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# Ibandronate: An effective treatment for metastatic bone pain

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ABSTRACT

Increasing evidence suggests that ibandronate, a single-nitrogen, non-cyclic bisphosphonate, provides relief of metastatic bone pain (MBP). In phase III trials, both intravenous and oral formulations of ibandronate significantly reduced MBP below baseline for up to 2 years, with concurrent improvements in patient functioning and quality of life compared with placebo. Phase II studies in patients with severe or opioid-resistant MBP suggest that loading-dose ibandronate (intravenous ibandronate 6 mg administered daily for 3 consecutive days) can provide rapid and substantial pain relief within a few days. These findings have been confirmed in clinical pilot studies. Ibandronate is the only intravenous bisphosphonate with a renal safety profile that allows loading-dose treatment. The efficacy of ibandronate in MBP should be considered when choosing a bisphosphonate treatment for metastatic bone disease.



## 1. Introduction

A high proportion of patients with advanced cancer and bone metastases will experience metastatic bone pain (MBP) as a result.[1] MBP has a substantial impact on patients' quality of life, mobility, and functional capacity. Palliative treatment is therefore an essential component of metastatic bone disease management. A number of different modalities are available for MBP and patients are typically managed with a multidisciplinary approach.[2] However, in many patients, current therapies do not adequately control pain and therapies can be associated with significant adverse events that impact on quality of life. The use of high-dose opioids is associated with a number of side effects, notably constipation and somnolence.[3] Radiotherapy or surgery can provide localized relief of bone pain to the affected area, although localized strategies are ineffective for patients with multiple metastases and pain reductions following radiotherapy may take several weeks to achieve.[4] Treatment advances for MBP are therefore still required.

Bisphosphonates are a standard of care for treating metastatic bone disease. Four bisphosphonates are available in Europe in the oncology setting: oral clodronate, intravenous pamidronate, intravenous zoledronic acid, and ibandronate, which is available in both oral and intravenous formulations. These have all been shown to reduce the incidence of new skeletal complications in patients with advanced cancer and bone metastases.[5–12] The ability of bisphosphonates to reduce bone pain has also been recognized.[1,2] The efficacy of intravenous and oral ibandronate for MBP relief has been assessed in detail.

## 2. Long-term pain relief with intravenous or oral ibandronate: phase III studies

MBP relief with intravenous or oral ibandronate was evaluated in three large, phase III, placebo-controlled, 2-year trials in patients with metastatic breast cancer and bone metastases. The primary endpoint of the trials demonstrated the efficacy of intravenous ibandronate 6 mg every 3–4 weeks or oral ibandronate 50 mg daily for significantly reducing the incidence of

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skeletal complications compared with placebo.[11,12] Bone pain scores were assessed every 4 weeks using a 5-point scale. Patients receiving either intravenous or oral ibandronate had significant decreases in pain scores below baseline ($P \leqslant 0.001$) that were maximal at 12 weeks and maintained throughout the 2-year study period (Fig. 1).[12–14] In contrast, placebo-treated patients had bone pain scores higher than baseline at study end. The similar effects observed in the trials suggest that with ibandronate, both intravenous and oral routes of administration have comparable efficacy in pain relief. Ibandronate is the only bisphosphonate to demonstrate relief of MBP below baseline for up to 2 years.

MBP relief with intravenous and oral ibandronate in phase III trials was accompanied by improvements in quality of life and patient functioning compared with placebo.[13,14] Quality of life was assessed using the 100-point European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). As expected in patients with advanced cancer, overall quality of life deteriorated from baseline for all treatment groups in the trials. However, with both intravenous and oral ibandronate, the decrease in quality of life was markedly and significantly reduced compared with placebo (intravenous ibandronate $P = 0.005$; oral ibandronate $P = 0.032$). Physical functioning, assessed as part of the quality of life evaluations, was also significantly preserved with both intravenous and oral ibandronate compared with placebo ($P < 0.05$ with both formulations). This possibly reflects improved patient mobility resulting from pain relief.

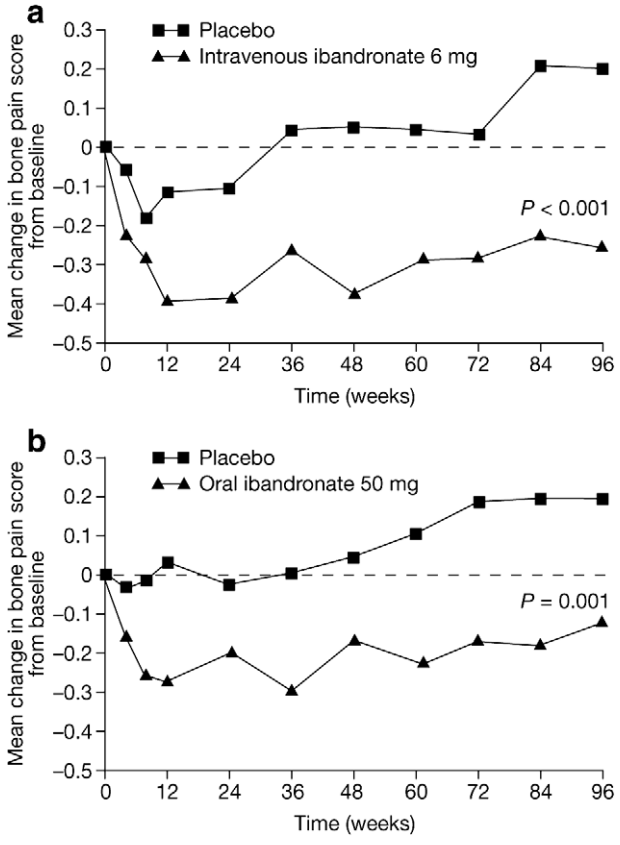


**Fig. 1 – Long-term relief of MBP in breast cancer patients with (a) intravenous ibandronate 6 mg every 3–4 weeks[12,14] or (b) oral ibandronate 50 mg daily[13] during 2 years of treatment: phase III data. In both studies, patients rated their pain using a 5-point scale, where 0 = no pain, 1 = mild, 2 = moderate, 3 = severe, and 4 = intolerable.**

Local radiotherapy and analgesics are the most common treatments for MBP. The use of these interventions is therefore a surrogate trial endpoint to indicate the level of MBP that patients are experiencing. In the phase III trials, both intravenous ibandronate 6 mg and oral ibandronate 50 mg significantly decreased the incidence of events requiring radiotherapy compared with placebo (intravenous ibandronate 16.5% reduction, $P = 0.011$; oral ibandronate 25.5% reduction, $P < 0.001$).[11,12] In addition, analgesic use was lower in ibandronate-treated patients compared with placebo (mean analgesic use scores versus placebo: intravenous ibandronate 0.90 versus 0.51, $P$ = not significant; oral ibandronate 0.85 versus 0.60, $P = 0.019$).[13,14] These data indicate that the significant pain relief observed with ibandronate did not result from increased use of other palliative treatments.

MBP relief with standard ibandronate dosing has been confirmed in post-marketing surveillance data from clinical practice.[15] In an open-label study of 551 patients receiving intravenous or oral ibandronate treatment, 73% experienced an overall improvement in pain scores compared with baseline. Although pain reduction was greatest in bisphosphonate-naïve patients (77% reporting bone pain relief), a pain reduction was also reported by the majority patients (69%) previously treated with a different bisphosphonate. Pain reductions were achieved without increased analgesic consumption.

## 3. Rapid pain relief with loading-dose ibandronate: phase II studies

Phase III data have confirmed that oral and intravenous ibandronate are effective in long-term control of MBP, with maximum pain relief achieved at approximately 12 weeks. Additional phase II studies suggest that initial treatment with high-dose ibandronate on consecutive days (loading-dose) provides rapid relief from moderate-to-severe MBP within days. Two open-label studies were conducted in patients with painful bone metastases following urologic cancer (prostate, renal, or bladder; $n = 53$)[16] or hormone-refractory prostate cancer ($n = 45$).[17,18] All patients received intravenous ibandronate 6 mg on 3 consecutive days (total dose 18 mg) followed by standard intravenous maintenance dosing (intravenous ibandronate 6 mg every 3–4 weeks). Pain was assessed using a visual analog scale (VAS; maximum pain score = 10). At baseline, mean pain scores in both studies were approximately 7 (indicating moderate-to-severe pain), but by Day 3 of treatment scores had decreased to approximately 3 (mild pain; Fig. 2). Decreases in pain scores were maintained until study end (20 weeks in the urologic cancer study). In both studies, more than 80% of patients achieved a significant pain reduction and a quarter of patients became totally pain free. Relief of MBP was accompanied by a dramatic improvement in patient functioning, with mean Karnofsky index scores showing an increase in patient functional capacity from confinement to bed to regaining mobility and independence.

A separate pilot study of intensive intravenous ibandronate therapy has been performed in patients with opioid-

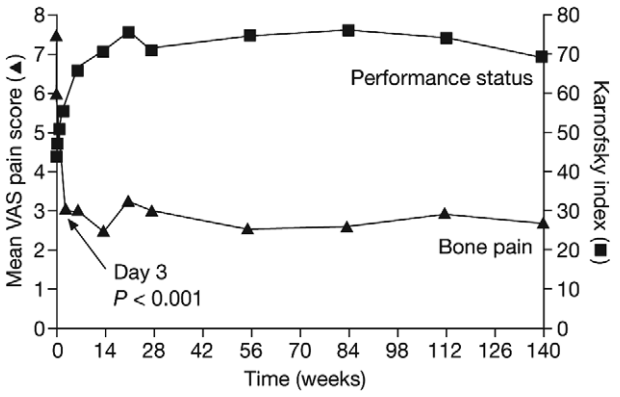


**Fig. 2 – Rapid relief of severe MBP within days with loading-dose ibandronate in patients with urologic cancer, with concurrent improvement in patient functioning (Karnofsky index).[16]**

resistant MBP caused by various primary cancers ($n = 18$).[19] Patients received a non-standard loading-dose treatment (intravenous ibandronate 4 mg on 4 consecutive days, total dose 16 mg) with no maintenance dosing. VAS pain scores decreased significantly within 7 days of initial treatment ($P < 0.001$), and decreases were sustained throughout the study period (6 weeks). In addition, ibandronate treatment significantly improved quality of life, patient functioning, and performance status (all $P < 0.05$).

Overall, studies of loading-dose ibandronate suggest that this treatment regimen provides MBP relief within days rather than weeks required with standard doses of intravenous or oral ibandronate, and that pain relief can be maintained with subsequent standard dosing. However, comparative studies of loading-dose ibandronate versus standard dosing for pain relief have not been performed. An ibandronate loading-dose regimen is possible because intravenous ibandronate has a renal safety profile comparable to placebo.[12,20] In contrast, because of renal toxicity,[21–25] zoledronic acid product labeling prohibits a dose higher than 4 mg every 3–4 weeks.[26,27] Ibandronate has not been associated with renal toxicity, even in patients with pre-existing renal impairment[28,29] or patients receiving loading-dose treatment.[16,18,19] Ibandronate is the only intravenous bisphosphonate, where product labeling allows loading-dose treatment.

## 4. Clinical experience with loading-dose ibandronate

The efficacy of loading-dose ibandronate in clinical practice has been confirmed in a case series of 11 patients suffering bone pain from osteolytic metastases (breast cancer $n = 8$, lung cancer $n = 2$, renal cancer $n = 1$).[30] All patients had not previously received bisphosphonates but had received analgesics and non-steroidal anti-inflammatory drugs. Patients were treated with loading-dose ibandronate (intravenous ibandronate 6 mg on 3 consecutive days). Bone pain was assessed using a patient-rated VAS from 0 to 10. All patients had severe bone pain (VAS 6–7) at baseline, but within 5–7 days this was reduced to mild pain (VAS 3–4). Increased pain medication was not observed. All patients received subsequent therapy as required (e.g., radiotherapy or surgery), demonstrating that loading-dose ibandronate treatment can be combined with other therapies. Although this case series is encouraging, it should be interpreted with caution because of the potential for a placebo effect following intravenous treatment.

## 5. Discussion

Various data suggest that ibandronate offers relief of MBP. In phase III trials, standard dosing with either intravenous or oral ibandronate was demonstrated to provide long-term MBP relief for up to 2 years. Pain reductions were associated with significant improvements in patient quality of life and functioning scores. MBP relief observed with standard dosing has also been confirmed in post-marketing surveillance data from clinical practice. Although pain reductions with standard doses of ibandronate are impressive, the onset of maximum pain relief typically takes weeks or months. Loading-dose ibandronate (intravenous ibandronate 6 mg administered on 3 consecutive days) represents a novel strategy for bisphosphonate MBP relief. In phase II trials, loading-dose ibandronate achieved maximum pain relief within 3 days in patients with moderate-to-severe MBP, with concurrent improvements in patient functioning. MBP relief with loading-dose ibandronate has also been reported in clinical pilot studies. Comparative studies of loading-dose ibandronate versus standard dosing are warranted to confirm the suggestion that loading-dose treatment is associated with a more rapid onset of pain relief. The renal safety profile of intravenous ibandronate enables loading-dose treatment; intensive intravenous dosing with other bisphosphonates is not recommended because of dose-limiting renal toxicity. In the future, all ibandronate-treated patients may receive loading-dose treatment initially, following by standard intravenous or oral maintenance dosing based on patient or physician preference or convenience. Current data suggest that with this treatment regimen, ibandronate will enable patients to experience both rapid and long-term relief from MBP.

## Conflict of interest statement

None declared.

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