Bisphosphonate Treatment Recommendations for Oncologists

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Key Words. Bisphosphonates • Ibandronate • Renal safety • Product labeling • Product information • Nephrotoxicity

ABSTRACT
Renal safety is an important consideration for oncologists who are treating patients with bisphosphonates. In recent years, there has been increasing awareness about the development of bisphosphonate-induced nephrotoxicity. This has emerged mainly from increased clinical experience with zoledronic acid (Zometa®; Novartis Pharmaceuticals Corporation, East Hanover, NJ, http://www.pharma.us.novartis.com). For this reason, the U.S. and European product labels for i.v. zoledronic acid were recently updated to include additional renal safety cautions, including dose adjustment in patients with mild-to-moderate renal impairment. However, renal toxicity is not a class effect. The product label for ibandronate (Bondronat®, F. Hoffmann-La Roche Ltd., Basel, Switzerland, http://www.roche.com) has remained unchanged since the launch of the drug in the European Union in 2003. Ibandronate does not require mandatory monitoring of kidney function prior to each infusion. In addition, ibandronate can be used in patients with varying degrees of renal impairment. It also can be used without restrictions for nephrotoxic medications, and dose adjustment is only required in patients with severe renal impairment. Clinical implications of the renal safety of ibandronate include reducing the physician and nursing time needed for managing the adverse renal events associated with bisphosphonate therapy and dosing based on renal function. There also are no added renal safety risks and fewer inconvenient hospital visits with ibandronate therapy. In addition to i.v. ibandronate, an oral formulation of the drug is available. Oral ibandronate therapy is especially desirable because the medication is convenient (with a small, once-daily tablet that can be taken at home), reducing the health care costs associated with infusions. Clinical studies also indicate that 50 mg oral ibandronate has an efficacy similar to that of i.v. bisphosphonates and is associated with a low incidence of adverse gastrointestinal events. The Oncologist 2005;10(suppl 1):19–24

INTRODUCTION
Bisphosphonate-induced nephrotoxicity is problematic for cancer patients and health care professionals. Clinically significant deterioration in renal function is a risk with some bisphosphonates [1, 2], requiring renal function monitoring and occasional drug discontinuation. In addition, renal impairment can progress to renal failure, prompting the need for renal dialysis and causing death in some patients. Estimates suggest that, in the U.S., approximately 7.3% of the people with pre-existing chronic kidney disease would be at a greater risk for renal deterioration during long-term bisphosphonate therapy [3].

Studies have reported renal toxicity with approved doses of i.v. zoledronic acid (Zometa®; Novartis Pharmaceuticals Corporation, East Hanover, NJ, http://www.pharma.us.novartis.com). In the adverse event reporting system of the U.S. Food and Drug Administration (FDA), 72 cases...
of renal dysfunction associated with zoledronic acid were identified from August 2001 to March 2003 [4]. Of the 72 patients, 27 required dialysis and 18 died. In addition, retrospective studies [5–7] have shown substantial deterioration in renal function with zoledronic acid. The studies revealed that the incidence of renal dysfunction was highest in patients with multiple myeloma [5] and those who were given pamidronate (Aredia®; Novartis Pharmaceuticals Corporation) prior to zoledronic acid therapy [7]. Because of patient safety concerns, the product label for zoledronic acid in the U.S. and European Union was updated to include additional warnings of nephrotoxicity and restrictions for patients with varying degrees of renal impairment [8, 9]. Evidence suggests that renal toxicity is not a class effect of bisphosphonates. Results of phase II/III clinical studies demonstrate that ibandronate (Bondronat®; F. Hoffmann-La Roche Ltd., Basel, Switzerland, http://www.roche.com) has a renal safety profile comparable with that of placebo [10]. For this reason, it is important to understand the differences among the newer bisphosphonates and to be informed about the best practices for maintaining renal safety when treating cancer patients with bone metastases.

**INDICATIONS**

In the U.S. and Europe, zoledronic acid is indicated in conjunction with standard antineoplastic therapy for treating patients with hypercalcemia of malignancy, multiple myeloma, and bone metastases from solid tumors [8, 9]. In Europe, ibandronate is indicated for preventing skeletal events such as pathologic fractures and bone complications requiring radiotherapy or surgery in patients with breast cancer and bone metastases [11]. In addition, ibandronate is approved for treating tumor-induced hypercalcemia with or without metastases.

Several clinical studies suggest that ibandronate may have pan-tumor effects. Results of a placebo-controlled trial show that i.v. ibandronate prevented skeletal events in a subset of 15 patients with colorectal cancer [12]. Research also shows that nonstandard, intensive i.v. ibandronate dosing provided rapid and sustained relief of bone pain in patients with hormone-refractory prostate cancer [13, 14] and other types of urologic cancer [15] and moderate-to-severe, opioid-resistant bone pain from a variety of malignant tumors [16].

**Infusion Duration and Dosage**

A 4-mg zoledronic acid infusion given over no fewer than 15 minutes every 3 or 4 weeks is recommended to prevent skeletal-related events in adults and elderly patients with advanced malignancies involving bone who have a creatinine clearance >60 ml/min [8, 9]. The recommended zoledronic acid doses for patients with reduced renal function are listed in Table 1. Zoledronic acid is not recommended in patients with bone metastases and severe renal impairment. Factors such as dehydration and the use of other nephrotoxic drugs that predispose patients to renal deterioration should be identified and managed if possible.

The product label for ibandronate has remained unchanged since the launch of the drug in 2003 [11]. The recommended dose of ibandronate for metastatic bone disease is 6 mg infused over 1 hour every 3–4 weeks. There is no need for dose adjustment in patients with mild or moderate renal impairment (patients with a creatinine clearance ≥30 ml/min). In addition, ibandronate can be used in patients with severe renal impairment (i.e., those with a creatinine clearance <30 ml/min). In those patients, the dose must be reduced to 2 mg infused over 1 hour every 3–4 weeks to maintain the same drug exposure achieved with the 6-mg standard dose. There are no dosing restrictions for ibandronate in patients who also are receiving cancer therapies with nephrotoxic side effects.

**Table 1. Recommended i.v. zoledronic acid and i.v. ibandronate dosing schedules for patients with varying degrees of renal function**

<table>
<thead>
<tr>
<th>Renal Impairment</th>
<th>i.v. zoledronic acid</th>
<th>i.v. ibandronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard regimen</td>
<td>4 mg given every 3–4 weeks over 15 minutes</td>
<td>6 mg given every 3–4 weeks over 1 hour</td>
</tr>
<tr>
<td>Mild-to-moderate</td>
<td>Dose adjustments required</td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td>&gt;60 ml/min = 4 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–60 ml/min = 3.5 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40–49 ml/min = 3.3 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–39 ml/min = 3.0 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60 ml/min = 4 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe renal impairment</td>
<td>Not recommended</td>
<td>Below 30 ml/min creatinine clearance, the dose should be reduced to 2 mg every 3–4 weeks, infused over 1 hour</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Recommended prior to each dose</td>
<td>Not mandatory; at physician’s discretion</td>
</tr>
</tbody>
</table>

15-MINUTE IBANDRONATE INFUSION

Results of a preliminary, parallel-group study in 57 healthy volunteers have shown that it may be possible to safely...
reduce the infusion time of 6 mg i.v. ibandronate from 60 minutes to 30 or 15 minutes [17]. Reducing the infusion time from 60 to 15 minutes increased the mean peak concentrations (307.9 ng/ml ± 44.8 ng/ml versus 396.7 ng/ml ± 94.5 ng/ml, respectively) with no adverse effect on renal function parameters such as creatinine clearance (Fig. 1), serum creatinine levels, and markers of tubular or glomerular damage (Fig. 2) during a 3-day follow-up. Similarly, there were no reports of renal adverse events in an open-label trial to assess the safety and effects on bone turnover of a single 15-minute infusion of 6 mg ibandronate on day 1, followed by daily oral dosing (50 mg/day) for 12 weeks in 39 patients with either breast cancer (n = 31) or multiple myeloma (n = 8) [18]. Calculated creatinine clearance levels also were similar at baseline and week 12 (Fig. 3). A comparative trial is under way to evaluate the renal safety of a 60-minute versus a 15-minute ibandronate infusion.

**RENAL MONITORING**

Renal toxicity associated with i.v. bisphosphonate administration increases the use of health care resources for patient care. Managing adverse renal events, regular serum creatinine monitoring, and dosing based on renal function increase a patient’s need for care, including physicians’ and nurses’ time. In addition, i.v. dosing is inconvenient for patients because it requires hospital visits.

Renal monitoring guidelines in the prescribing information for zoledronic acid recommend that serum creatinine be measured before each dose of zoledronic acid. The guidelines also suggest treatment be withheld in patients with renal deterioration [8]. Although clinical studies have not shown evidence of deterioration in renal function with long-term ibandronate therapy [19], renal function should be monitored according to clinical assessment of the patient. Mandatory monitoring of renal function, however, is not required (Table 1) [11].

**ORAL FORMULATIONS**

Some patients prefer oral treatment because it can be taken as a simple, once-daily dose at home, precluding the need for regular hospital visits. Oral treatment also gives patients more control over their treatment, allowing them to include it in their daily routine. The clinical benefits of self-administration include increased availability of infusion equipment for other patients (i.e., those receiving chemotherapy). Oral bisphosphonate therapy is ideal for patients who have completed i.v. chemotherapy.

Although oral clodronate (Bonefas®, Schering AG, Berlin, http://www.schering.de) has been available for many years, clinical experience indicates that it is less effective than i.v. bisphosphonates [20, 21]. To achieve
therapy concentrations, oral clodronate is administered in large tablets once or twice daily at least 1 hour before food (Table 2). In a study of oral clodronate in patients with metastatic bone pain (n = 55), 11% of the patients discontinued treatment because of difficulty swallowing the capsules [22]. High incidences of adverse gastrointestinal events commonly contribute to noncompliance with oral clodronate. In an update of a 2-year breast cancer study [23, 24], the proportion of patients with adverse gastrointestinal events during the medication period was significantly higher with clodronate (1,600 mg/day) than with placebo (57.1% versus 45.3%, respectively; p < .05), and there was a significantly higher proportion of patients with diarrhea (15.1% versus 6.8%, respectively; p < .05). Monitoring patients and administering medication to treat the side effects increases health care costs and decreases the availability of hospital beds.

Although oral bisphosphonates have traditionally been considered inferior in efficacy to i.v. agents, recent studies show that i.v. and oral ibandronate have similar benefits. Three phase III studies of similar design (one i.v. and two oral trials) have shown that the reduction in the risk for skeletal events in breast cancer patients given a daily, oral, 50-mg dose of ibandronate was comparable with that of 6 mg i.v. ibandronate given every 3–4 weeks [18, 25]. Similar to i.v. ibandronate, the oral formulation significantly reduced and maintained bone pain scores below baseline over 2 years of treatment and improved quality of life [25–28]. In addition, a 12-week, head-to-head, open-label trial of breast cancer patients with bone metastases demonstrated equivalent effects of oral ibandronate (50 mg/day; n = 128) and i.v. zoledronic acid (4 mg infused over 15 minutes every 4 weeks; n = 126) on biochemical markers of bone turnover [29].

### Table 2. Comparison of the characteristics of oral clodronate and oral ibandronate treatments

<table>
<thead>
<tr>
<th>Oral clodronate</th>
<th>Oral ibandronate</th>
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<tbody>
<tr>
<td>Tablet size</td>
<td>400 or 800 mg</td>
</tr>
<tr>
<td>Dosing regimen</td>
<td>1,600 mg/day</td>
</tr>
<tr>
<td></td>
<td>(800 mg/day to</td>
</tr>
<tr>
<td></td>
<td>3,200 mg/day</td>
</tr>
<tr>
<td>Post-dose fasting interval</td>
<td>2 hours</td>
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</table>

In the phase III study of 50 mg oral ibandronate in breast cancer patients, the incidence of mild treatment-related adverse gastrointestinal events (reported by ≥2% of patients in any treatment group), such as abdominal pain, dyspepsia, nausea, and esophagitis, were low (≤7.0%) [26]. Oral ibandronate (50 mg) was also well tolerated in 115 patients who agreed to enter a 2-year extension phase [30]. Of the 7% of adverse events considered possibly or probably related to treatment with ibandronate, the most common were dyspepsia (2.6%), hypocalcemia (2.6%), and esophagitis (1.7%). No treatment-related adverse events led to withdrawal from the study. There were no renal adverse events or laboratory abnormalities of clinical relevance in patients receiving oral ibandronate.

Ibandronate is given once daily in a small tablet (approximately 1 cm in length). In the phase III and open-label extension trials, no patients withdrew because of swallowing difficulties [26, 30]. Patients are required to fast only overnight and for a minimum of 30 minutes after taking the capsules (Table 2).

### Case Histories of Patients Treated with Bisphosphonates

**Patient A**

Patient A is a 64-year-old female with breast cancer and metastatic bone disease. In May 2003, she began zoledronic acid (4 mg) and received monthly infusions for 19 months. In our hospital, the average time taken for the analysis of a patient’s blood sample is 30–40 minutes. After calculating Patient A’s creatinine clearance using the Cockcroft-Gault formula, the medical team adjusted Patient A’s zoledronic acid dose to reflect her actual creatinine clearance. If her renal functioning was worse, the clinician asked about any other potentially nephrotoxic prescription or over-the-counter medications she had taken. Because of the patient’s concerns about her deteriorating renal function, the health care team had to reassure her that the dose change was needed because of the drug and was not due to disease progression. Although zoledronic acid provided symptom relief, patient A commented that waiting in the hospital substantially disrupted her quality of life. Patient A has type II diabetes mellitus and takes nonsteroidal anti-inflammatory drugs (NSAIDs) because of skeletal pain. With higher NSAID doses, the patient suffered from mild renal insufficiency. After reducing the NSAID dose, her renal function normalized. We decided to change the bisphosphonate to ibandronate. The patient has now received 7 doses of i.v. ibandronate in conjunction with her NSAID therapy. The patient’s serum creatinine levels are within normal limits.
**Patient B**

Patient B, a 51-year-old woman with breast cancer, was diagnosed with bone metastases in September 2004. After receiving i.v. ibandronate, patient B was started on oral ibandronate at a dose of 50 mg/day in April 2005. At each monthly hospital visit, a blood sample is taken as part of routine clinical practice. Patient B then receives a prescription for a 3-month supply of oral ibandronate. By using oral ibandronate, there is no need for the health care team to wait for the laboratory results and adjust the patient’s dose according to her creatinine clearance. Furthermore, there are no concerns about concomitant nephrotoxic medications. Oral ibandronate is very well tolerated by this patient; in particular, there have been no gastrointestinal side effects. Patient B prefers at-home self-administration over the prior i.v. infusion in the hospital setting.

**Conclusions**

Renal toxicity is not a class effect of bisphosphonates. Trials and postmarketing experience revealed renal deterioration, renal failure, and dialysis in some patients treated with zoledronic acid (including those treated with the approved 4-mg dose infused over 15 minutes) [1, 2, 4–7]. Ibandronate has a renal safety profile comparable with that of placebo. For these reasons, clinicians must be aware of differences among bisphosphonates and realize how best to maintain renal safety in patients with bone metastases who are being treated with bisphosphonates.

Ibandronate’s favorable renal safety profile provides several key benefits to health care professionals and patients, including no need for renal monitoring before each infusion and no dosing based on renal function in patients with mild-to-moderate renal impairment. Ibandronate also does not increase the toxicity of concomitant prescribed or over-the-counter nephrotoxic drugs. In addition, there are no added renal safety risks and complications, fewer hospital visits for renal monitoring or management of adverse events, and lower risks for discontinuing chemotherapy or bisphosphonate therapy. Studies show that it may be possible to safely reduce the infusion time for 6 mg i.v. ibandronate from 60 minutes to 30 or 15 minutes, reducing the burden of administering bisphosphonates in hospital i.v. therapy units. Confirmatory studies are under way.

Oral bisphosphonate therapy can be more attractive than i.v. administration because the medication is convenient and causes no problems with renal safety factors, which decreases health care costs. Clinical studies indicate that 50 mg oral ibandronate has an efficacy similar to those of i.v. bisphosphonates and is associated with a low incidence of adverse gastrointestinal events.

In i.v. and oral formulations, ibandronate provides physicians and patients with a continuum of bisphosphonate therapy that can be extended from the hospital to home. In choosing the optimal bisphosphonate, clinicians must consider drug benefits, the risks for side effects, and convenience. Although considerations differ according to each patient’s needs, the favorable renal safety profile of ibandronate makes it a useful treatment option.

**Acknowledgments**

I thank Thomson Gardiner-Caldwell US for their editorial assistance.

**Disclosure of Potential Conflicts of Interest**

Dr. von Moos is a consultant for Roche and Schering Plough and has an unrestricted grant from Schering Plough.

**References**


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Patients Previously Transfused or Treated with Epoetin Alfa at Low Baseline Hemoglobin Are at Higher Risk for Subsequent Transfusion: An Integrated Analysis of the Canadian Experience

IAN QUIRT, MICHAEL KOVACS, FÉLIX COUTURE, A. ROBERT TURNER, MICHAEL NOBLE, RONALD BURKES, SEAN DOLAN, RICHARD K. PLANTE, CATHERINE Y. LAU, JOSÉ CHANG

The Oncologist 2006;11:73–82; doi: 10.1634/theoncologist.11-1-73

In Figure 3, RR was incorrectly labeled as “response rate” when it should have been called out as “relative risk.” Here we reprint the figure in its entirety. A corrected figure has been posted on http://www.TheOncologist.com.

Figure 3. Relative risk of subsequent transfusion was calculated as a function of baseline Hb strata relative to baseline Hb strata > 11 g/dl. (A): Relative risk of subsequent transfusion calculated in patients transfused after day 28 of epoetin alfa treatment. Patients initiating epoetin alfa therapy at a baseline Hb <10 g/dL had a RR of 2.65 (95% CI, 1.54–4.56) of receiving subsequent transfusions compared to patients initiating therapy earlier (Hb 10–11 g/dL). (B): Relative risk of subsequent transfusion calculated in patients transfused from baseline to end of study. Patients initiating epoetin alfa therapy at a baseline Hb <10 g/dL had a RR of 2.29 (95% CI, 1.54–3.42) of receiving subsequent transfusions compared to patients initiating therapy earlier (Hb 10–11 g/dL). Abbreviations: CI, confidence interval; Hb, hemoglobin; RR, Relative risk.

Figure 4 was incorrectly labeled. The upper line should be labeled “Baseline pre-transfusion” rather than “No baseline pretransfusion.” Here we reprint the figure in its entirety. A corrected figure has been posted on http://www.TheOncologist.com.

Figure 4. Number of units of blood received by all patients and the subset of pretransfused patients during epoetin alfa treatment from day 1 to end of study as a linear function of baseline hemoglobin level.

It is regrettable that Fernando Camacho, Ph.D., statistician, was not included as a co-author. His contributions and input in establishing the per-patient database and carrying out the statistical analyses were, unfortunately and inadvertently, not acknowledged in the original manuscript. Dr. Fernando Camacho should correctly have been listed as a co-author on the manuscript published in The Oncologist. The online version has been corrected in departure from print.
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Table 2 erroneously included a row labeled “Renal toxicity.” Here we reprint the corrected table in its entirety. A corrected table has been posted on http://www.TheOncologist.com.

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