsburgh, PA 15213, USA
Tel.: +1 412 648 6583;
Fax: +1 412 648 6579;
E-mail: brufskyam@msx.upmc.edu

Zoledronic acid has received international approval for the treatment of bone metastases and bone lesions from cancer. Phase III studies established the efficacy and safety profile of zoledronic acid in a broad range of tumor types. A direct comparison study with pamidronate demonstrated that zoledronic acid had a similar safety profile and provided superior clinical benefits in patients with breast cancer. Exploratory analyses of the large Phase III databases have demonstrated a survival benefit in patients with breast or lung cancer who achieved normalization of their biochemical marker of bone resorption, N-terminal telopeptide of Type I collagen, within 3 months of zoledronic acid therapy. Ongoing studies are evaluating zoledronic acid for the prevention of accelerated bone loss associated with aromatase inhibitors in patients with breast cancer and for the prevention of new bone metastases.

Keywords: bisphosphonates, bone loss, bone metastases, breast cancer, pamidronate, pharmacokinetics, prostate cancer, renal cell carcinoma, skeletal complications, zoledronic acid

future medicine part of fsg

Bone metastases are associated with considerable skeletal morbidity in patients with cancer. In fact, up to 75% of patients with prostate or breast cancer may develop skeletal complications [1]. Typically, the first symptom is bone pain, and acute pain episodes despite analgesia can occur in these patients [2]. Advanced disease is also associated with pathologic fractures, spinal cord compression or vertebral collapse, required palliative radiotherapy, necessary surgery to bone and hypercalcemia of malignancy, collectively known as skeletal-related events (SREs) [1]. Each of these SREs may decrease patients' quality of life (QoL) and reduce the ability to function independently [3,4]. Moreover, among patients with prostate or breast cancer, pathologic fractures are associated with a 23–32% increased risk of mortality [5].

Bisphosphonates have provided oncologists with an important tool for the prevention of skeletal morbidity from bone metastases in patients with cancer. The rationale for bisphosphonate therapy stems from the observation that bone metastases are associated with dramatic increases in bone metabolism [1]. For example, the biochemical markers of bone resorption are typically increased [6]. Moreover, elevated levels of particular markers of bone resorption may be associated with the presence of bone metastases [6]. Bisphosphonates preferentially bind to bone surfaces undergoing active remodeling and inhibit bone resorption [7]. First-generation bisphosphonates, such as etidronate, produced encouraging clinical results but had to be administered at relatively high doses [7]. Later generations of bisphosphonates, including zoledronic acid, have improved potency and clinical efficacy [7].

Zoledronic acid is the only bisphosphonate to receive international approval for the treatment of bone metastases independent of the primary tumor type and bone lesions from multiple myeloma [8,9]. Pamidronate is internationally approved for the treatment of primary bone lesions from multiple myeloma or bone metastases secondary to breast cancer [10]. Oral clodronate is also approved in Europe for the treatment of primary bone lesions from multiple myeloma or bone metastases secondary to breast cancer [11]. Additionally, oral and intravenous ibandronate are approved in Europe for the treatment of bone metastases secondary to breast cancer [12].

A literature review of PubMed using the key words: bisphosphonates, bone markers, bone metastases, bone mineral density, breast cancer, osteonecrosis of the jaw, pharmacokinetics, pharmacodynamics, prostate cancer, renal cell carcinoma (RCC), renal function, skeletal morbidity and/or zoledronic acid was used for reference information. In addition, recent oncology congresses with online searchable databases were used for abstract information as well as the US government clinical trials database.

Pharmacology of zoledronic acid

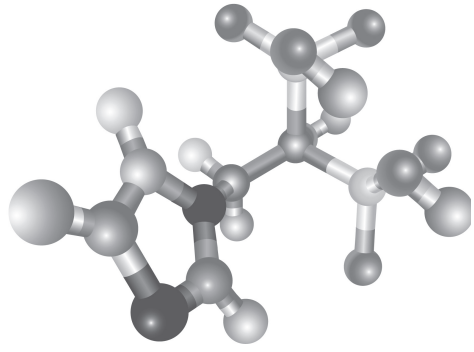
All bisphosphonates have a core moiety that resembles inorganic pyrophosphate, with different R^2 side chains. There are two classes of

10.2217/14750708.4.3.241 © 2007 Future Medicine Ltd ISSN 1475-0708

bisphosphonates that have different mechanisms of action based on the side-chain atoms: non-nitrogen containing and nitrogen containing [13]. Nitrogen-containing bisphosphonates (NCBs) accumulate in the bone matrix, are released during bone resorption, and are then internalized by osteoclasts [13]. After osteoclast internalization, they inhibit farnesyl pyrophosphate synthase in the mevalonate pathway and result in inhibition of protein prenylation [13]. This inhibition interferes with cellular mechanisms that require prenylated proteins for activity, such as signaling molecules involved in the regulation of cellular proliferation, survival and cytoskeletal organization [13]. For example, inhibition of Ras, which requires prenylation, results in intracellular vesicle transport defects, and osteoclasts are not able to form the tight-sealing zones or the ruffled borders that are required for bone resorption [13]. NCBs may also induce the production of an ATP analogue (triphosphoric acid 1-adenosin–5′-yl ester 3-[3-methylbut-3-enyl] ester) that may directly induce apoptosis [13]. Bisphosphonate side-chain structures may also determine relative potency and possibly safety profiles of the individual agents [14]. Zoledronic acid contains two nitrogen atoms as part of its heterocyclic imidazole R^2 side chain (**Figure 1**) [15].

Among patients with cancer and bone metastases in a Phase I study (n = 36), zoledronic acid exhibited a multicompartmental model of distribution, with a prolonged decline in plasma concentration in the terminal phase [14]. Peak systemic concentrations declined rapidly, and less than 1% of the maximum plasma concentration was detectable at 24 h post dose.

Figure 1. Zoledronic acid.



Reproduced with permission from [15]. Copyright © Novartis Pharmaceuticals Corp., 2003.

However, low concentrations were observed for up to 7 days after the zoledronic acid 4-mg dose and up to 29 days following the 8- and 16-mg doses. Presumably, the slow terminal decline of plasma levels is from a deep tissue-binding compartment, such as bone tissue. Dose proportionality was observed from 4 to 16 mg of zoledronic acid [14]. Within 24 h of zoledronic acid administration (via 15-min infusion), 37–41% of the dose was excreted as unchanged drug. Zoledronic acid was detectable in urine for up to 28 days after the 8- and 16-mg doses, but the cumulative excretion beyond 24 h was negligible. Urinary excretion was independent of dose and infusion time. However, estimated baseline creatinine clearance (CrCL) levels indicated that renal impairment was prevalent in the study population (median, 82 ml/min) compared with a similar healthy population. After three consecutive monthly doses of zoledronic acid, pharmacokinetic parameters such as AUC ratios were unchanged. Urinary excretion was also independent of the number of zoledronic acid doses, with an average of 41, 42 and 41% of the dose excreted after the first, second and third doses, respectively. Renal function was also stable over the 3 months of treatment; the average CrCL was 81 and 82 ml/min after the second and third doses, respectively. In a separate study among patients with bone metastases from cancer and varying degrees of renal function, zoledronic acid exhibited similar pharmacokinetics between patients with normal renal function and those with mildly or moderately impaired renal function [16]. The estimated differences in maximum zoledronic acid concentration ranged from 11–15% in the mildly impaired group and 0–17% in the moderately impaired group relative to the normal group. However, the differences did not reach statistical significance. Furthermore, plasma accumulation of zoledronic acid did not occur after repeated doses. Urinary excretion also remained consistent in the three groups after repeated doses.

Pharmacodynamic assessments of biochemical markers of bone resorption have demonstrated that zoledronic acid produces dramatic and sustained suppression of bone resorption marker levels. In a Phase I study of patients with bone metastases from a broad range of tumor types, all levels of bone resorption markers, except for bone-specific alkaline phosphatase, showed significant declines from baseline in serum and/or creatinine-corrected

urinary levels after the administration of intravenous zoledronic acid 4, 8 or 16 mg ($p < 0.002$) [14]. The maximal decline for serum C-terminal telopeptide of Type I collagen was observed at the first evaluation at 24 h and at day 8 for the other bone resorption markers. Thereafter, no significant differences in bone resorption levels were observed through the last evaluation at day 29. Urinary C-terminal telopeptide of Type I collagen and N-terminal telopeptide of Type I collagen (NTX) declined 74 and 69%, respectively. There was no dose response between the bone resorption marker levels and zoledronic acid at 4, 8 or 16 mg, suggesting that maximal effect was achieved with zoledronic acid 4 mg. In a similar Phase I study of zoledronic acid that included 1- and 2-mg doses, zoledronic acid 1 mg decreased urinary NTX and deoxypyridinoline maximally at 1 week but subsequent levels increased from 2 to 8 weeks [17]. Zoledronic acid 2 mg produced similar results to those of the 4-mg dose, whereby bone resorption marker levels remained maximally decreased versus baseline from weeks 1–8. These data suggest that a dose–response relationship may exist between bone resorption marker levels and zoledronic acid at doses less than 2 mg. In another similar Phase I study in patients with osteolytic bone metastases, zoledronic acid doses of 0.1–1.5 mg demonstrated a dose–response relationship with the extent and duration of urinary bone resorption marker levels [18]. Therefore, zoledronic acid doses over 2 mg should provide maximum effect on bone metabolism in patients with bone lesions from cancer.

Efficacy & safety of zoledronic acid in placebo-controlled trials

The efficacy and safety profile of zoledronic acid was established in four large, Phase III, randomized trials in patients with bone lesions from a broad range of tumor types and encompassed more than 3200 patients [19–22]. Except for the placebo-controlled study in patients with breast cancer and osteolytic bone lesions, patients with all types of bone lesions such as osteolytic, sclerotic and mixed lesions, were eligible for study entry. The primary SRE end point in each of these four trials excluded hypercalcemia of malignancy (HCM) as a SRE as required by regulatory authorities. Because HCM is a serious and potentially life-threatening condition that is a common skeletal morbidity among patients with bone metastases from cancer [1], the analyses reported herein included HCM as a SRE. However, specific mentions are made where the results are different from the analyses that excluded HCM. One trial was a direct comparison with pamidronate 90 mg, and the results are presented in the following section. Three of the trials were placebo controlled, and detailed efficacy and safety results are also presented in this section. Two of the zoledronic acid placebo-controlled trials and the comparison trial between zoledronic acid and pamidronate were originally designed with a 5-min infusion rate, and zoledronic acid was dosed at 4 and 8 mg. After increasing serum creatinine levels were noted, the infusion rate was increased to 15 min, and the zoledronic acid 8-mg dose was reduced to 4 mg during the trial to ensure the renal safety of all patients receiving treatment. Zoledronic acid 8 mg is not an approved dose; therefore, only the 4-mg results are presented herein.

Breast cancer

This was a multicenter, double-blind study in which Japanese women with bone metastases from breast cancer (n = 228) were evenly randomized to receive either zoledronic acid 4 mg or placebo via a 15-min infusion every 4 weeks for up to 1 year [19]. The primary end point was the SRE rate (total number of SREs divided by total years on study) among patients in the zoledronic acid group divided by the SRE rate among patients in the placebo group. SREs were defined as pathologic fracture, spinal cord compression, surgery or radiotherapy to bone, and HCM. Secondary end points included the proportion of patients who experienced a SRE, time to first SRE, and change from baseline Brief Pain Inventory (BPI) composite scores and bone resorption marker levels. Multiple event analysis using the Andersen–Gill methodology was performed for the risk of developing a SRE.

Patient demographics and baseline disease characteristics were well balanced between the treatment groups, and 67% of the zoledronic acid group and 64% of the placebo group completed the study. Approximately 66% of the patients in each treatment group had an Eastern Cooperative Oncology Group (ECOG) performance status of zero and a median age of 53 years. The SRE rate was 0.63 events per year in the zoledronic acid group compared with 1.10 events per year in the placebo group ($p = 0.016$). Zoledronic acid also significantly

reduced the percentage of patients with a SRE (p = 0.001) and increased the median time to first SRE (p = 0.004) compared with placebo (**Table 1**) [19,23–26]. By multiple event analysis, zoledronic acid significantly reduced the risk of SREs by 44% compared with placebo (p = 0.009; **Figure 2**) [19,23–26]. Furthermore, zoledronic acid significantly reduced baseline pain scores from 4 weeks until study end (week 52; $p < 0.05$; **Figure 3**) [19]. Zoledronic acid was well tolerated in this patient population, with no evidence of decreased renal function. Pyrexia, fatigue, abdominal pain and hypocalcemia were reported more frequently in the zoledronic acid group, and bone pain was reported more frequently in the placebo group.

Prostate cancer

This was a double-blind study in which patients with bone metastases from prostate cancer (n = 643) were randomized to receive either zoledronic acid 4 mg (n = 214) or 8 mg (n = 221) or placebo (n = 208) via a 15-min infusion every 3 weeks for up to 2 years [22,24]. The primary end point was the proportion of patients with an on-study SRE. SREs were defined as pathologic fracture, spinal cord compression, surgery or radiotherapy to bone, and changes in antineoplastic therapy for bone pain. Secondary end points included the time to first SRE, skeletal morbidity rate ([SMR]: annual incidence of SREs/person), and change from baseline BPI composite scores and bone resorption marker levels. Multiple event analysis using the Andersen–Gill methodology was performed for the risk of developing a SRE.

Patient demographics and baseline disease characteristics were well balanced between the treatment groups, and 49 patients of the zoledronic acid group and 36 patients of the placebo group completed 24 months of the study [24]. Approximately 92% of the patients in each treatment group had an ECOG performance status of 0 or 1 and a median age of 73 years [22]. Zoledronic acid significantly reduced the percentage of patients with a SRE (p = 0.028), increased the median time to first SRE (p = 0.009), and reduced the mean SMR (p = 0.005) compared with placebo (**Table 1**) [19,23–26]. By multiple event analysis, zoledronic acid significantly reduced the risk of SREs compared with placebo (p = 0.002; **Figure 2**) [19,23–26]. Analyses for treatment efficacy from months 16 to 24 only demonstrated that zoledronic acid continued

Table 1. Summary of zoledronic acid efficacy across tumor types*.

	Zoledronic acid	Placebo or pamidronate	p-value	Ref.
Breast cancer				
Patients with ≥ 1 SRE (%)	31	52	0.001	[19]
Time to first SRE, median	NR	360	0.004	
Skeletal morbidity rate, mean	0.63	1.10	0.016‡	
Breast cancer & multiple myeloma				
Patients with ≥ 1 SRE (%)	48	52	0.198	[23]§
Time to first SRE, median	376	356	0.151	
Skeletal morbidity rate, mean	1.04	1.39	0.084	
Prostate cancer				
Patients with ≥ 1 SRE (%)	38	49	0.028	[24]
Median time to first SRE, days	488	321	0.009	
Skeletal morbidity rate, mean	0.77	1.47	0.005	
Lung cancer & other solid tumors				
Patients with ≥ 1 SRE (%)	39	48	0.039	[25]
Median time to first SRE, days	236	155	0.009	
Skeletal morbidity rate, mean	1.74	2.71	0.012	
Renal cancer				
Patients with ≥ 1 SRE (%)	41	79	0.011	[26]
Median time to first SRE, days	424	72	0.007	
Skeletal morbidity rate, mean	2.58	3.13	0.009	

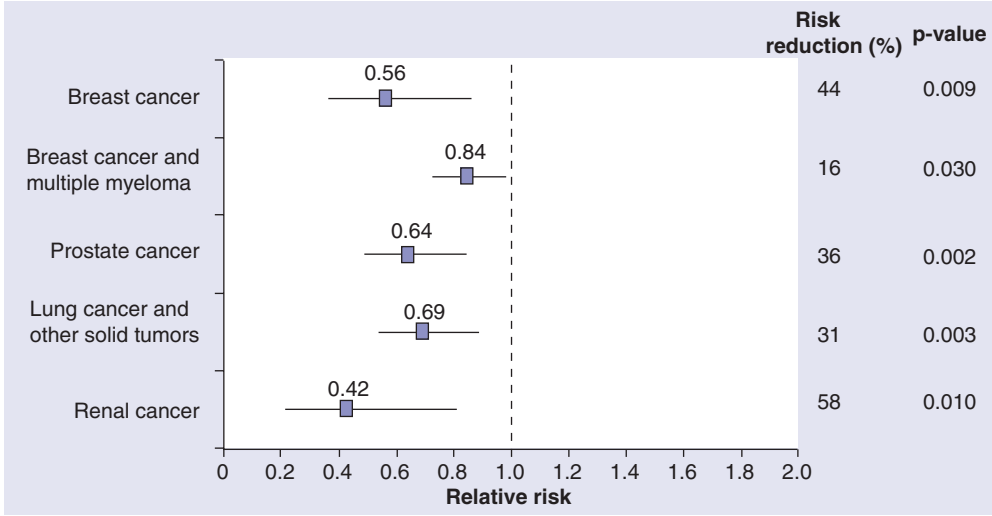
**All data includes hypercalcemia of malignancy as a SRE.*

‡Permutation test.

§This is the only study that has pamidronate as a comparator.

NR: Not reached; SRE: Skeletal-related event.

Figure 2. Zoledronic acid reduced the risk of skeletal-related events across tumor types compared with placebo or pamidronate.



All tumor types are compared with placebo except for patients with either breast cancer or multiple myeloma. Length of horizontal line represents the 95% confidence interval. Data from [19,23–26].

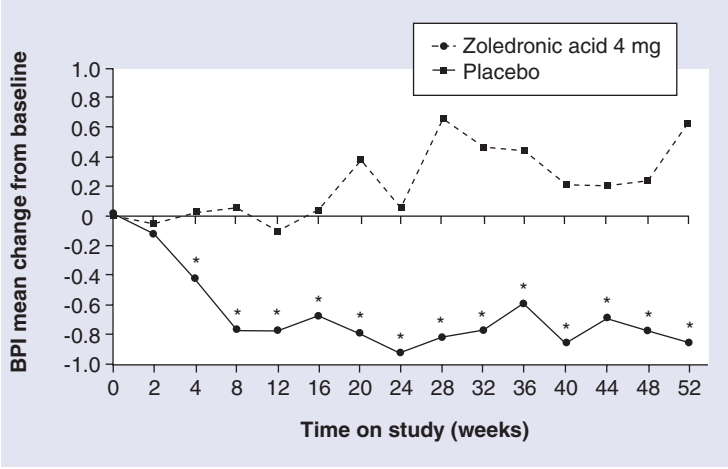
to provide significant reductions in the proportion of patients with a SRE ($p = 0.017$), time to first SRE ($p = 0.036$), SMR ($p = 0.016$), and the risk of SREs ($p = 0.022$) compared with placebo [27]. Zoledronic acid also reduced the mean BPI pain scores compared with placebo at all time points throughout the study and achieved a significant difference at months 3, 9, 21 and 24 ($p < 0.03$ for all). Furthermore, zoledronic acid significantly delayed the requirement for radiation to bone by 33% compared with placebo (mean, $p = 0.034$), although there was no statistically significant difference in the total QoL measures. Zoledronic acid was well tolerated and had a similar incidence of serum creatinine increase as placebo (15 vs 12%, respectively). Fatigue, myalgia, fever, anemia and lower limb edema were reported more frequently in the zoledronic acid group, and bone pain was reported more frequently in the placebo group.

Exploratory analyses of the study database have yielded important efficacy results in subsets of patients [27–29]. Among patients without pain at study entry, zoledronic acid decreased the percentage of patients with one or more SREs by 39% relative to placebo and reduced the mean annual incidence of SREs by 49% compared with placebo [29]. These results represent a greater benefit than that achieved in patients with pain at baseline. Among patients with over three bone lesions, zoledronic acid significantly reduced the risk of SREs compared with placebo by 32% ($p = 0.035$), although zoledronic acid provided similar reductions among patients with three bone lesions or fewer (37%; $p = 0.047$) [28]. Furthermore, among patients with a previous SRE, zoledronic acid reduced the proportion of patients with a SRE by 20% relative to the placebo group [27]. However, zoledronic acid provided similar reductions among patients with no history of a SRE relative to placebo (21%). These results suggest that patients at higher risk for SREs derive benefits from zoledronic acid therapy. Although several bisphosphonates have been studied in this population, only zoledronic acid has demonstrated significant objective long-term benefits.

Lung cancer & other solid tumors

This was a multicenter, double-blind study in which patients with bone metastases from lung cancer or other solid tumors ($n = 773$) were randomized to receive either zoledronic acid 4 mg ($n = 257$) or 8 mg ($n = 266$) or placebo ($n = 250$) via a 15-min infusion every 3 weeks for up to 9 months [21] with a continued study period for up to 21 months [25]. The primary end point was the proportion of patients with an on-study SRE. SREs were defined as pathologic fracture, spinal cord compression, surgery or radiotherapy to bone and HCM. Secondary

Figure 3. Mean BPI composite score change from baseline in patients with breast cancer.



*p < 0.05.
BPI: Brief Pain Inventory.
Reprinted with permission from the American Society of Clinical Oncology [19].

end points included the time to first SRE, SMR and change from baseline BPI composite scores and bone-resorption marker levels. Multiple-event analysis using the Andersen–Gill methodology was performed for the risk of developing a SRE.

Patient demographics and baseline disease characteristics were well balanced between the treatment groups; 24% of the zoledronic acid group and 23% of the placebo group completed 21 months of the study. Approximately 84% of the patients in each treatment group had an ECOG performance status of 0 or 1 and a median age of 63 years. Zoledronic acid significantly reduced the percentage of patients with a SRE (p = 0.039), increased the median time to first SRE (p = 0.009), and reduced the SMR (p = 0.012) compared with placebo (**Table 1**) [19,23–26]. When HCM was excluded from the analysis, zoledronic acid reduced the percentage of patients with a SRE, but the reduction did not reach statistical significance (p = 0.127). By multiple event analysis, zoledronic acid significantly reduced the risk of SREs (including HCM as a SRE) compared with placebo (p = 0.003; **Figure 2**) [19,23–26]. Although not all results were statistically significant, the results of these analyses provide valuable information about the natural history of the disease in patients who had a median survival of approximately 6 months and demonstrate the benefit of treatment with zoledronic acid. In general, mean BPI scores increased from baseline over time in both treatment groups; however, the zoledronic acid group had a smaller increase from baseline compared with placebo. Zoledronic acid was well tolerated and had a similar incidence of serum creatinine increase as placebo (11 vs 7%, respectively). Nausea, vomiting and dyspnea were reported more frequently in the zoledronic acid group, and bone pain was reported more frequently in the placebo group.

Exploratory analyses of this database have demonstrated that among patients with more than 3 bone lesions or a previous SRE before study entry, zoledronic acid significantly reduced the risk of SREs by 42% (p = 0.010) and by 31% (p = 0.009), respectively, and extended the time to first SRE by 87 days (p = 0.005) and by 109 days (p = 0.011), respectively, compared with placebo [28,30]. Among patients with three or fewer bone lesions or no history of SREs, zoledronic acid reduced the risk of SREs by 28% (p = 0.041) and 23% (p = 0.308), respectively. These results support the data from the prostate cancer study and suggest that patients at higher risk for SREs may derive greater benefit from zoledronic acid. In this patient population, only zoledronic acid has demonstrated significant benefits and has received widespread regulatory approval in this setting.

Renal cell carcinoma

Zoledronic acid was also evaluated for efficacy in a subset of patients with RCC (n = 74) [26,31]. At 21 months, zoledronic acid significantly reduced the percentage of patients with a SRE by 38% (p = 0.011), increased the median time to first SRE by 352 days (p = 0.007), and reduced the mean SMR (p = 0.009) compared with placebo (**Table 1**) [19,23–26]. By multiple event analysis, zoledronic acid significantly reduced the risk of SREs by 58% compared with placebo (p = 0.010; **Figure 2**) [19,23–26]. Moreover, the median time to progression of bone lesions was significantly longer for patients who were treated with zoledronic acid compared with placebo (586 vs 89 days, respectively; p = 0.014) [26]. This was the first evidence to show that bisphosphonates may have a clinically significant effect on bone lesion progression in this population of patients and supports further exploration. Among patients with RCC, zoledronic acid was well tolerated and had a similar incidence of renal-related adverse events as placebo (22 vs 20%, respectively) [26].

Summary
These Phase III trials have established the efficacy of zoledronic acid for the treatment of bone metastases in multiple tumor types. Exploratory analyses have shown that zoledronic acid may provide clinical benefits to patients if administered earlier in the course of their disease and that zoledronic acid provides continued benefits through the second year of treatment. Zoledronic acid is also well tolerated, although serum creatinine levels should be monitored in patients with impaired renal function.

Postmarketing experience

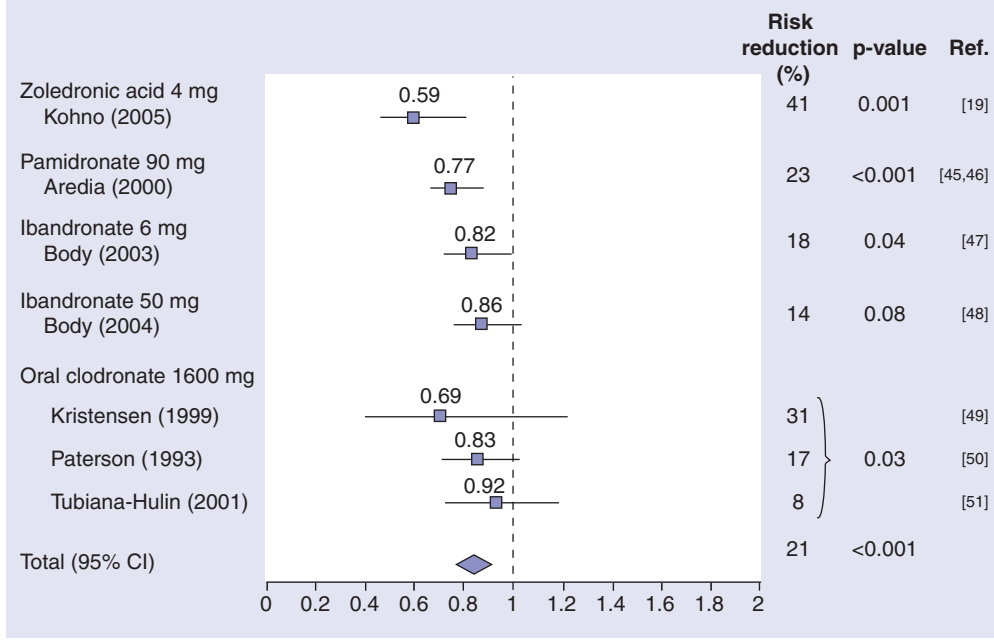
Zoledronic acid has been used to treat malignant bone disease in more than 1 million patients over the past 5 years. During this time, additional adverse events have been reported as bisphosphonate use has become more common. Although no cases of osteonecrosis of the jaw (ONJ) were reported in the registration trials for zoledronic acid and pamidronate [23–25,32,33], it has since been reported as an uncommon event among patients with cancer receiving multiple systemic therapies that include bisphosphonates [34]. The estimation of ONJ in this patient population varies from less than 0.02 to 12.8% in the published literature [35–37]. The pathophysiology and etiology of ONJ are not fully characterized and poorly understood [38]. However, it is characterized by the appearance of exposed necrotic bone in the oral cavity [38]. Because ONJ has been most commonly reported following invasive dental procedures, patients should be encouraged to have a dental examination before initiating bisphosphonate treatment and to have regular dental maintenance care (approximately every 6 months or when appropriate) while they are receiving bisphosphonate therapy [34].

With the additional experiences from postmarketing use, dose adjustments of zoledronic acid for patients with reduced renal function (mild and moderate renal impairment) have been developed [8]. These doses are calculated to achieve the same AUC as that achieved in patients with a CrCL of 75 ml/min. The majority of data reported on renal adverse events during the postmarketing period showed mild-to-moderate increases in serum creatinine levels. A French retrospective review identified seven patients who experienced renal adverse events; four with acute renal failure and three with a worsening of their chronic renal failure [39]. Three patients fully recovered, one patient partially recovered, two patients died and one patient's outcome was unknown. However, the total number of patients reviewed was not given in the abstract, and it is unknown if the patients who died had previous chronic renal failure. Another retrospective review of 122 patients with hormone-refractory prostate cancer identified 23.8% of patients with a serum creatinine increase of 0.5 mg/dl or more from a baseline of less than 1.4 mg/dl or serum creatinine increase of 1.0 mg/dl or more from a baseline of 1.4 mg/dl or more [40]. However, the majority of patients with increased serum creatinine levels (86%) had grade 1 or 2 renal impairment. Risk factors that were significantly correlated with increased serum creatinine levels, identified by multivariate analysis, included increasing age; previous pamidronate treatment; and a history of hypertension, renal disease and smoking. A prospective study of 67 patients with bone lesions from solid tumors or multiple myeloma reported notable serum creatinine level increases in 9% of patients [41]. A larger retrospective review of 446 patients with bone lesions from solid tumors or multiple myeloma also reported 9% of patients who experienced increases in serum creatinine levels (median: 1.0 mg/dl) [42]. Furthermore, supportive care recommendations have been developed to manage common adverse events such as the acute-phase reaction (flu-like symptoms) that occurs most often after the first NCB infusion [43,44].

Zoledronic acid in comparison with other bisphosphonates

Zoledronic acid produced the largest reduction in skeletal morbidity among bisphosphonates investigated in patients with breast cancer (**Figure 4**) [19,45–52]. However, only pamidronate and zoledronic acid have been compared head-to-head in a double-blind, randomized, Phase III trial [20,23]. The results of this comparative study demonstrated that zoledronic acid produced significant benefits beyond those of pamidronate in patients with multiple myeloma or breast cancer. Although a poster was presented at the 1999 Annual Meeting of the American Society of Clinical Oncology comparing oral and intravenous clodronate with intravenous pamidronate in patients with bone metastases from breast cancer, a final published paper is not evident [53]. Results suggest that intravenous pamidronate achieved

Figure 4. In patients with breast cancer, zoledronic acid provided the greatest risk reduction of skeletal-related events among approved bisphosphonates in placebo-controlled studies.



CI: Confidence interval.
Reproduced with permission from [52], Corp. © The Cochrane Collaboration. Published by John Wiley & Sons.

greater pain reduction compared with either oral or intravenous clodronate, and the proportion of patients who experienced fractures in each treatment group was similar. A study comparing oral ibandronate and intravenous zoledronic acid in patients with breast cancer who are newly diagnosed with bone metastases is ongoing [101].

In the international, multicenter zoledronic acid study, patients with bone metastases from breast cancer or at least one osteolytic lesion from multiple myeloma (Durie–Salmon Stage III eligibility requirement) (n = 1648) were randomized to receive either zoledronic acid 4 mg (n = 564) or 8 mg (n = 526) or placebo (n = 558) via a 15-min infusion every 3–4 weeks for up to 24 months, with the last assessment at month 25 [20,23]. Patients with breast cancer were also stratified on study entry based on treatment (chemotherapy and hormonal therapy). As reported previously, zoledronic acid 8 mg is not an approved dose; therefore, only the 4-mg results are presented herein. The primary end point was the proportion of patients who had an on-study SRE. SREs were defined as pathologic fracture, spinal cord compression, surgery or radiotherapy to bone, and HCM. Secondary end points included the time to first SRE, SMR, and change from baseline BPI composite scores and bone resorption marker levels. Multiple event analysis using the Andersen–Gill methodology was performed for the risk of developing a SRE.

Patient demographics and baseline disease characteristics were well balanced between the treatment groups, and 22% of each treatment group completed 24 months of the study [23]. Approximately 82% of the patients in each treatment group had an ECOG performance status of 0 or 1 and a median age of 59 years [20]. Zoledronic acid numerically reduced the percentage of patients with a SRE, increased the median time to first SRE, and reduced the mean SMR compared with pamidronate (**Table 1**) [19,23–26]. However, the differences between zoledronic acid and pamidronate did not achieve statistical significance as was expected in a noninferiority trial design. Notably, by multiple event analysis, zoledronic acid significantly reduced the risk of SREs compared with pamidronate (p = 0.030; **Figure 2**) [19,23–26]. Among patients with multiple myeloma or breast cancer, zoledronic acid was well tolerated and had a similar incidence as

pamidronate of serum creatinine increase (11 vs 9%, respectively). Reported adverse events were similar between the treatment groups.

In the subset of patients with breast cancer, zoledronic acid provided superior objective benefits compared with pamidronate [54,55]. Zoledronic acid numerically reduced the percentage of patients with a SRE, increased the median time to first SRE, and reduced the mean SMR compared with pamidronate [54]. Multiple event analysis showed that zoledronic acid significantly reduced the overall risk of developing a SRE by an additional 20% compared with pamidronate ($p = 0.025$) and significantly reduced the risk of developing subsequent SREs by 31% compared with pamidronate ($p = 0.045$) [54]. Moreover, during the 12-month extension phase, zoledronic acid significantly reduced the risk of developing a SRE by an additional 41% compared with pamidronate ($p = 0.026$) [54]. Among patients with osteolytic lesions from breast cancer, multiple event analysis demonstrated that zoledronic acid significantly reduced the risk of developing a SRE by 30% compared with pamidronate ($p = 0.01$) [55].

Regulatory status

Zoledronic acid has received widespread regulatory approval for the treatment of bone lesions in patients with multiple myeloma or solid tumors. Initial approval was achieved in the USA and Europe in 2001 for the treatment of HCM [56]. In 2002, the indications for zoledronic acid were expanded in the USA and Europe to include the treatment of patients with bone lesions from multiple myeloma or documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy [9,56]. In 2003, the European Agency for the Evaluation of Medicinal Products granted an expansion of the current marketing authorization for zoledronic acid to include long-term treatment data for patients with bone lesions from advanced cancers [102]. In the USA, zoledronic acid is supplied as a 4 mg/5 ml concentrate [8]. In Europe, zoledronic acid is supplied as either a 4 mg powder with solvent or as a 4 mg/5 ml concentrate [9]. In both cases the zoledronic acid solution is administered as an infusion in 100 ml of normal saline (0.9%) or 5% dextrose solution [8,9].

Conclusion

Taken together, these results demonstrate that zoledronic acid provides clinically meaningful improvements in patients with cancer. The QoL and functionality of patients may be maintained through the prevention and delay of SREs. Moreover, reduction of pain and the requirement for radiation to bone may improve patients' QoL and functional independence. Zoledronic acid has demonstrated efficacy in a broad range of tumor types and has demonstrated superiority over pamidronate in patients with breast cancer or multiple myeloma.

Exploratory analyses of the large zoledronic acid databases have shown that greater benefits may be provided in patients with asymptomatic disease, suggesting that earlier treatment may be beneficial to patients in whom overt symptoms have not yet developed. Furthermore, patients at higher risk for SREs also receive clinically meaningful improvements from zoledronic acid treatment. Therefore, patients who have experienced a previous SRE should continue to receive treatment to reduce the risk of further skeletal complications.

In spite of the large amount of information available for the treatment of patients with zoledronic acid, some questions still remain. Optimization of schedule and duration of treatment are ongoing issues that current studies are evaluating. These future results are eagerly anticipated. Additional ongoing studies that are evaluating zoledronic acid for the prevention of bone metastases [103], and the utility of bone markers for directing the therapeutic treatment of bisphosphonates [104] are presented in the future perspective.

Future perspective

Preliminary evidence from ongoing and recently completed studies suggests that zoledronic acid may provide clinical benefits beyond supportive care. Future arenas for zoledronic acid include therapy for bone loss from hormonal therapies for breast or prostate cancer and prevention of bone metastases. Identification of patient subsets most likely to benefit from zoledronic acid therapy and monitoring response to zoledronic acid therapy are also new avenues of exploration for the future optimization of treatment.

Zoledronic acid treatment for the prevention of aromatase inhibitor-associated bone loss in breast cancer or bone loss from androgen-deprivation therapy in prostate cancer has been evaluated in several studies. The Austrian Breast and Colorectal Cancer Study Group-12 trial randomized premenopausal patients with breast cancer receiving adjuvant hormonal therapy (goserelin plus either tamoxifen or anastrozole) to intravenous zoledronic acid 4 mg every 6 months or no

further treatment (n = 401) [57]. Data are available up to the 36-month assessment; the 60-month assessment is still ongoing. Zoledronic acid prevented bone loss in both the lumbar spine and hip regardless of the type of endocrine therapy. In contrast, patients without zoledronic acid treatment had an overall loss from baseline of bone mineral density (BMD) in the lumbar spine of 14% ($p < 0.0001$) and in the trochanter of 8%. Zoledronic acid also significantly prevented decreases in mean T-scores in both treatment groups compared with no further treatment. In patients without zoledronic acid treatment, mean T-scores for the lumbar spine and trochanter decreased 1.4% ($p < 0.0001$) and 0.6% ($p = 0.0017$), respectively. No SREs were recorded thus far in the study. The combination of endocrine therapy with zoledronic acid was well tolerated without any evidence of additive toxicity. No changes in renal function were reported during the trial. Therefore, zoledronic acid appears to be effective for the prevention of bone loss associated with hormone inhibition in premenopausal women with breast cancer.

Two additional studies (Zometa–Femara adjuvant synergy trials; Z-FAST in the USA and ZO-FAST in Europe) evaluated optimal strategies for managing bone loss in postmenopausal patients with breast cancer receiving letrozole, administering zoledronic acid concomitantly with hormone inhibition (upfront) or initiating zoledronic acid after bone loss has developed (delayed) [58]. An integrated analysis of the two trials (n = 1667) at 12 months has demonstrated that the upfront zoledronic acid group had significantly improved BMD of the lumbar spine by 5.1% compared with the delayed zoledronic acid group ($p < 0.001$) [59]. Improvement was also reported in the total hip BMD; zoledronic acid significantly increased BMD by 3.4% compared with the delayed zoledronic acid group ($p < 0.001$). Moreover, 11% of the patients in the delayed group initiated zoledronic acid treatment because of a T-score decrease below -2.0 or a fracture.

Zoledronic acid has also demonstrated improved BMD at 1 year in men with prostate cancer receiving androgen-deprivation therapy [60,61]. Bone loss in this patient population is similar to or higher than that reported in postmenopausal women, and vertebral fractures have been significantly correlated with reduced BMD ($p = 0.001$) [60]. A study in men receiving androgen-deprivation therapy (n = 106) who were randomized to zoledronic acid 4 mg or placebo every 3 months for 1 year showed that mean BMD in the lumbar spine was significantly increased by 5.6% in the zoledronic acid group compared with a decrease of 2.2% in the placebo group ($p < 0.001$) [61]. Similar results were reported for the femoral neck, trochanter and total hip. These results suggest that zoledronic acid maintains bone health and, therefore, should reduce fracture risk. Notably, in this patient population, reducing the risk of fractures may provide a survival benefit [62].

Levels of biochemical markers of bone metabolism are being evaluated in ongoing zoledronic acid studies for monitoring response to treatment. The rationale for these ongoing studies is a result of exploratory analyses of the large study databases. In patients with breast cancer, zoledronic acid-mediated normalization of the bone marker NTX significantly decreased the risk of experiencing a first SRE ($p = 0.0020$) and significantly increased overall and SRE-free survival compared with persistently elevated NTX ($p < 0.0017$ and $p = 0.0004$, respectively) [63]. In patients with prostate cancer, zoledronic acid-mediated normalization of NTX significantly decreased the risk of experiencing a first SRE ($p = 0.0411$) and significantly increased overall and SRE-free survival compared with persistently elevated NTX ($p < 0.0001$ and $p = 0.0009$, respectively) [63]. These analyses have identified patients who are likely to receive long-term benefits from zoledronic acid treatment through the use of bone marker assessments. Bone marker levels may also have utility for the scheduling of bisphosphonate treatment. The ongoing, randomized, controlled, open-label study in the UK (BisMARK) is comparing the efficacy of two dosing schedules of zoledronic acid: the administration of zoledronic acid when bone marker levels increase and the currently approved every 3–4 week schedule [104]. The frequency and timing of SREs (fractures, radiotherapy to bone, HCM, orthopedic surgery and spinal cord compression) are the primary end points.

Ongoing studies are also evaluating the potential of zoledronic acid to prevent bone metastases. Early preclinical models suggested that bisphosphonates have antitumor effects and can prevent the formation of new bone metastases [13]. Indeed, zoledronic acid was shown to decrease cell numbers in two breast cancer lines in a dose- and time-dependent manner ($p < 0.001$), and increase cell apoptosis ($p < 0.005$) [64]. Moreover, zoledronic acid in combination with paclitaxel showed a synergistic four- to fivefold increase in cell apoptosis ($p < 0.02$). Zoledronic acid has shown synergistic activity with other cytotoxic cancer therapies

such as tamoxifen and doxorubicin in breast cancer cell lines [65]. Zoledronic acid has also shown synergistic activity with cytotoxic cancer therapies in different cell lines of tumor types including prostate cancer, lung cancer and myeloma cells [65]. In mice with either xenografts of breast cancer or intratibial tumors from breast cancer, zoledronic acid and doxorubicin synergistically decreased tumor burden, and this was most apparent by the sequential administration of doxorubicin first followed by zoledronic acid [66].

Clinical evidence from oral clodronate studies suggests that the incidence of bone metastases can be reduced in patients with breast cancer and provided the rationale for an exploration of zoledronic acid in this setting [51,67,68]. Preliminary evidence from zoledronic acid clinical studies also suggests that bone metastasis-free survival may be prolonged in patients with solid tumors [63]. The ongoing AZURE study randomized women with breast cancer receiving adjuvant chemotherapy and/or endocrine therapy to either no additional treatment or zoledronic acid (n = 3360) [103]. The primary end point is disease-free survival and will be assessed annually for 10 years. Interim efficacy outcomes are expected in late 2008 or 2009, depending on the event rate. Information on reported adverse events was recently presented [69]. The incidence of serious adverse events was not different between the treatment groups (20% in patients without additional treatment and 23% in patients receiving zoledronic acid). A total of 23 patients developed grade 1 or 2 increased serum creatinine levels; 11 patients without additional treatment and 12 patients receiving zoledronic acid. Serious renal adverse events were reported in one patient without additional treatment and three patients receiving zoledronic acid (three unrelated and one possibly related to zoledronic acid). Seven (0.2%) cases of ONJ have been reported in patients receiving zoledronic acid after a median of eight treatments. These results suggest that zoledronic acid may be combined with adjuvant chemotherapy without increasing the toxicities associated with chemotherapy.

Disclosure

Funding for medical editorial assistance was provided by Novartis Pharmaceuticals Corp. The author thanks Tamalette Loh, PhD, ProEd Communications, Inc., for her medical editorial assistance with this manuscript.

Executive summary

- Zoledronic acid is currently administered for the treatment of hypercalcemia of malignancy and bone metastases in patients with cancer.
  - The efficacy and safety profiles of zoledronic acid have been established in Phase III studies.
  - Over 1 million patients worldwide have been treated.
- Zoledronic acid, compared with other bisphosphonates, appears to be the most effective treatment for bone metastases in patients with breast cancer.
  - In a comparison study, zoledronic acid was demonstrated to be superior to pamidronate in the reduction of skeletal-related event risk.
- Questions that warrant further investigation include when to start treatment and duration of treatment.
  - Preliminary evidence from exploratory analyses and ongoing studies suggest that the greatest benefit from zoledronic acid may be obtained when initiated earlier than the current recommendations (presence of symptomatic disease).
- Future study results may provide support for earlier treatment with zoledronic acid (in the adjuvant setting) for the prevention of bone metastases and protection of bone loss.

Bibliography

Papers of special note have been highlighted as of interest (•) or of considerable interest (••) to readers.

1. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat. Rev.* 27(3), 165–176 (2001).
2. Sabino MA, Mantyh PW. Pathophysiology of bone cancer pain. *J. Support. Oncol.* 3(1), 15–24 (2005).
3. Weinfurt KP, Castel LD, Li Y, Timbie JW, Glendenning GA, Schulman KA. Health-related quality of life among patients with breast cancer receiving zoledronic acid or pamidronate disodium for metastatic bone lesions. *Med. Care.* 42(2), 164–175 (2004).
4. 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.* 16(4), 579–584 (2005).
5. Saad F, Cook R, Chen Y-M, Bock T. Greater fractures are associated with an increased risk of death in patients with bone metastases from breast or prostate cancer. Presented at: *Multinational Association of Supportive Care in Cancer (MASCC)/International Society for Oral Oncology (ISOO) 18th International Symposium.* Toronto, ON, Canada, June 22–24, 2006 (Abstract 1626).
6. 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.* 97(1), 59–69 (2005).
7. Green JR. Preclinical pharmacology of zoledronic acid. *Semin Oncol.* 29(6 Suppl. 21), 3–11 (2002).
8. Zometa® (zoledronic acid) injection concentrate for intravenous infusion –

prescribing information. Novartis Pharmaceuticals Corp., East Hanover, NJ, USA (2005).
9. Zometa® (zoledronic acid) summary of product characteristics. Novartis Europharm Limited, West Sussex, UK (2003).
10. Aredia® (pamidronate disodium) for injection for intravenous infusion – prescribing information. Novartis Pharmaceuticals Corp., East Hanover, NJ, USA (2005).
11. Bonefos® capsules summary of product characteristics. Schering Health Care Limited, West Sussex, UK (2005).
12. Bondronat® (ibandronic acid) summary of product characteristics. Roche Registration Limited, Hertfordshire, UK (2001).
13. Green JR. Bisphosphonates: preclinical review. *Oncologist* 9(Suppl. 4), 3–13 (2004).
14. Chen T, Berenson J, Vescio R *et al.*: Pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with bone metastases. *J. Clin. Pharmacol.* 42(11), 1228–1236 (2002).
15. Yarbro CH, O'Kelly P, de Mattos Pimenta CA, Caponero R, Aranda S. *Advances in Bisphosphonate Therapy for Malignant Bone Disease.* Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA 1–12 (2003).
16. Skerjanec A, Berenson J, Hsu CH *et al.*: The pharmacokinetics and pharmacodynamics of zoledronic acid in cancer patients with varying degrees of renal function. *J. Clin. Pharmacol.* 43(2), 154–162 (2003).
17. Berenson JR, Vescio R, Henick K *et al.*: A phase I, open label, dose ranging trial of intravenous bolus zoledronic acid, a novel bisphosphonate, in cancer patients with metastatic bone disease. *Cancer* 91(1), 144–154 (2001).
18. Berenson JR, Vescio RA, Rosen LS *et al.*: A phase I dose-ranging trial of monthly infusions of zoledronic acid for the treatment of osteolytic bone metastases. *Clin. Cancer Res.* 7(3), 478–485 (2001).
19. 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.* 23(15), 3314–3321 (2005).
- **Demonstrates the efficacy of zoledronic acid compared with placebo in breast cancer.**
20. 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.* 7(5), 377–387 (2001).
21. 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.* 21(16), 3150–3157 (2003).
22. 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.* 94(19), 1458–1468 (2002).
23. 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* 98(8), 1735–1744 (2003).
- **Study shows the comparative efficacy of zoledronic acid with pamidronate after 2 years of treatment in multiple myeloma or breast cancer.**
24. 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.* 96(11), 879–882 (2004).
- **Demonstrates the efficacy of zoledronic acid over 2 years of treatment in prostate cancer.**
25. 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* 100(12), 2613–2621 (2004).
- **Illustrates the efficacy of zoledronic acid in a broad range of solid tumors.**
26. Lipton A, Seaman J, Zheng M. Efficacy and safety of zoledronic acid in patients with bone metastases from renal cell carcinoma. Presented at: *What Is New in Bisphosphonates? Seventh Workshop on Bisphosphonates—From the Laboratory to the Patient.* Davos, Switzerland, March 24–26, 2004. Poster 28.
27. Saad F, Gleason DM, Murray R *et al.*: Zoledronic acid has continuing benefit in long-term therapy for the prevention of skeletal complications in men with advanced prostate cancer [abstract]. *Ann. Oncol.* 15 (Suppl. 3), iii 123 (2004) (Abstract 462PD).
28. Coleman RE, Shirina N, Chen Y-M. Greater number of bone metastases are associated with an increased risk of skeletal complications and greater benefit of zoledronic acid. Presented at: *Multinational Association of Supportive Care in Cancer (MASCC)/International Society for Oral Oncology (ISOO) 18th International Symposium.* Toronto, ON, Canada, June 22–24, 2006 (Abstract 07–057).
29. Lothman H, Saad F. Zoledronic acid provides immediate and long-term reduction of pain in prostate cancer patients. Presented at: *14th International Conference on Cancer Nursing*; Toronto, ON, Canada, 27 September-1 October, 2006.
30. 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.* 6(3), 170–174 (2004).
31. Lipton A, Zheng M, Seaman J. Zoledronic acid delays the onset of skeletal-related events and progression of skeletal disease in patients with advanced renal cell carcinoma. *Cancer* 98(5), 962–969 (2003).
- **Exploratory analysis that demonstrates the efficacy of zoledronic acid in renal cell carcinoma.**
32. 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.* 16(2), 593–602 (1998).
33. 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* 88(5), 1082–1090 (2000).
34. 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) (Epub ahead of print) doi:10.1016/j.critrevonc.2006.12.005.
35. Tarassoff P, Hei Y-J, Maladorno D. Renal failure with the use of zoledronic acid [response to Chang JT *et al.*: *N. Engl. J. Med.* 349(17), 1676–1678 (2003)] *N. Engl. J. Med.* 349(17), 1678–1679 (2003).

36. Dimopoulos MA, Kastritis E, Anagnostopoulos A *et al.*: Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: evidence of increased risk after treatment with zoledronic acid. *Haematologica* 91(7), 968–971 (2006).
37. Mehrotra B, Ruggiero S. Bisphosphonate complications including osteonecrosis of the jaw. *Hematology Am. Soc. Hematol. Educ. Program* 356–360 (2006).
38. Migliorati CA, Siegel MA, Elting LS. Bisphosphonate-associated osteonecrosis: a long-term complication of bisphosphonate treatment. *Lancet Oncol.* 7(6), 508–514 (2006).
39. Munier A, Gras V, Andrejak M *et al.*: Zoledronic acid and renal toxicity: data from French adverse effect reporting database. *Ann. Pharmacother.* 39(7–8), 1194–1197 (2005).
40. Oh WK, Proctor K, Nakabayashi M *et al.*: The risk of renal impairment in hormone-refractory prostate cancer patients with bone metastases treated with zoledronic acid. *Cancer* 109(6), 1090–1096 (2007).
41. Aguiar Bujanda D, Bohn Sarmiento U, Cabrera Suarez M, Aguiar Morales J. Assessment of renal toxicity and osteonecrosis of the jaws in patients receiving zoledronic acid for bone metastasis. *Ann. Oncol.* 18(3), 556–560 (2007).
42. McDermott RS, Kloth DD, Wang H, Hudes GR, Langer CJ. Impact of zoledronic acid on renal function in patients with cancer: Clinical significance and development of a predictive model. *J. Support. Oncol.* 4(10), 524–529 (2006).
43. Berenson JR. Recommendations for zoledronic acid treatment of patients with bone metastases. *Oncologist* 10(1), 52–62 (2005).
44. 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.* 7(4), 403–408 (2003).
45. Hortobagy 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.* 335(24), 1785–1791 (1996).
46. 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.* 16(6), 2038–2044 (1998).
47. 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.* 14(9), 1399–1405 (2003).
48. 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* 111(3), 306–312 (2004).
49. Kristensen B, Ejlertsen B, Groenvold M *et al.*: Oral clodronate in breast cancer patients with bone metastases: a randomized study. *J. Intern. Med.* 246(1), 67–74 (1999).
50. Paterson AH, Powles TJ, Kanis JA *et al.*: Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. *J. Clin. Oncol.* 11(1), 59–65 (1993).
51. 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* 88(7), 701–707 (2001).
52. Pavlakis N, Schmidt RL, Stockler M. Bisphosphonates for breast cancer. *The Cochrane Database of Systematic Reviews*, Issue 3. Art. no. CD003474.pub2 (2005).
•• **Cochrane review of bisphosphonates for efficacy in patients with breast cancer.**
53. Diel IJ, Marschner N, Kindler M *et al.*: Continual oral versus intravenous interval therapy with bisphosphonates in patients with breast cancer and bone metastases [abstract]. Presented at: *1999 Annual Meeting of the American Society of Clinical Oncology*, May 15–18, 1999, Atlanta, GA, USA (Abstract 488).
54. Zheng M, Rosen L, Gordon D *et al.*: Continuing benefit of zoledronic acid for the prevention of skeletal complications in breast cancer patients with bone metastases. Presented at: *St. Gallen Oncology Conference: Primary Therapy of Early Breast Cancer.* St. Gallen, Switzerland, January 26–29,(2005). Poster 104.
55. 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* 100(1), 36–43 (2004).
56. Ibrahim A, Scher N, Williams G *et al.*: Approval summary for zoledronic acid for treatment of multiple myeloma and cancer bone metastases. *Clin. Cancer Res.* 9(7), 2394–2399 (2003).
57. Gnant MF, Mlineritsch B, Luschin-Ebengreuth G *et al.*: Zoledronic acid effectively prevents cancer treatment-induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: A report from the Austrian Breast and Colorectal Cancer Study Group. *J. Clin. Oncol.* 25(7), 820–282 (2007).
58. Aapro M. Improving bone health in patients with early breast cancer by adding bisphosphonates to letrozole: The Z-ZO-E-ZO-FAST program. *Breast* 15(suppl 1), S30–S40 (2006).
59. Brufsky A, Bundred N, Coleman RE *et al.*: An integrated analysis of zoledronic acid (ZA) for the prevention of aromatase inhibitor associated bone loss (AIBL) in postmenopausal women (PMW) with early breast cancer (BCa) receiving adjuvant letrozole (LET). Presented at: *29th Annual San Antonio Breast Cancer Symposium.* San Antonio, Texas, USA. December 14–17, 2006 (Abstract 107).
60. Green JR. Skeletal complications of prostate cancer: pathophysiology and therapeutic potential of bisphosphonates. *Acta Oncol.* 44(3), 282–292 (2005).
61. Smith MR, Eastham J, Gleason DM, Shasha D, Tchekmedyian S, Zinner N. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. *J. Urol.* 169(6), 2008–2012 (2003).
62. Oefelein MG, Ricchiuti V, Conrad W, Resnick MI. Skeletal fractures negatively correlate with overall survival in men with prostate cancer. *J. Urol.* 168(3), 1005–1007 (2002).
63. Lipton A, Cook RJ, Coleman RE, Major P, Shirina N. Prognostic significance of persistently elevated N-telopeptide levels in patients with bone metastases from solid tumors [poster]. *Ann. Oncol.* 17(Suppl. 9), ix254 (2006). Abstract 870P.
64. Jagdev SP, Coleman RE, Shipman CM, Rostami-H A, Croucher PI. The bisphosphonate, zoledronic acid, induces apoptosis of breast cancer cells: evidence for synergy with paclitaxel. *Br. J. Cancer* 84(8), 1126–1134 (2001).
65. Neville-Webbe HL, Rostami-Hodjegan A, Evans CA, Coleman RE, Holen I. Sequence- and schedule-dependent enhancement of zoledronic acid induced apoptosis by doxorubicin in breast and prostate cancer cells. *Int. J. Cancer* 113(3), 364–371 (2005).

66. Ottewell PD, Jones M, Lefley DV, Coleman RE, Holen I. Combined effects of cytotoxic drugs and anti-resorptive agents *in vivo* [poster]. Presented at: 29th Annual San Antonio Breast Cancer Symposium; San Antonio, TX, USA. December 14–17, (2006); Abstract 6102.
67. Powles T, Paterson A, McCloskey E *et al.*: Reduction in bone relapse and improved survival with oral clodronate for adjuvant treatment of operable breast cancer [ISRCTN83688026]. *Breast Cancer Res.* 8(2), R13 (2006).
68. Saarto T, Vehmanen L, Virkkunen P, Blomqvist C. Ten-year follow-up of a randomized controlled trial of adjuvant clodronate treatment in node-positive breast cancer patients. *Acta Oncol.* 43(7), 650–656 (2004).
69. Coleman RE, Thorpe H, Cameron D *et al.*: Zoledronic acid is well tolerated and can be safely administered with adjuvant chemotherapy – First safety data from the AZURE trial (BIG01/04) [poster]. Presented at: *29th Annual San Antonio Breast Cancer Symposium*, San Antonio, TX, USA, December 14–17, 2006 (Abstract 2080).

Websites

101. Zoledronate versus ibandronate comparative evaluation (ZICE) study protocol. www.wctu.org.uk/Zice%20Folder/Protocol/ZICE%20Protocol%20v3.0_190706.pdf
102. Novartis Pharmaceuticals USA Press Release. EMEA updates Zometa® label to include longer-term efficacy data on prevention of bone complications in advanced cancers. www.pharma.us.novartis.com/newsroom/pressReleases/releaseDetail.jsp?PRID=844
103. US National Institutes of Health clinical trials database. Chemotherapy and/or hormone therapy with or without zoledronate in treating women with stage II or stage III breast cancer. www.clinicaltrials.gov/ct/show/NCT00072020?order=1
104. University of Leeds Clinical Trials Research Unit. BISMARK Cost-effective use of BISphosphonates in metastatic bone disease-a comparison of bone MARKer directed zoledronic acid therapy vs. a standard schedule. www.leeds.ac.uk/medicine/nyctru/ProjectPage_Bismark.htm