

Symptom Management and Supportive Care

Recommendations for Zoledronic Acid Treatment of Patients with Bone Metastases

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe new indications for the use of i.v. bisphosphonates in patients with metastatic bone disease.
2. Explain the importance of infusion time on potential adverse renal events from bisphosphonates.
3. List the types of adverse events that are associated with i.v. bisphosphonate therapy.

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ABSTRACT

The introduction of zoledronic acid, a new-generation bisphosphonate, has greatly extended the use of bisphosphonates in the treatment of patients with bone metastases. On the basis of results from three large, randomized, phase III clinical trials enrolling more than 3,000 patients, zoledronic acid (4 mg via 15-minute infusion) was approved in the United States for the treatment of patients with documented bone metastases from solid tumors in conjunction with standard antineoplastic therapy and patients with multiple myeloma. Zoledronic acid is also approved in Europe for the prevention of skeletal-related events in patients with advanced malignancies involving bone. Current treatment guidelines published by the American Society of Clinical Oncology recommend the use of intravenous bisphosphonates at first radiographic evidence of osteopenia in patients with multiple myeloma or osteolytic

bone lesions in patients with breast cancer to significantly reduce the occurrence and delay the onset of skeletal complications. Zoledronic acid has also demonstrated efficacy in the treatment of bone metastases in patients with prostate cancer, lung cancer, and other solid tumors. Bisphosphonate therapy is generally well tolerated but can be associated with increases in serum creatinine. Therefore, monitoring renal function is required for all patients receiving bisphosphonate therapy. Serum creatinine should be monitored before each dose and treatment withheld until any serum creatinine elevations have resolved to baseline levels. Caution should be exercised when treating patients who are receiving other potentially nephrotoxic therapies. With these simple precautions, intravenous bisphosphonate therapy is safe for long-term use and provides durable treatment benefits. *The Oncologist* 2005;10:52-62

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INTRODUCTION

Skeletal complications contribute substantially to the burden of disease in patients with bone metastases from solid tumors and in patients with multiple myeloma. Bone metastases are the most common cause of cancer-related pain [1] and often require palliative radiotherapy. Patients with advanced cancer involving bone frequently develop painful and debilitating pathologic fractures and spinal cord compression that can seriously limit mobility and may require surgical intervention. These and other skeletal complications contribute to the deterioration in quality of life and independence of many cancer patients [2]. Median survival after the development of bone metastases ranges from 6–48 months, depending on tumor type [2]. Malignant bone disease can result in chronic morbidity that often requires repeated interventions over several years.

Approximately half of all patients with solid tumors that metastasize to bone experience one or more skeletal events (including pathologic fractures, spinal cord compression, radiotherapy or surgery to bone, and hypercalcemia) during the course of their disease [3, 4]. The incidence of these skeletal events varies depending on the type of primary cancer. For example, patients with predominantly osteolytic bone metastases secondary to advanced breast cancer are at high risk. Without bisphosphonate therapy, these patients will experience an average of four skeletal events, including two pathologic fractures, each year [4]. Patients with multiple myeloma, or bone metastases from prostate cancer, lung cancer, or renal cell carcinoma (RCC) are also at high risk of skeletal complications. Patients with multiple myeloma experience an average of two skeletal events per year [5, 6], and patients with prostate cancer have a mean annual incidence of 1.5 events per year [7]. Notably, approximately 80% of patients with bone metastases from RCC will develop a skeletal complication without bisphosphonate therapy [8].

Currently available palliative therapies for patients with malignant bone disease include radiation, chemotherapy, hormone therapy, orthopedic surgery, and i.v. bisphosphonates. Bisphosphonate therapy has emerged as an important component of the overall management strategy for malignant bone disease. Randomized, placebo-controlled trials have shown that when i.v. bisphosphonates are administered in conjunction with standard anticancer therapy, the incidence of skeletal complications is significantly reduced. Pamidronate has been widely used as palliative therapy in patients with osteolytic lesions from multiple myeloma or metastatic breast cancer, based on evidence that 90 mg pamidronate every 3–4 weeks significantly reduced the incidence and delayed the onset of skeletal complications in these patients compared with placebo [3, 4, 6, 9]. Moreover,

bisphosphonates have been shown in a variety of studies to have analgesic effects on bone pain in patients with bone metastases [10]. Until recently, other than in breast cancer or multiple myeloma, no bisphosphonate has demonstrated significant clinical benefits for cancer patients whose cancer has metastasized to bone (e.g., prostate, lung, and renal cancers).

Recently, the clinical benefits of a new-generation bisphosphonate, i.e., zoledronic acid, have been extended to patients with bone metastases secondary to a broad range of solid tumors including prostate cancer, lung cancer, and RCC. Zoledronic acid recently received broad regulatory approval for the treatment of bone metastases secondary to all solid tumor types and bone lesions from multiple myeloma based on the results of three large, randomized, phase III clinical trials enrolling more than 3,000 patients. These trials demonstrated that zoledronic acid (4 mg via 15-minute i.v. infusion every 3–4 weeks) effectively reduced the incidence of skeletal complications associated with malignant bone disease for patients with breast cancer, multiple myeloma, prostate cancer, or solid tumors other than breast or prostate cancer [7, 11, 12]. The primary efficacy end point in all three trials was the proportion of patients who experienced at least one skeletal-related event (SRE), defined as a pathologic fracture, spinal cord compression, radiotherapy to bone, or surgery to bone. Change in antineoplastic therapy to palliate bone pain was also included as an SRE only in the trial evaluating patients with prostate cancer. Hypercalcemia of malignancy (HCM) was included as an SRE in the analysis of secondary end points, including time to first SRE, the mean annual incidence of SREs (i.e., skeletal morbidity rate), and a multiple event analysis using the Andersen-Gill method. Multiple event analysis takes into account all clinically relevant SREs and the time to each event over a period of time, thereby providing a rigorous and sensitive assessment of skeletal morbidity. These three international trials were the largest bisphosphonate trials ever conducted, and unlike the previous pamidronate trials, they included patients with all types of bone lesions (i.e., osteolytic, mixed, and osteoblastic based on their radiographic appearance).

In the first of these trials to be published, zoledronic acid was compared with pamidronate in 1,648 patients with stage IV breast cancer with at least one bone lesion or Durie-Salmon stage III multiple myeloma. The results from this trial at 13 months demonstrated that zoledronic acid (4 mg via 15-minute infusion) was at least as effective as pamidronate (90 mg via 2-hour infusion) in the overall efficacy analysis, with a similar safety profile [11]. In addition, zoledronic acid significantly reduced the incidence of radiotherapy to bone compared with pamidronate (15% versus 20%;

$p = 0.031$). Most notably, multiple event analysis showed that zoledronic acid significantly reduced the risk of developing SREs by an additional 16% ($p = 0.030$) compared with pamidronate during the 24 months of treatment [13, 14].

Zoledronic acid was compared with placebo in 643 patients with bone metastases from prostate cancer that had progressed during hormone therapy [7]. These patients develop primarily osteoblastic lesions. Zoledronic acid (4 mg) significantly reduced the proportion of patients who experienced at least one SRE at 15 months compared with placebo (33% versus 44%; $p = 0.021$), and zoledronic acid displayed consistent efficacy across all secondary end points. The majority of SREs in this patient population were pathologic fractures and radiation to bone. Of note, 22% of patients in the placebo group had a fracture in the first 15 months compared with 13% of patients treated with 4 mg zoledronic acid ($p = 0.015$). Patients treated with zoledronic acid also had lower mean pain scores (Brief Pain Inventory composite score) compared with placebo at every time point, and these differences were statistically significant ($p < 0.05$) at the 3- and 9-month time points. This is the first randomized, placebo-controlled trial to demonstrate that a bisphosphonate can provide objective and durable clinical benefits to patients with prostate cancer with bone metastases.

In the most recently published of these phase III trials, zoledronic acid was compared with placebo in 773 patients with bone metastases secondary to solid tumors other than breast or prostate cancer (including lung, renal, and bladder cancers) [12]. Half of the patients enrolled in this study had non-small cell lung cancer (NSCLC), and median survival was only approximately 6 months for the entire patient population. Although the primary end point did not reach statistical significance when HCM was excluded from the analysis, 4 mg zoledronic acid significantly decreased the proportion of patients who experienced an SRE compared with placebo when HCM was included in the analysis (38% versus 47%; $p = 0.039$). Zoledronic acid also significantly prolonged time to first SRE; the median time was prolonged by more than 2 months ($p = 0.007$) [15], which may be a more meaningful assessment of treatment effect in this poor-prognosis patient population [12]. Furthermore, in the overall patient population and the NSCLC stratum, multiple event analysis demonstrated that treatment with 4 mg zoledronic acid significantly reduced the risk of developing SREs by 29% compared with placebo ($p = 0.036$) [16].

On the basis of results from these trials, zoledronic acid is emerging as the new standard of care for managing skeletal morbidity in patients with advanced cancers involving bone. Zoledronic acid has also been shown to reduce skeletal morbidity in patients with both osteolytic and osteoblastic bone lesions [17]. Zoledronic acid can be safely administered

via a 15-minute infusion, compared with the minimum recommended infusion time of 2 hours for pamidronate. Since receiving U.S. and European regulatory approval, zoledronic acid has been used to treat >800,000 patients with bone metastases. In the context of its widespread application, we have developed treatment recommendations for zoledronic acid therapy to ensure safety and efficacy, based on the available data.

CONVENIENCE OF A 15-MINUTE INFUSION

The infusion protocol for zoledronic acid has been standardized and is now available online at <http://www.us.zometa.com/hcp/productinfo/infusioninstructions.jsp>. Preinfusion assessments include a physical examination, vital signs, and laboratory testing of serum creatinine levels and hydration status. Because all i.v. bisphosphonates have the potential to cause an increase in serum creatinine and patients with serum creatinine ≥ 3.0 mg/dl were excluded from the phase III zoledronic acid trials, patients must be adequately hydrated and have serum creatinine levels < 3.0 mg/dl (< 4.5 mg/dl in patients with HCM [18] if the benefits of treatment are considered to outweigh the risk) before receiving i.v. bisphosphonates. Patients should be encouraged to drink two glasses of water before receiving their bisphosphonate infusion, but i.v. hydration is not typically necessary. The maximum recommended dose of zoledronic acid for the treatment of bone metastases or hypercalcemia of malignancy is 4 mg infused over no less than 15 minutes. Zoledronic acid powder (4 mg) can easily be reconstituted in 5 ml sterile water for injection USP and diluted in no less than 100 ml of 0.9% sodium chloride USP or 5% dextrose injection USP [11]. A concentrated solution of zoledronic acid (4 mg in 5 ml sterile water) is also available, eliminating the need for reconstitution. A 5-ml aliquot of the concentrate (4 mg zoledronic acid) should be mixed with 100 ml of calcium-free diluent before infusion. If not used immediately, the diluted solution can be stored in the refrigerator and should be re-equilibrated to room temperature and infused within 24 hours [19]. A peripheral i.v. line should be inserted and the diluted zoledronic acid solution infused over 15 minutes. The patient's vital signs and the i.v. site should be monitored periodically during the infusion and again after the infusion has been completed.

Zoledronic acid has the shortest infusion time of any i.v. bisphosphonate (Table 1) [18, 20, 21]. The recommended 15-minute infusion time for zoledronic acid is significantly shorter than the 2-hour infusion time recommended for 90 mg pamidronate (4 hours for patients with multiple myeloma) [21] and results in less time spent in the infusion center for the patient [22], which many patients prefer [23]. Additionally, the shorter infusion time will allow for

Table 1. Recommended doses and infusion times for intravenous bisphosphonates^a

Bisphosphonate	Dose (mg)	Recommended infusion volume (ml) ^b	Minimum infusion time (minutes)
Clodronate	1,500	500	≥120
Ibandronate	2-6	250–500	120
Pamidronate	90	500	120 ^c
Zoledronic acid	4	100	15

^aData from Major et al. [18] and Body et al. [20].

^bBisphosphonates should be diluted in saline or 5% dextrose. Do not administer bisphosphonates with any solutions containing calcium (e.g., lactated Ringer's solution).

^c240 minutes for patients with multiple myeloma [21].

increased throughput in busy infusion centers [24]. Indeed, a microcosting analysis of patients receiving bisphosphonate therapy determined that the average visit time required to receive zoledronic acid was 66 minutes, compared with 172 minutes for patients receiving pamidronate, and the shorter infusion time of zoledronic acid resulted in a savings of \$47 in indirect costs per infusion [22]. Based on an average of eight patients treated each day with i.v. bisphosphonates and the average infusion chair occupancy time for each agent, a typical infusion center would open up 1.8 infusion chairs per day when infusing zoledronic acid compared with pamidronate [22]. Therefore, in addition to the potential quality-of-life benefits for the patient, the shorter infusion time for zoledronic acid compared with pamidronate may reduce the demand on health care resources in busy infusion centers and hospitals.

PATIENT SELECTION AND TIMING FOR INITIATION OF THERAPY

The role of bisphosphonate therapy in the treatment of malignant bone disease has evolved over the past several years. With the introduction of zoledronic acid, all patients with bone metastases secondary to solid tumors or bone lesions from multiple myeloma can potentially benefit from bisphosphonate therapy. Because of the substantial burden of skeletal complications in patients with malignant bone disease and improvements in bisphosphonate therapy, treatment guidelines were recently established by the American Society of Clinical Oncology (ASCO) [25, 26]. According to these ASCO guidelines, all patients with multiple myeloma who have radiographic evidence of osteolytic bone disease or osteopenia in the absence of radiographically detectable bone disease should receive i.v. bisphosphonate therapy [25]. For patients with breast cancer, bisphosphonate therapy should be initiated at the first radiographic evidence of bone destruction or an abnormal bone scan with localized pain [26]. Patients who are receiving bisphosphonate therapy should continue to do so throughout

the course of their disease as long as it is tolerated [25, 26]. Although no guidelines have been developed for patients with solid tumors other than breast cancer, treatment with zoledronic acid at the first diagnosis of metastatic bone disease is a reasonable approach supported by the results of the large phase III trials of zoledronic acid in prostate cancer and in lung cancer or other solid tumors [7, 15]. Therefore, all patients with advanced cancer should have periodic radiographic evaluations to detect bone lesions. In a recent study of prostate cancer patients without evidence of bone metastases who were receiving androgen deprivation therapy, administration of zoledronic acid (4 mg every 3 months) significantly increased bone mineral density [27], suggesting that bisphosphonates may be beneficial even earlier in the course of therapy, before bone metastases develop.

Recommendations for zoledronic acid administration that are consistent with the above guidelines and the available clinical data are summarized in Table 2 [25, 26]. Once initiated, zoledronic acid therapy should be continued as long as the patient is able to tolerate therapy or until the patient has a substantial decline in performance status.

Although zoledronic acid therapy is widely recommended for patients with malignant bone disease and is generally safe and well tolerated with long-term use, it is contraindicated in patients with clinically significant hypersensitivity to zoledronic acid or other bisphosphonates and is not recommended for patients with severe renal impairment. Patients with serum creatinine >3.0 mg/dl were excluded from the phase III clinical trials [7, 11, 12]. Therefore, there are no prospective data on the safety of zoledronic acid in these patients. However, for patients with serum creatinine >3.0 mg/dl who are considered at high risk of developing skeletal complications, the potential benefits of zoledronic acid may outweigh the risk of any potential adverse effects on renal function. For example, patients with life-threatening HCM and patients with extensive osteolytic lesions at weight-bearing bone sites may be considered at high risk,

Table 2. Administration guidelines for patients treated with zoledronic acid

Timing of bisphosphonate therapy	
Topic	Recommendations
Initiation of bisphosphonate therapy	<ul style="list-style-type: none"> • At first diagnosis of osteolytic destruction or abnormal bone scan and localized pain in patients with breast cancer [26] • At first diagnosis of osteolytic bone disease or osteopenia in patients with multiple myeloma [25] • At first diagnosis of bone metastases in patients with solid tumors. Prostate cancer should have progressed after treatment with at least one hormonal therapy regimen
Duration of bisphosphonate therapy	<ul style="list-style-type: none"> • Continue as long as the patient is able to tolerate therapy or until evidence of a substantial decline in performance status [25, 26]
Patient eligibility	
Topic	Recommendations
Patients who are receiving pamidronate	<ul style="list-style-type: none"> • All patients who are safely receiving pamidronate and who have serum creatinine levels <3.0 mg/dl can be safely treated with zoledronic acid • Exercise caution when initiating zoledronic acid therapy in patients with the following risk factors: <ul style="list-style-type: none"> —Diagnosis of multiple myeloma —Advanced age —Concomitant use of agents that could affect renal function (e.g., NSAIDs or thalidomide)
Contraindications or warnings	<ul style="list-style-type: none"> • Zoledronic acid is not recommended under the following circumstances: <ul style="list-style-type: none"> —Pregnancy —Severe renal impairment —A history of elevated serum creatinine associated with prior bisphosphonate treatment —A history of hypersensitivity to zoledronic acid —Serum creatinine levels ≥ 3.0 mg/dl at baseline^a
Renal monitoring guidelines	
Topic	Recommendations
Timing of serum creatinine measurements	<ul style="list-style-type: none"> • A serum creatinine measurement should be obtained within 7–10 days before the first infusion of zoledronic acid • Serum creatinine measurements should be obtained before each subsequent dose of zoledronic acid
Criteria for delaying bisphosphonate infusions	<ul style="list-style-type: none"> • Therapy should be temporarily interrupted in patients with serum creatinine \geq twice the individual baseline or an increase of ≥ 0.5 mg/dl for patients with normal baseline serum creatinine (<1.4 mg/dl) or ≥ 1.0 mg/dl for patients with abnormal baseline serum creatinine (≥ 1.4 mg/dl) until the serum creatinine level returns to within 10% of baseline • Bisphosphonate therapy should be discontinued if serum creatinine elevations do not resolve within 4–8 weeks
Use of potentially nephrotoxic drugs during zoledronic acid therapy	<ul style="list-style-type: none"> • Agents with the potential for renal toxicity (e.g., NSAIDs, thalidomide, radiographic contrast dye) should be avoided during therapy with zoledronic acid • If these agents must be used in patients treated with zoledronic acid, they should be administered at least 24 hours after the zoledronic acid infusion
Adverse events	
Adverse event	Recommendations
Acute-phase reaction	<ul style="list-style-type: none"> • Inform patients of the possibility of an acute-phase reaction after the first and possibly after the second bisphosphonate infusion <ul style="list-style-type: none"> —Symptoms (i.e., low-grade fever, arthralgia or myalgias, nausea, and increased bone pain) occur in approximately 10%–15% of patients —Symptoms will typically occur within 24 hours of the infusion and resolve in 48 hours • Reassure patients that the acute-phase reaction is transient, should be less severe with the second infusion, and should not occur with the third infusion

Table 2. Administration guidelines for patients treated with zoledronic acid (continued)

Adverse event	Recommendations
	<ul style="list-style-type: none"> • Prophylaxis is not recommended and there are no criteria to identify patients at risk • Management strategies <ul style="list-style-type: none"> — Antiemetics and/or analgesics as necessary. NSAIDs are not recommended — Assess dehydration and electrolyte levels — Monitor vital signs and nutritional status
Anemia ^b	<ul style="list-style-type: none"> • Red blood cell transfusion • Erythropoietin
Myalgia/arthralgia or headache ^b	<ul style="list-style-type: none"> • Analgesics
Constipation ^b	<ul style="list-style-type: none"> • Stool softeners • Maintain adequate fluid intake
Anorexia ^b	<ul style="list-style-type: none"> • Nutritional counseling • Nutritional supplements • Appetite stimulants
Edema (lower limb) ^b	<ul style="list-style-type: none"> • Elevate extremities • Compression stockings

^aZoledronic acid may be administered to patients with renal cell carcinoma and elevated serum creatinine levels at physician's discretion if they are considered at high risk for developing skeletal complications. Strict compliance with renal monitoring guidelines must be followed.

^bThese adverse events have been reported during i.v. bisphosphonate therapy but are not necessarily causally related to the use of zoledronic acid (see Table 4).

and zoledronic acid therapy may be initiated at the physician's discretion despite pre-existing renal impairment. Because of the inherent prevalence of renal impairment and the widespread use of potentially nephrotoxic therapies in patients with multiple myeloma, clinical experience suggests that zoledronic acid should be administered cautiously in that patient population, especially in those receiving thalidomide therapy. Renal function monitoring guidelines will be discussed further in the section on managing adverse events.

Caution should be exercised when starting bisphosphonate therapy or when switching from one bisphosphonate to another in patients who have other renal-related risk factors (refer to guidelines in Table 2) [25, 26]. Risk factors include a diagnosis of multiple myeloma, diabetes mellitus, hypertension, advanced age, and the use of concomitant medications that are known to affect renal function (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs]). Therefore, zoledronic acid or i.v. bisphosphonates should be used with caution for patients receiving drugs that may have a deleterious effect on kidney function.

MANAGING BISPHOSPHONATE-RELATED ADVERSE EVENTS

Bisphosphonate therapy is associated with mainly mild to moderate adverse events. The safety profile of zoledronic acid has been well established, based on randomized

controlled trials and the collective experiences of more than 800,000 patients treated with zoledronic acid. Recommendations have been developed (Table 2) [25, 26] to ensure the safety and comfort of patients during bisphosphonate therapy. The renal monitoring guidelines and treatment interruption criteria detailed in the prescribing information are the same for zoledronic acid and pamidronate.

Acute-Phase Reactions

The most common adverse events associated with the administration of i.v. bisphosphonates are self-limiting flu-like symptoms related to an acute-phase reaction [28]. Patients may have low-grade fever, arthralgia/myalgia, and increased bone pain. The incidence of these symptoms ranges from 1%-18% of patients treated with zoledronic acid and is similar to the incidence in patients receiving pamidronate (Table 3) [11, 29]. The onset of these symptoms typically occurs within 24 hours after the first infusion, and symptoms generally persist for ≤ 48 hours [28]. Acute-phase reactions usually diminish and/or disappear following the second or third infusion. Patients who are switching from pamidronate to zoledronic acid may also experience acute-phase reactions, even if they did not experience them when receiving pamidronate. Patients should be advised of the possibility that they may experience these symptoms. However, because these reactions do not occur in the majority of patients, prophylactic pretreatment regimens

Table 3. Acute-phase reactions reported within 14 days of the first and second bisphosphonate infusions in patients with breast cancer or multiple myeloma

Acute-phase symptom	Patients, n (%)			
	Zoledronic acid (4 mg)		Pamidronate (90 mg)	
	First infusion (n = 563)	Second infusion (n = 542)	First infusion (n = 556)	Second infusion (n = 538)
Arthralgia	18 (3.2)	10 (1.9)	14 (2.5)	15 (2.8)
Bone pain	85 (15.1)	55 (10.2)	65 (11.7)	50 (9.3)
Fever	65 (11.6)	24 (4.3)	44 (7.9)	21 (3.9)
Myalgia	16 (2.8)	20 (3.7)	17 (3.1)	10 (1.9)

Data from the trial by Rosen et al. [11]; table adapted with permission from Maxwell et al. [29].

are not recommended. Acetaminophen and oral fluids can be used to manage flu-like symptoms, and antiemetics are recommended for nausea. It is important to recognize that the flu-like syndrome is unlikely to persist after subsequent infusions. In patients with fatigue that is accompanied by anemia, erythropoietin or transfusion support is occasionally recommended. The recommendations for supportive care during zoledronic acid therapy are summarized in Table 2 [25, 26].

Effects on Renal Function

A less common but potentially serious adverse event is decreased renal function, which may occur after the administration of any i.v. bisphosphonate. Adherence to the renal monitoring guidelines will minimize the risk of renal sequelae. Approximately 10% of patients treated with zoledronic acid (4 mg via 15-minute infusion) develop renal function deterioration (defined as an increase of 0.5 mg/dl in patients with normal baseline serum creatinine [<1.4 mg/dl] or an increase of 1.0 mg/dl in patients with abnormal baseline serum creatinine [≥ 1.4 mg/dl]) during the course of their treatment, similar to the frequency reported for patients treated with 90 mg pamidronate via 2-hour infusion [11]. Furthermore, the time to first increase in serum creatinine was similar during 4-mg zoledronic acid or 90-mg pamidronate treatment (Fig. 1) [13]. Patients receiving long-term bisphosphonate therapy or patients at risk for renal dysfunction may have a greater risk of developing renal function deterioration when treated with i.v. bisphosphonates. However, serum creatinine increases are generally mild to moderate in severity and are mostly transient in duration. In the phase III trials of zoledronic acid, $<2\%$ of patients treated with zoledronic acid (4 mg via 15-minute infusion every 3–4 weeks) developed \geq grade 3 serum creatinine elevations (i.e., $>$ three times the upper limit of normal according to the National Cancer Institute common toxicity criteria) [19]. Furthermore, in the two placebo-controlled trials of patients with bone metastases from prostate cancer

or other solid tumors (not including breast cancer), increases in serum creatinine occurred in considerable proportions of patients in the placebo groups (12.8% and 7.4%, respectively), suggesting that underlying disease-related factors may contribute to the incidence of renal impairment in patients with advanced cancer [7, 15]. Moreover, in the more than 800,000 patients treated with zoledronic acid, spontaneous renal function impairment has been uncommon, and nearly half of these cases were in patients with multiple myeloma, a disease associated with increased risk of renal failure [30, 31]. Although the information on these events is limited, many occurred in patients who had abnormal serum creatinine (≥ 1.4 mg/dl) at baseline or who had previously received long-term treatment with pamidronate. Therefore, there may be an increased risk of renal impairment in patients with abnormal serum creatinine at baseline, and prior long-term bisphosphonate therapy may predispose patients to decreased renal function.

Renal Monitoring Guidelines

Renal monitoring guidelines have been established to minimize the risk of renal deterioration during bisphosphonate

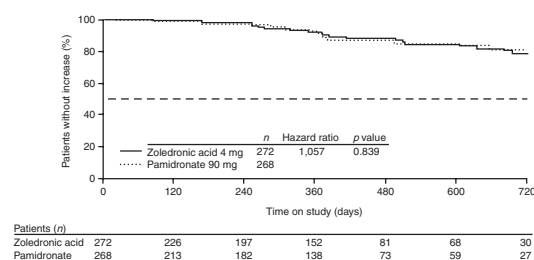


Figure 1. Time to first increase in serum creatinine. Kaplan-Meier estimates of time to first increase in serum creatinine in patients with breast cancer or multiple myeloma treated with pamidronate (90 mg via 2-hour infusion) or zoledronic acid (4 mg via 15-minute infusion) in a randomized, phase III trial. Data from the trial by Rosen et al. [13].

therapy (Table 2) [25, 26]. The renal monitoring guidelines for pamidronate have recently been updated, and these guidelines are the same as those for zoledronic acid. The hydration status of patients should be monitored, and bisphosphonates should not be administered to patients with suspected dehydration. Serum creatinine should be measured within 7 to 10 days of the first zoledronic acid infusion (baseline value) and measured before the administration of each subsequent dose. Infusion of zoledronic acid should be withheld from any patient whose serum creatinine level has increased by 50% above the individual baseline, from patients with normal baseline serum creatinine whose levels have increased by ≥ 0.5 mg/dl, and from patients with abnormal baseline serum creatinine whose levels have increased by ≥ 1.0 mg/dl. The zoledronic acid infusion can be resumed after serum creatinine has returned to within 10% of baseline, which may take from several weeks to months to occur. A slower infusion time may reduce the risk of further episodes of rises in serum creatinine.

In patients who are receiving potentially nephrotoxic therapies or who have abnormal renal function at baseline, additional considerations must be made. At this time, there are insufficient clinical data to generate specific renal monitoring recommendations for zoledronic acid in patients receiving nephrotoxic drugs such as radiographic contrast media. If possible, zoledronic acid and nephrotoxic drugs should not be administered on the same day. Anecdotal evidence from clinical experience and a small open-label trial suggest that concomitant therapy with thalidomide may potentiate adverse renal effects [32]. However, in the phase III clinical trial setting, concomitant therapy with thalidomide was not identified as a risk factor in patients with multiple myeloma [11]. Drugs with the potential for renal toxicity, such as NSAIDs, should also be administered with caution to patients who are receiving zoledronic acid, and use of these chronically administered medications may need to be avoided around the time of i.v. bisphosphonate therapy. Waiting 24 hours after the administration of zoledronic acid before administering any drugs that are potentially nephrotoxic may minimize the risk of renal impairment. Further, clinical experiences suggest that increasing the infusion time for zoledronic acid from 15 to 30 minutes may possibly further reduce the risk of serum creatinine increases in these patients. However, this has not been confirmed in controlled studies.

Other Adverse Events

The most commonly reported adverse events among patients treated with zoledronic acid or pamidronate are shown in Table 4 [11]. Severe adverse events are rare. The majority of these adverse events can be managed with

Table 4. Most common adverse events^a occurring in $\geq 15\%$ of patients with breast cancer or multiple myeloma receiving zoledronic acid (4 mg) or pamidronate (90 mg)

Adverse event	Patients, <i>n</i> (%)	
	Zoledronic acid (4 mg) (<i>n</i> = 563)	Pamidronate (90 mg) (<i>n</i> = 556)
Bone pain	312 (55)	303 (55)
Nausea	250 (44)	245 (44)
Fatigue	217 (39)	212 (38)
Fever	200 (36)	160 (29)
Vomiting	166 (30)	164 (30)
Anemia	153 (27)	155 (28)
Myalgia	144 (26)	130 (23)
Diarrhea	141 (25)	139 (25)
Dyspnea	138 (25)	134 (24)
Cough	135 (24)	114 (21)
Constipation	134 (24)	132 (24)
Arthralgia	125 (22)	95 (17)
Weakness	113 (20)	91 (16)
Headache	106 (19)	131 (24)
Anorexia	105 (19)	70 (13)
Edema (lower limb)	92 (16)	108 (19)
Alopecia	89 (16)	72 (13)

^aIncludes all adverse events, regardless of relationship with study drug.

Adapted with permission from Rosen et al. [11].

standard supportive care, as summarized in Table 2 [25, 26]. Serum ion fluctuations (e.g., hypocalcemia, hypophosphatemia, and hypermagnesemia) may occur during therapy with any bisphosphonate. Therefore, dietary vitamin D supplements are recommended to minimize these events. Occasional untoward effects on the eye (uveitis) have been reported with i.v. bisphosphonates.

Adverse Events Can Be Minimized by Adherence to Administration Guidelines

The proper administration, dose, and schedule of zoledronic acid are crucial to minimize the incidence and severity of adverse events. Zoledronic acid can be safely administered at a dose of 4 mg with a minimum infusion time of 15 minutes every 3–4 weeks. Although a shorter infusion time (i.e., 5 minutes) was investigated in phase I and II clinical trials [33–35], infusion times < 15 minutes resulted in an increased incidence of serum creatinine elevations during the early stages of phase III clinical testing and therefore are not recommended [7, 11]. Furthermore, in the phase III trials, administration of 8 mg zoledronic acid did not provide any treatment benefit over that achieved with 4 mg, but did

increase the incidence of elevated serum creatinine and renal adverse events [7, 11]. Therefore, the 8-mg dose is not recommended for clinical use at this time using any infusion duration. Ongoing monitoring of serum creatinine, serum ion levels, and hydration status are recommended to minimize adverse events with patients receiving any i.v. bisphosphonate.

Duration of Bisphosphonate Therapy

There are limited data on the optimal duration of zoledronic acid therapy. Current guidelines suggest that, once initiated, bisphosphonate therapy should be continued as long as it is well tolerated or until there is a significant decrease in performance status in patients with bone metastases from breast cancer [36]. Although there are no consensus guidelines for the duration of bisphosphonate therapy in patients with prostate cancer, recently published recommendations from a multidisciplinary panel suggest that bisphosphonate treatment should be ongoing after bone metastases are diagnosed [37]. This is supported by recent reports that the efficacy of zoledronic acid does not appear to decrease during long-term use [38] or in patients who have already experienced SREs [39]. Moreover, zoledronic acid demonstrated early and sustained palliation of pain compared with placebo during a 24-month course of treatment [38]. In patients with bone metastases from solid tumors other than breast or prostate cancer, no formal recommendations have been published. However, zoledronic acid has demonstrated significant benefits in this setting in patients who have experienced prior SREs [40], so treatment should not be discontinued on the basis of SRE history.

SUMMARY AND CONCLUSIONS

Zoledronic acid is the first bisphosphonate to demonstrate significant and durable clinical benefit in reducing skeletal complications for patients with malignant bone involvement from multiple myeloma and a variety of solid tumors, including breast cancer, prostate cancer, and lung cancer [7, 11, 12]. Treatment with zoledronic acid can prevent or delay debilitating skeletal complications, and therefore may slow the erosion of quality of life experienced by patients with advanced cancer involving the bone. Importantly, long-term treatment with zoledronic acid has been shown to be safe and well tolerated during its widespread use in clinical practice. Adherence to renal monitoring will ensure renal safety.

The development of an effective and safe i.v. bisphosphonate therapy that can be administered in only 15 minutes is an important therapeutic advance that provides a direct quality-of-life benefit to the patient. Furthermore, the 15-minute infusion protocol for zoledronic acid has renal and overall safety profiles similar to those of the 2-hour infusion of pamidronate, the former standard of care for patients with breast cancer or multiple myeloma [11]. In summary, with the proper dose, schedule, and patient monitoring, zoledronic acid represents an important advance in the management of patients with bone metastases.

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REFERENCES

1 Mercadante S. Malignant bone pain: pathophysiology and treatment. *Pain* 1997;69:1–18.

2 Coleman RE. Skeletal complications of malignancy. *Cancer* 1997;80(suppl 8):1588–1594.

- 3 Theriault RL, Lipton A, Hortobágyi GN et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Group. *J Clin Oncol* 1999;17:846–854.
- 4 Lipton A, Theriault RL, Hortobágyi GN et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. *Cancer* 2000;88:1082–1090.
- 5 Menssen HD, Sakalova A, Fontana A et al. Effects of long-term intravenous ibandronate therapy on skeletal-related events, survival, and bone resorption markers in patients with advanced multiple myeloma. *J Clin Oncol* 2002;20:2353–2359.
- 6 Berenson JR, Lichtenstein A, Porter L et al. Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. Myeloma Aredia Study Group. *J Clin Oncol* 1998;16:593–602.
- 7 Saad F, Gleason DM, Murray R et al. A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *J Natl Cancer Inst* 2002;94:1458–1468.
- 8 Lipton A, Colombo-Berra A, Bukowski RM et al. Zometa® (zoledronic acid) reduces skeletal complications in patients with bone metastases from renal cell carcinoma. Presented at the XVIIIth Congress of the European Association of Urology, Madrid, Spain. March 12–15, 2003. Abstract 379.
- 9 Hortobágyi GN, Theriault RL, Lipton A et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. *J Clin Oncol* 1998;16:2038–2044.
- 10 Wong R, Wiffen PJ. Bisphosphonates for the relief of pain secondary to bone metastases. *Cochrane Database Syst Rev* 2002;CD002068.
- 11 Rosen LS, Gordon D, Kaminski M et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. *Cancer J* 2001;7:377–387.
- 12 Rosen L, Gordon D, Tchekmedyan S et al. Zoledronic acid (Zol) significantly reduces skeletal-related events (SREs) in patients with bone metastases from solid tumors. *Proc Am Soc Clin Oncol* 2002;21:295a.
- 13 Rosen LS, Gordon D, Kaminski M et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer* 2003;98:1735–1744.
- 14 Coleman RE, Rosen LS, Gordon D et al. Zoledronic acid (4 mg) significantly reduces the relative risk of developing a skeletal-related event compared with pamidronate (90 mg) in patients with breast cancer and bone metastasis. *Breast Cancer Res Treat* 2002;76(suppl 1):S95.
- 15 Rosen LS, Gordon D, Tchekmedyan S et al. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial—the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol* 2003;21:3150–3157.
- 16 Data on file. Novartis Pharma AG: Basel, Switzerland, 2000.
- 17 Lipton A, Small E, Saad F et al. The new bisphosphonate, Zometa (zoledronic acid), decreases skeletal complications in both osteolytic and osteoblastic lesions: a comparison to pamidronate. *Cancer Invest* 2002;20(suppl 2):45–54.
- 18 Major P, Lortholary A, Hon J et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol* 2001;19:558–567.
- 19 ZOMETA® [package insert]. Zoledronic acid prescribing information. East Hanover, NJ: Novartis Pharmaceuticals Corporation, 2003.
- 20 Body JJ, Bartl R, Burckhardt P et al. Current use of bisphosphonates in oncology. International Bone and Cancer Study Group. *J Clin Oncol* 1998;16:3890–3899.
- 21 Aredia® [package insert]. Pamidronate disodium prescribing information. East Hanover, NJ: Novartis Pharmaceuticals Corporation, 2002.
- 22 DesHarnais Castel L, Bajwa K, Markle JP et al. A microcosting analysis of zoledronic acid and pamidronate therapy in patients with metastatic bone disease. *Support Care Cancer* 2001;9:545–551.
- 23 Joseph D, Chern B, Pittman K et al. An assessment of patient preferences for intravenous zoledronic acid or pamidronate in patients commencing bisphosphonate therapy for malignant disease in bone. *Blood* 2002;100:388b.
- 24 Joshua DE, Chern B, Dalley D et al. Resource use by zoledronic acid or pamidronate infusions in multiple myeloma and cancer. *Blood* 2002;100:496b.
- 25 Berenson JR, Hillner BE, Kyle RA et al. American Society of Clinical Oncology clinical practice guidelines: the role of bisphosphonates in multiple myeloma. *J Clin Oncol* 2002;20:3719–3736.
- 26 Hillner BE, Ingle JN, Berenson JR et al. American Society of Clinical Oncology guideline on the role of bisphosphonates in breast cancer. American Society of Clinical Oncology Bisphosphonates Expert Panel. *J Clin Oncol* 2000;18:1378–1391.
- 27 Smith MR, Eastham J, Gleason DM et al. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. *J Urol* 2003;169:2008–2012.
- 28 Zojer N, Keck AV, Pecherstorfer M. Comparative tolerability of drug therapies for hypercalcaemia of malignancy. *Drug Saf* 1999;21:389–406.
- 29 Maxwell C, Swift R, Goode M et al. Nursing guidelines for administering zoledronic acid to patient with bone metastases. *Topics in Advanced Nursing Practice e-Journal* 2003;4. Available at: www.medscape.com/viewarticle/462348?src=search. Accessed November 17, 2004.
- 30 Kyle RA. Update on the treatment of multiple myeloma. *The Oncologist* 2001;6:119–124.

- 31 Corso A, Zappasodi P, Lazzarino M. Urinary proteins and renal dysfunction in patients with multiple myeloma. *Biomed Pharmacother* 2002;56:139–143.
- 32 Myers B, Jones SG, McMillan AK et al. Zoledronic acid, hypocalcaemia and renal dysfunction in thalidomide-treated myeloma patients. *Blood* 2002;100:211a.
- 33 Berenson JR. Zoledronic acid in cancer patients with bone metastases: results of phase I and II trials. *Semin Oncol* 2001;28(suppl 6):25–34.
- 34 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* 2001;7:478–485.
- 35 Berenson JR, Rosen LS, Howell A et al. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. *Cancer* 2001;91:1191–1200.
- 36 Hillner BE, Ingle JN, Chlebowski RT et al. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. *J Clin Oncol* 2003;21:4042–4057.
- 37 Carroll PR, Altwein J, Brawley O et al. Management of disseminated prostate cancer. In: Denis L, Bartsch G, Khoury S et al., eds. *Prostate Cancer: 3rd International Consultation on Prostate Cancer—Paris*. Paris: Health Publications, 2003:249–284.
- 38 Saad F, Gleason DM, Murray R et al. Continuing benefit of zoledronic acid for the prevention of skeletal complications in men with advanced prostate cancer. *Proc Am Soc Clin Oncol* 2004;23:399.
- 39 Chin JL, Saad F, Gleason DM et al. Clinical benefit of zoledronic acid for the prevention of skeletal complications in patients with prostate cancer based on history of skeletal complications. *Proc Am Soc Clin Oncol* 2004;23:399.
- 40 Hirsh V, Tchekmedyian NS, Rosen L et al. Clinical benefit of zoledronic acid in patients with lung cancer and other solid tumors: analysis based on prior history of skeletal complications. *Proc Am Soc Clin Oncol* 2004;23:669.