Renal Safety of Ibandronate

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Abstract
Despite their efficacy in treating complications associated with metastatic bone disease, there are concerns about the potential nephrotoxicity of certain i.v. bisphosphonates for the long-term management of cancer patients. Clinical data suggest, however, that i.v. ibandronate (Bondronat®; F. Hoffman-La Roche Ltd., Basel, Switzerland, http://www.roche.com), unlike other bisphosphonates, has a renal safety profile comparable with that of placebo. In a 2-year, phase III study of patients with breast cancer metastatic to bone, the incidence of adverse renal events in patients treated with 6 mg i.v. ibandronate was low and comparable with that of placebo (4% versus 4.5% with placebo). Two-year assessments of time to serum creatinine increase also demonstrated renal safety comparable with that of placebo (patients with creatinine increase: 6% versus 12% with placebo). Long-term (4-year) renal safety of ibandronate was demonstrated in a 2-year extension of the trial. Phase II, open-label studies show that intensive ibandronate dosing does not compromise renal safety in patients with metastatic bone pain from a variety of tumor types. In addition, i.v. ibandronate is well tolerated, with no evidence of renal toxicity in multiple myeloma and urologic cancer patients with existing renal impairment. The potential nephrotoxicity of some bisphosphonates has prompted additional renal safety precautions in product labeling for these agents. The precautions are not, however, contained in the label for ibandronate, which may thus simplify patient management. The Oncologist 2005;10(suppl 1):14–18

Introduction
The introduction of newer bisphosphonates, such as zoledronic acid (Zometa®; Novartis Pharmaceuticals Corporation, East Hanover, NJ, http://www.pharma.us.novartis.com) and ibandronate (Bondronat®; F. Hoffmann-La Roche Ltd., Basel, Switzerland, http://www.roche.com), has greatly improved the management of advanced cancer patients with bone metastases. Because of the high morbidity associated with metastatic bone disease, however, clinicians must balance the benefits of the therapies with the potential risks. Preclinical data have shown that bisphosphonate-related renal toxicity is not a class effect and that renal safety profiles vary among drugs [1–3]. The differences are reflected in clinical data that show that zoledronic acid is associated with renal impairment [4–7]. Patients at greatest risk for renal deterioration include those with advancing or progressive cancer, those receiving other potentially nephrotoxic drugs (e.g., chemotherapies), and those with coexisting conditions such as chronic
renal failure, hypertension, or diabetes [7]. There also have been occasional reports of acute renal failure with zoledronic acid that resulted in drug discontinuation, the need for renal dialysis, and death in some patients [7]. The increasing evidence that zoledronic acid can cause renal toxicity in their patients concerns physicians and may hinder the clinical utility of the agent. In contrast, data suggest that ibandronate is an effective treatment for clinical complications of bone metastases with renal safety comparable with that of placebo [8–10].

This paper reviews the renal safety data for i.v. ibandronate when used as standard or intensive dosing in patients with bone metastases from a variety of tumor types, either with or without renal impairment.

**CLINICAL TRIALS OF IV. IBANDRONATE**

**Two-Year Phase III Trial in Patients with Metastatic Bone Disease from Breast Cancer**

The efficacy and safety of 6 mg i.v. ibandronate infused over 1–2 hours every 3–4 weeks (n = 154) compared with placebo (n = 158) were investigated in a 2-year, randomized, double-blind, placebo-controlled phase III study of patients with breast cancer and bone metastases [8]. In addition to recording adverse renal events, a post hoc Kaplan-Meier analysis, using the same criteria to measure renal function deterioration as in the phase III zoledronic acid trials, was used to assess time to renal function deterioration with ibandronate. Deteriorated renal function was defined as an increase in serum creatinine of 0.5 mg/dl from baseline, if baseline serum creatinine was <1.4 mg/dl, and 1.0 mg/dl from baseline, if baseline serum creatinine was >1.4 mg/dl, or twice the baseline value [11].

Results of that study show that there was no evidence of renal toxicity associated with i.v. ibandronate treatment. The incidence of adverse renal events was low and did not differ between the placebo and ibandronate groups (Table 1). None of the adverse renal events with 6 mg i.v. ibandronate were considered serious or caused patients to withdraw from the study [11]. The proportion of patients with increased serum creatinine levels (300 mM) was low and similar between treatment groups (Table 1) [11]. The Kaplan-Meier analysis showed that after 12 and 24 treatment months, the proportion of patients with defined increases in serum creatinine was lower in the 6 mg i.v. ibandronate group than in the placebo group (Table 1). Although the separation between ibandronate and placebo remained consistent throughout the study (shown in Figure 1 as the proportion of patients without defined increases in serum creatinine), the difference did not reach statistical significance (p = .22) [11].

**Table 1. Renal safety data for 6 mg i.v. ibandronate in a 2-year phase III clinical trial of patients with breast cancer and metastatic bone disease [8, 11].**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 158)</th>
<th>Ibandronate 6 mg (n = 154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of renal adverse events (%) [8]</td>
<td>4.5</td>
<td>4.0</td>
</tr>
<tr>
<td>Patients with increased creatinine (%) [8]</td>
<td>1.3</td>
<td>2.6</td>
</tr>
<tr>
<td>Patients with defined increases in serum creatinine (Kaplan-Meier analysis) [11]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients at 1 year (%)</td>
<td>4.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Patients at 2 years (%)</td>
<td>12.0</td>
<td>6.0*</td>
</tr>
</tbody>
</table>

* p = .22 versus placebo.

**Figure 1.** Proportion of metastatic breast cancer patients without renal function deterioration over 2 years of treatment with 6 mg i.v. ibandronate or placebo [11].

**Long-Term Safety Follow-Up**

The long-term (4-year) safety of the standard i.v. ibandronate dosing regimen was assessed in a 2-year, noncontrolled, follow-up study to the 2-year pivotal phase III trial [12]. In the extension study, 62 patients with metastatic bone disease from breast cancer were allocated to follow-up treatment; 16 had previously received placebo and 46 had previously received 6 mg i.v. ibandronate. During the 2-year follow-up, there were no clinically relevant adverse renal events in the patients or alterations in laboratory parameters that indicated renal toxicity associated with i.v. ibandronate.

**RENAL SAFETY OF HIGH-DOSE IBANDRONATE FOR METASTATIC BONE PAIN**

In an open-label pilot study of 18 patients with moderate-to-severe, opioid-resistant bone pain from metastatic breast...
cancer \((n = 10)\) or other tumor types \((n = 8)\), 4 mg i.v. ibandronate was infused over 2 hours on four consecutive days (with a 16-mg total dose) [13]. Results show that ibandronate significantly reduced bone-pain scores within 7 days \((p < .001)\). In addition, the significant reductions from baseline in bone-pain scores with ibandronate were maintained at day 21 \((p < .0001)\) and day 42 \((p < .05)\). Despite the high-dose schedule, the renal safety of ibandronate was uncompromised. No adverse renal events were noted, and there were no significant treatment-related effects on renal function measures such as urea or creatinine, or white or red blood cell counts.

**Renal Safety of Loading-Dose Ibandronate for Metastatic Bone Pain**

The absence of drug accumulation with repeated doses of ibandronate in preclinical studies [1, 2] supports the use of loading doses to treat severe metastatic bone pain.

Two, open-label, nonrandomized, prospective phase II trials investigated the effect of i.v. loading-dose ibandronate on metastatic bone pain in 45 patients with hormone-refractory prostate cancer and 55 patients with metastatic urologic cancer [14–16]. In both studies, patients with severe metastatic bone pain were treated with 6 mg i.v. ibandronate infused over 1 hour on three consecutive days (18-mg total loading dose), followed by a single 6-mg ibandronate infusion every 4 weeks until the end of the studies.

The mean visual analogue scores for metastatic bone pain were significantly lower than baseline scores on day 3 \((p < .001\) for both) and remained below baseline throughout the remainder of the trials. Despite the use of i.v. loading-dose ibandronate in the studies, there was no renal toxicity.

**Renal Safety of Ibandronate in Patients with Existing Renal Impairment**

Because some bisphosphonates are associated with an increased risk of renal toxicity in patients with normal renal function, their use in patients with renal insufficiency warrants greater caution. Preclinical and clinical studies demonstrate that ibandronate, however, has a favorable renal safety profile in these circumstances. Ibandronate prevented the increase in erosion depth and bone turnover in a rat model of renal insufficiency without further compromising renal safety, compared with vehicle-treated rats [17]. Investigations such as that one provided the rationale for using i.v. ibandronate in patients with existing renal impairment. The renal safety of ibandronate has been assessed in three clinical studies, including two in multiple myeloma patients [18, 19] and one in urologic cancer patients [15, 20].

**Multiple Myeloma Patients**

Renal failure occurs frequently in patients with multiple myeloma, affecting up to 20% of patients at the onset and up to 50% of patients during the course of their disease [21]. Selecting the most appropriate bisphosphonate is therefore an important consideration for multiple myeloma patients.

In an open-label study, the renal safety of 6 mg i.v. ibandronate infused over 30 minutes was assessed in patients with multiple myeloma \((n = 21,\) creatinine clearance 8–120 ml/min) [18]. Four of the patients had normal renal function, and 17 had varying degrees of pre-existing renal insufficiency at baseline. Results show that serum creatinine (Fig. 2) and markers of tubular damage, such as \(\alpha\)-glutathione-S-transferase (Fig. 3) and \(\beta\)-N-acetylglucosaminidase, did not change significantly within 72 hours of ibandronate infusion.
In another study, the renal safety of ibandronate was investigated in seven patients with multiple myeloma and pre-existing renal failure caused by hypercalcemia or nephrocalcinosis [19]. Ibandronate, 6 mg, was infused over 30 minutes prior to administering cytoreductive therapy except in one patient whose dose was reduced to 2 mg to accommodate concurrent hemodialysis and in two patients who received a subsequent dose of ibandronate, 4 mg or 6 mg, every 3–4 weeks. Renal function was monitored by measuring serum calcium levels and diuresis. Kidney biopsies also were performed in four patients. Treatment with ibandronate caused elevated calcium levels to decrease to within a normal range and returned renal function to normal or almost normal levels in all patients. Patients who received more than one dose of ibandronate also experienced improved renal function, and none of the patients required hemodialysis. Ibandronate treatment was well tolerated, and no treatment-related adverse events were reported.

Urologic Cancer Patients
Renal safety with bisphosphonates is particularly important for patients with metastatic bone disease from urologic malignancies because 10%–15% of the patients already have renal insufficiency.

In the study of urologic cancer patients, renal function assessed by measuring serum creatinine levels was constant over 28 days following i.v. loading-dose ibandronate (6 mg infused over 1 hour on three consecutive days) in patients with compensated renal insufficiency at baseline (Fig. 4) [20]. No adverse renal events were reported.

**Figure 4.** Renal function in urological cancer patients with compensated renal insufficiency following treatment with loading-dose ibandronate (6 mg infused over 1 hour on 3 consecutive days) [15, 20].

**CONCLUSIONS**
Bisphosphonates are the standard of care for treating skeletal complications caused by metastatic bone disease. Despite these benefits, some drugs in the bisphosphate class are associated with renal toxicity even at standard clinical doses. Data indicate that ibandronate, however, has a favorable renal safety profile, even when administered as a loading dose.

At standard doses, the renal safety of 6 mg i.v. ibandronate was comparable with that of placebo over 2 years in a phase III clinical trial of breast cancer patients with metastatic bone disease. In addition, a Kaplan-Meier analysis showed no evidence for drug-related accumulation of renal toxicity in the patients, and renal safety was maintained for up to 4 years. There also were no renal safety issues with i.v. loading doses of ibandronate up to threefold higher than the approved dose. Because of the risk for renal toxicity with loading-dose zoledronic acid, it is unlikely that bisphosphonates will be used to relieve metastatic bone pain.

Emerging evidence suggests that ibandronate, unlike other bisphosphonates, is well tolerated, with no evidence of renal toxicity in multiple myeloma and urologic cancer patients who have pre-existing renal deterioration. The studies in metastatic urologic cancer patients with renal insufficiency used intensive loading doses of ibandronate, suggesting the approach is also feasible in this high-risk group.

Selecting bisphosphonate therapy for patients with metastatic bone disease is best determined by benefits of long-term renal safety and clinical efficacy. Clinicians should consider the risk for nephrotoxicity in caring for their cancer patients. For example, the product label for zoledronic acid [22, 23] contains renal safety precautions that are not included in the label for i.v. ibandronate [24]. Monthly monitoring of renal function is recommended prior to each dose of zoledronic acid [25], and dose adjustments may be necessary to minimize the incidence of adverse renal events in patients with mild-to-moderate renal impairment. Approved product labeling for ibandronate in the European Union, however, recommends monitoring renal function according to clinical assessment of each patient at the discretion of the physician. This recommendation is necessary because of the patient’s underlying disease, rather than because ibandronate is used. In addition, zoledronic acid is contraindicated in patients with severe renal impairment, whereas ibandronate can be used with a dose adjustment to compensate for renal excretion in patients with a creatinine clearance of <30 ml/min [26]. Unlike zoledronic acid, there also are no precautions related to the concomitant use of ibandronate with nephrotoxic
medications such as chemotherapeutic agents.

Increased use of valuable nursing time and health care resources and patient inconvenience are associated with corrective management of deteriorating renal function with certain i.v. bisphosphonates. By promoting effective care without increasing the risk for renal toxicity, the favorable renal safety profile of ibandronate may simplify patient management.

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**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

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**REFERENCES**


