Ibandronate: Its Role in Metastatic Breast Cancer

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Abstract

Bisphosphonates are the most effective agents for treating and/or preventing complications of bone metastases and are the standard of care in this setting. Currently, four bisphosphonates are available for metastatic bone disease (MBD): clodronate, pamidronate, zoledronic acid, and ibandronate. Although all four of these bisphosphonates have been shown to reduce the incidence of skeletal-related events in patients with bone metastases, there are substantial differences among these agents in their potency, dose and route of administration, and side effects. Ibandronate and zoledronic acid, the two newer aminobisphosphonates, appear to have similar biochemical efficacies when phase III trial data are compared. Both agents were equally effective in reducing markers of bone resorption in the only prospective comparative trial carried out to date, but no data on relative clinical efficacy are available from head-to-head comparisons. Both the oral and i.v. formulations of ibandronate have also shown long-term efficacy in managing metastatic bone pain (MBP), but the onset of action of standard bisphosphonate treatment is not sufficient when rapid relief of pain is required. Because of its favorable renal safety profile, i.v. ibandronate can be administered daily for 3 days, as a so-called “loading dose.” This dosing regimen has allowed rapid and effective relief of MBP without the unwanted side effects associated with opioids and other analgesics. Ibandronate is thus an effective, flexible, and well-tolerated bisphosphonate that can meet the varying requirements of patients with MBD. The Oncologist 2006;11(suppl 1):27–33

Introduction

Bone metastasis is a significant debilitating feature of many advanced cancers, particularly breast and prostate cancer, where up to 75% of patients will experience bone metastasis [1]. Although the presence of bone metastases generally indicates that the cancer cannot be cured, many patients may live for several years: in patients with advanced breast cancer, the median survival time after the diagnosis of bone metastases is approximately 2.5 years [2, 3]. The morbidity associated with metastatic bone disease (MBD), including pain and fracture risk, means that effective treatment is essential to allow patients to live as normally as possible.

Bisphosphonates are the most effective agents for preventing complications of bone metastases and are the standard of care in this setting. Currently, four bisphosphonates are available for MBD: clodronate (Bonefos®, Schering AG, Berlin; and Ostac®, Loron®, F. Hoffmann-La Roche Ltd, Basel, Switzerland), pamidronate (Aredia®, Novartis Pharmaceuticals Corporation, East Hanover, NJ), zoledronic acid (Zometa®; Novartis Pharmaceuticals Corporation), and ibandronate (Bondronat®, F. Hoffmann-La Roche Ltd). All four have been shown to be effective against skeletal complications, but their activities are by no means identical, and there may be substantial differences among the bisphosphonates in their biology as well as mode of administration, convenience, and tolerability. It is therefore appropriate to consider what patients require from bisphosphonate treatment and how different bisphosphonates may meet these requirements.
The primary requirement for any bisphosphonate is that it should be effective in treating and preventing skeletal complications because this is the principal reason for administration. Assuming this essential efficacy criterion is met, however, the ability to alleviate bone pain in a rapid and sustained fashion is also an important consideration. Bone pain is experienced by 60%–80% of patients and has a major impact on quality of life [4]. Other important issues in bisphosphonate therapy include effects on mobility and function, allowing patients to resume or continue their normal lives, and differences in tolerability and administration schedules, which can have significant impact on patient quality of life in terms of compliance and convenience. This review considers the efficacy and tolerability of i.v. and oral ibandronate in these contexts.

**The Efficacy of Ibandronate in Reducing Skeletal-Related Events**

The efficacy of ibandronate in reducing skeletal complications of MBD has been demonstrated in three randomized, placebo-controlled phase III trials in patients with breast cancer and bone metastases. i.v. ibandronate was assessed in one trial, and oral ibandronate was assessed in the other two. In each trial, ibandronate reduced the risk of new bone complications by approximately 40%.

In the trial of i.v.-administered ibandronate, 312 patients with bone metastases resulting from breast cancer were randomized to receive either ibandronate (6 mg) or placebo every 3–4 weeks for up to 2 years. New bone complications were defined as any of the following: vertebral fractures, pathological nonvertebral fractures, radiotherapy, or surgery for bone pain or impending fractures. The primary efficacy parameter was the skeletal morbidity period rate (SMPR), which was calculated as the number of 12-week periods in which new bone complications occurred divided by the total observation time (in 12-week periods). The SMPR allows for the fact that bone events occurring close together are frequently related and thus avoids multiple counting of such related events. Patients in the 6-mg ibandronate group had a significantly lower SMPR than patients in the placebo group (1.19 vs. 1.48; \( p = .004 \)) [5]. The mean number of new bone events per patient was also significantly lower (2.65 vs. 3.64; \( p = .032 \)), and the time to first new bone event was significantly longer in the ibandronate group (50.6 weeks vs. 33.1 weeks; \( p = .018 \)). A multivariate Poisson regression analysis showed that the risk for a new bone event was 40% lower for patients in the 6-mg ibandronate group [6].

For oral ibandronate, the two identical trials were analyzed together, as specified and preplanned in the trial protocols [7]. In total, 564 patients were randomized to receive oral ibandronate (50 mg) or placebo daily for up to 2 years. The primary efficacy parameter was the SMPR. Patients in the 50-mg ibandronate group had a significantly lower SMPR than those in the placebo group (0.95 vs. 1.18; \( p = .004 \)). The mean number of events per patient was also significantly lower (1.15 vs. 1.85; \( p = .008 \)). A multivariate Poisson regression analysis showed that the risk for a new bone event was 38% lower for patients in the 50-mg ibandronate group.

These three trials established that both i.v. and oral ibandronate were effective in reducing skeletal-related events (SREs) in patients with metastatic breast cancer, and both formulations were approved for this indication in the European Union in 2003. Currently, there are no randomized prospective data comparing the efficacy of ibandronate in reducing skeletal events with the efficacies of other bisphosphonates used for the treatment of MBD. Such trials are currently underway (see below) but will take some years to complete. However, a comparison of oral ibandronate and i.v. zoledronic acid has been conducted using markers of bone turnover as a surrogate measure of bisphosphonate SRE efficacy [8]. Serum concentrations of bone turnover markers, such as crosslinked collagen C-terminal telopeptide (CTX), reflect the rate of bone resorption, and this has been shown to be predictive for the incidence of SREs [9–11]. In an open-label, 12-week study in patients with breast cancer and bone metastases, serum CTX was decreased by 76% in patients treated with ibandronate and by 73% in patients treated with zoledronic acid (Fig. 1) [8]. Similar results were obtained for other bone markers, such as bone alkaline phosphatase, amino-terminal procollagen propeptides, and osteocalcin, indicating that ibandronate and zoledronic acid have comparable effects on bone turnover. Subgroup analyses also demonstrated that the effects of the two bisphosphonates were similar in patients with high,
medium, or low levels of bone markers at baseline [8]. This is the first trial to compare the newer bisphosphonates ibandronate and zoledronic acid and suggests comparable bone marker efficacy.

Moreover, available data suggest that ibandronate and zoledronic acid may also be comparable in terms of SRE efficacy. In a randomized, placebo-controlled, phase III trial in 228 patients with breast cancer and bone metastases, zoledronic acid reduced the frequency of SREs [12]. The skeletal event rate was calculated as the number of skeletal events divided by time on study, and the primary efficacy end point in that study was the SRE ratio between treatment groups, that is, the SRE rate in the zoledronic acid group divided by the SRE rate in the placebo group. The SRE ratio (adjusted for patients with prior fracture) was 0.61, indicating that zoledronic acid reduced the frequency of SREs by 39%. According to Andersen-Gill multiple-event analysis, zoledronic acid reduced the overall risk of experiencing an SRE by 41%. Tripathy and Budde [13] reported similar risk reductions for ibandronate when the data from the pivotal trials were reanalyzed using the Andersen-Gill method. i.v. ibandronate was associated with a risk reduction of 29% ($p = .0183$), while oral ibandronate reduced the risk for an event by 38% ($p < .0001$). Such cross-trial comparisons naturally need to be treated with caution because patient populations, end points, and protocols may differ widely between trials. Nevertheless, in the absence of prospective, randomized data for prevention of SREs, current evidence and data using markers of bone turnover as a surrogate for clinical efficacy suggest that zoledronic acid and ibandronate are likely to have comparable efficacy for preventing SREs.

Two large, randomized, phase III trials comparing oral ibandronate with i.v. zoledronic acid are currently under way, one in the U.S. and one in the United Kingdom. The U.S. trial, conducted by the Southwest Oncology Group (SWOG; trial S0308), is randomizing 488 patients with breast cancer and bone metastases to oral ibandronate (50 mg/day) or zoledronic acid (4 mg) by i.v. infusion every 4 weeks, both for 18 months [14]. The primary end point is the proportion of patients suffering new SREs, with secondary end points including time to first SRE, quality of life assessments, overall survival, and safety. The UK National Cancer Research Network trial is known as ZICE (zoledronic acid vs. oral ibandronate comparative evaluation). A total of 1,400 patients will be randomized to 50-mg oral ibandronate or 4-mg i.v. zoledronic acid for 2 years [15]. The primary end point of the ZICE trial is the frequency and timing of SREs during the 2-year treatment period. Secondary end points include the proportion of patients experiencing new SREs, time to first SRE, quality of life, resource utilization, and safety. Both of these trials are designed to determine noninferiority, that is, if ibandronate has at least equal efficacy to zoledronic acid in reducing SREs. If this can be shown, physicians will be able to prescribe the most appropriate bisphosphonate based on other factors such as safety, convenience, and quality of life without any concern that the choice of an oral agent could compromise efficacy.

**Relief of Metastatic Bone Pain**

The phase III trials of i.v. and oral ibandronate included assessments of bone pain using patient-reported pain scores. In both studies, patients in the ibandronate arm experienced significantly lowered pain scores throughout the 2 years of treatment (Fig. 2) [16, 17]. The shape of the curves were remarkably similar for the oral and i.v. formulations, with maximum pain relief achieved at 12 weeks then maintained below baseline throughout the study period in each case. This was also reflected in quality of life assessments, with similar improvements in quality of life (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire).

![Figure 2. Long-term relief of metastatic bone pain over 2 years with i.v (A) [16] or oral (B) [17] ibandronate.](http://theoncologist.alphamedpress.org/)

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Life Questionnaire C30) observed in both trials. Oral and i.v. ibandronate thus appear equally effective in achieving long-term relief of metastatic bone pain (MBP) and improving quality of life. However, because maximum pain relief is not achieved until 12 weeks, acute, moderate-to-severe bone pain may not be alleviated in a timely manner with standard ibandronate therapy, or indeed with other bisphosphonates. Rapid pain relief with intensive dosing schedules of ibandronate has been investigated in three phase II studies. Mancini et al. [18] showed that, in patients with opioid-resistant bone pain, intensive ibandronate therapy (4 mg for 4 consecutive days, total 16 mg) provided significant analgesic effects and was well tolerated. Two studies in patients with urologic cancer or prostate cancer have examined the effects of intensive dosing followed by standard maintenance therapy [19, 20]. In those trials, i.v. ibandronate was administered as a loading dose (6 mg on 3 consecutive days) followed by 6 mg every 4 weeks for 20 weeks. In the urologic cancer study, >80% of patients had at least a three-point reduction in bone pain assessed by visual analogue scale, with maximum pain relief achieved by day 3 [20]. In addition, 25% of patients became totally pain free. Functional capacity increased so markedly that patients who were previously bedridden reported increased mobility within 1 week of starting their bisphosphonate. Similar results were observed in the prostate cancer trial [19].

Loading-dose ibandronate is now being evaluated in phase III randomized trials in patients with moderate-to-severe bone pain. Because oral and i.v. ibandronate are equally effective in long-term relief of MBP, two trials are being conducted (Bon-O-Pain/BO 18039 and Bon-I-Pain/BO 18040) [21] using either oral or i.v. maintenance therapy after the initial loading dose [22]. The comparator arm in both trials is zoledronic acid every 4 weeks (Fig. 3). It is not possible to give zoledronic acid as a loading dose on consecutive days because of safety considerations, in particular, renal toxicity (see below). The trials are blinded, and therefore treatment with placebo infusions or tablets will be given in parallel where appropriate to maintain blinding.

**SAFETY OF IBANDRONATE AND OTHER BISPHOSPHONATES**

Because bisphosphonate therapy for MBD is generally palliative in patients with bone metastases, tolerability is a very important consideration. Adverse events (AEs) vary among different bisphosphonates and between different routes of administration. The main AEs associated with bisphosphonate therapy are acute-phase reactions, gastrointestinal toxicity, renal toxicity, and a rare but severe effect associated with some bisphosphonates, osteonecrosis of the jaw (ONJ).

**Acute-Phase Reactions**

Acute-phase reactions cover a spectrum of flu-like symptoms, joint pain, pyrexia, and other reactions that may occur following an i.v. infusion. These reactions are generally transient, lasting up to 1–2 days, and are more commonly associated with the first infusion. Two trials have assessed the safety of ibandronate in comparison with zoledronic acid. In the first trial, 77 patients with metastatic breast cancer or multiple myeloma were treated with i.v. ibandronate (6 mg on day 1) followed by oral ibandronate (50 mg daily from day 2), or i.v. zoledronic acid (4 mg every 3–4 weeks) [22]. The second trial compared oral ibandronate (50 mg daily) with i.v. zoledronic acid (4 mg every 3–4 weeks) in 274 patients with metastatic breast cancer [8]. In both studies, the overall incidence of AEs was lower for patients receiving ibandronate, particularly the incidence of pyrexia and flu-like symptoms on days 1–3 (Fig. 4) [8, 23]. As expected, fewer patients on oral treatment experienced pyrexia and flu-like symptoms than patients on zoledronic acid (2% vs. 27%) [8]. However, only 13% of patients in the i.v. ibandronate arm experienced symptoms, compared with 26% in the zoledronic acid arm [23].

**Gastrointestinal Effects**

Gastrointestinal AEs have been associated with oral bisphosphonate treatment, particularly clodronate, because of the large tablet size and dosing regimen (up to 2,400 mg/day).
daily in two doses) [24]. This has led to compliance difficulties in patients on long-term therapy. However, in phase III trials of oral ibandronate, the incidence of gastrointestinal AEs was reported as very low [7]. Patients in these studies were also permitted to continue receiving oral ibandronate for a further 2 years after the 2-year study period. Follow-up of these patients revealed a similar AE profile to that of the main study, and there were no withdrawals resulting from AEs in the extension period [25], indicating that gastrointestinal and other AEs remained low when oral ibandronate was administered for up to 4 years.

**ONJ**

ONJ is a relatively recently described AE involving exposure of the bone of the maxilla and spontaneous loss of teeth, primarily after long-term exposure to bisphosphonates [26, 27]. Current data suggest that ONJ may occur more frequently in patients treated long term with zoledronic acid than with pamidronate [28, 29]. The pathophysiology of ONJ is not yet fully understood, but patients on long-term bisphosphonate therapy should be monitored for the condition. A dental examination should be considered prior to treatment, and patients should avoid elective jaw surgery. There have been 18 reports of ONJ in the 720,000 patients treated with ibandronate since 1996, and the majority of these patients had also been treated with another bisphosphonate [30]. Thus ONJ appears to be an infrequent AE with ibandronate therapy but, because of the relatively recent identification of the condition, the true frequency has not yet been established.

**Renal Safety**

The i.v. bisphosphonates pamidronate and zoledronic acid have been associated with instances of acute and chronic nephrotoxicity [31–36]. Renal damage is associated with high doses and short infusion times, particularly in the case of zoledronic acid, where an 8 mg dose evaluated in phase III trials was discontinued because of the degree of renal toxicity [37–39]. Labeling for zoledronic acid now prohibits the use of doses higher than 4 mg, and serum creatinine must be measured before starting treatment, with dose reductions for those with evidence of renal impairment at baseline [40, 41].

Renal toxicity may not be a class effect of i.v. bisphosphonates. In phase III trials and later follow-up, there were no differences in renal toxicity between the ibandronate (administered via 60-minute infusions) and placebo groups. Patients treated with i.v. ibandronate experienced renal toxicity only to the same degree as those given placebo [22, 42]. In a study in 29 elderly patients with multiple myeloma, 25 of whom had renal impairment at baseline, i.v. ibandronate treatment did not result in significant changes in serum creatinine or other markers of renal damage [43]. The lack of renal toxicity associated with i.v. ibandronate means that, in contrast to zoledronic acid, the recommended 6-mg dose does not need to be adjusted for patients with renal impairment. Even when administered as a loading dose, no impairment of renal function was reported with ibandronate [20]. Based on its excellent renal safety profile, a rapid (15-minute) infusion of ibandronate is currently being evaluated. The results are expected toward the end of 2006.

**LOADING-DOSE Ibandronate: A Case History**

The use of loading-dose ibandronate for relief of MBP features in the following case history, which provides an example of how loading-dose ibandronate may fit into strategies for pain relief.

The patient was a female, 63-year-old, retired swimming instructor with breast cancer and symptomatic bone metastases in the pelvis and femora. Previously a very fit and independent woman, her MBP was preventing her from leading a normal life. Her average pain score at rest was only 1/10, but on movement it rose to 8/10. On response to Brief Pain Inventory questionnaires, she reported pain as completely interfering with general activity, walking ability, normal work, and enjoyment of life. The use of opioids for pain relief was itself causing problems because these drugs were making her unacceptably sedated, and she had stopped using oral morphine for breakthrough pain. The patient was given loading-dose ibandronate (3 × 6 mg on days 1–3). At day 3, ibandronate therapy was associated with a meaningful impact on her quality of life, and the patient was able to resume normal activities of daily living (Table 1).
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occurring exacerbations in pain, pain on movement, and breakthrough pain. Large-scale phase III trials of loading-dose ibandronate are now underway to determine the optimal use of this strategy in patients with moderate-to-severe bone pain.

**Discussion**

Bisphosphonates are the standard treatment for patients with MBD, and four bisphosphonates—pamidronate, clodronate, zoledronic acid, and ibandronate—are currently available for this indication. Although all four of these bisphosphonates have been shown to reduce the incidence of SREs in patients with bone metastases, there are substantial differences among these agents in their potency, dose and route of administration, and side effects.

**Table 1.** Patient case history: Brief Pain Inventory responses before and after loading-dose ibandronate

<table>
<thead>
<tr>
<th>Question</th>
<th>Before loading dose</th>
<th>After loading dose (day 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worst pain in the past 24 hours</td>
<td>8/10</td>
<td>2/10</td>
</tr>
<tr>
<td>% pain relief in past 24 hours</td>
<td>40%</td>
<td>80%</td>
</tr>
<tr>
<td>In the past 24 hours, has pain interfered with? (0 = does not interfere, 10 = completely interferes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General activity</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Mood</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Walking ability</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Normal work</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Relations with other people</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Sleep</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Enjoyment of life</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

Ibandronate and zoledronic acid, the two newer amino­bisphosphonates, appear to have similar efficacies when phase III trial data are compared. Both agents were equally effective in reducing markers of bone resorption in the only prospective comparative trial carried out to date. The results of ongoing, randomized, phase III comparisons are required before firm conclusions can be drawn on their relative efficacy in reducing SREs. The two bisphosphonates do differ markedly in other aspects, notably, the availability of both oral and i.v. ibandronate formulations that have equal efficacy and ibandronate’s favorable safety profile. Ibandronate has also shown long-term efficacy in managing MBP, but the onset of action of standard bisphosphonate treatment is not sufficient when rapid relief of pain is required. Because of its renal safety profile, i.v. ibandronate can be administered as a loading dose. This dosing regimen has allowed rapid and effective relief of MBP without the unwanted side effects associated with opioids and other analgesics. Ibandronate is thus an effective, flexible, and well-tolerated bisphosphonate that can meet the varying requirements of patients with MBD.

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**Disclosure of Potential Conflicts of Interest**

D. C. has acted as a consultant for Roche and Novartis. I. D. has acted as a consultant for Roche and Schering and has received support from Roche, Novartis, Schering, AstraZeneca, Amgen, and Medac. M. F. has acted as a consultant for Roche.

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