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Ibandronate: a well-tolerated intravenous and oral treatment for metastatic bone disease

I.J. Diel

Institute for Gynaecological Oncology, CGG-Klinik GmbH, Quadrat P7, 16–18, Mannheim 68161, Germany

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Abstract

Tolerability of drug therapies is an important factor when selecting palliative treatments for use in cancer patients. This is particularly the case when choosing long-term bisphosphonate therapy for management of skeletal metastases, because of the high disease-related morbidity burden and the toxicities associated with anticancer drugs. In a phase III trial of patients with bone metastases from breast cancer, intravenous (i.v.) ibandronate 6 mg infused every 3–4 weeks for 96 weeks has a similar safety profile to placebo, with no renal safety concerns. Pooled data from two phase III studies of oral ibandronate found that a daily 50 mg dose was well-tolerated, with few gastrointestinal side effects. These results suggest that oral and i.v. ibandronate have important safety and tolerability advantages over existing i.v. and oral bisphosphonate treatments.

1. Introduction

Many patients with advanced cancer develop metastatic bone disease, a painful and disabling condition characterised by clinical complications including pathological fractures, compression of the spinal cord and hypercalcaemia [1,2]. Tolerability is of considerable importance in the selection of palliative therapy for patients with skeletal metastases, because of the high disease burden and toxicities associated with the treatment of their underlying malignancy [3]. While cancer therapies such as radiotherapy and chemotherapy relieve the symptoms of metastatic bone disease [4], associated side effects limit their use.

Bisphosphonates have proven efficacy against the skeletal complications of metastatic bone disease [5–8]. However, they can be associated with unpleasant adverse events (AEs). Oral bisphosphonate therapy (e.g. clodronate) is associated with gastrointestinal (GI) disturbances, such as oesophagitis, gastritis and diarrhoea [9,10]. Infusion of bisphosphonates can lead to injection-site reactions (affecting up to 6% of patients) and an acute phase reaction (a flu-like syndrome observed in up to a third of patients, typically lasting 1–2 days following first administration) [10]. Some patients receiving i.v. zoledronic acid and pamidronate develop renal complications, which are occasionally severe [10,12,13]. Rare side effects of bisphosphonate therapy include hypocalcaemia (symptomatic), ocular side effects (retinitis, uveitis, scleritis), asthmatic attacks (in patients sensitive to aspirin), skin rashes, phlebitis and taste distortions [10,12,13].

Despite the existence of class-related toxicities, the safety and tolerability profiles of individual bisphosphonates do vary. This paper reviews the safety data for i.v. and oral ibandronate, from phase III studies of patients with metastatic bone disease from breast cancer.

2. I.V. ibandronate safety

Although safety data for the recommended 6 mg dose of intravenous ibandronate have been collected in relatively few patients compared with other intravenous bisphosphonates, clinical trial evidence supports the tolerability of this agent in metastatic bone disease. A multicentre, randomised, double-blind placebo-controlled trial of patients with skeletal metastases from breast cancer examined the safety of i.v. ibandronate 6 mg ($n=157$) versus placebo ($n=152$) infused every 3–4 weeks for 96 weeks of treatment [14,15]. A summary of the clinical efficacy findings of this study is provided in this supplement [16].

The results showed that approximately 40% of patients receiving i.v. ibandronate 6 mg or placebo completed the 96-week treatment period. The median

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time on study was longer in the 6 mg group (72.3 weeks) than in the placebo group (52.3 weeks). As would be expected in a patient population with advanced cancer, almost all patients (93.4% in the ibandronate group and 98.7% in the placebo group) experienced an AE during the 2-year study period. The majority of AEs reported were related to malignancy progression, affecting 53% and 40% of patients in the ibandronate and placebo groups, respectively.

Drug-related AEs were experienced by a slightly higher percentage of patients receiving i.v. ibandronate (55.3%) than with placebo (49.7%), primarily due to an increased incidence of myalgia, flu-like syndrome, and diarrhoea (Table 1). There was no evidence of renal toxicity with i.v. ibandronate treatment, as the incidence of renal AEs was low and comparable to placebo (Table 2). None of the renal AEs with ibandronate were graded serious, or led to withdrawal from treatment.

Table 1
Summary of treatment-related AEs with i.v. ibandronate versus placebo (MF 4265)

Event	Placebo ($n=157$) %	Ibandronate 6 mg ($n=152$) %
Patients reporting at least one event	49.7	55.3
Body as a whole		
Asthenia	5.1	6.6
Fever	6.4	5.9
Flu-like syndrome	1.3	5.3
Digestive system		
Nausea	4.5	3.3
Diarrhoea	0.6	5.3
Musculoskeletal system		
Myalgia	3.8	5.3
Nervous system		
Headache	2.5	5.9
Respiratory system		
Upper respiratory infection	4.5	4.6

Table 2
Summary of renal AEs with i.v. ibandronate versus placebo (MF 4265)

Renal event	Placebo ($n=157$)	Ibandronate 6 mg ($n=152$) (%)
Kidney failure	1.3	–
Kidney pain	0.6	0.0
Acute kidney failure	–	0.7
Creatinine increased	1.3	2.6
Hydronephrosis	1.3	0.7
Total	4.5	4.0

3. Oral ibandronate safety

The safety of oral ibandronate 50 mg/day ($n=286$) versus placebo ($n=277$) was investigated in a pooled analysis of two 96-week, multicenter, randomised, double-blind studies [15]. Efficacy data from these studies are summarised in a separate paper [16].

The 96-week treatment period was completed by 42% of patients in the oral ibandronate group and 38% of patients in the placebo group. Median time from randomisation to study end was 79.1 weeks with oral ibandronate and 69.7 weeks with placebo. As seen in the i.v. trial, the percentage of patients experiencing any AE was similar between the ibandronate 50 mg (94.4%) and placebo (95.3%) groups.

There was a slightly higher incidence of drug-related AEs with ibandronate 50 mg (26.6%) than with placebo (17.7%), owing to more reports of hypocalcaemia in the ibandronate group (an AE associated with the use of any bisphosphonate) (Table 3). Ibandronate 50 mg was associated with a slightly higher incidence of drug-related upper GI AEs (dyspepsia and esophagitis) than placebo. Oral ibandronate 50 mg had no renal safety concerns, as shown by the percentage of patients with elevated creatinine levels (1.4% versus 2.2% with placebo) and the overall incidence of renal AEs (5.2% versus 4.7% with placebo).

4. Discussion

Data from three phase III clinical studies demonstrated that both i.v. and oral ibandronate are well tolerated over 2 years of treatment in patients with metastatic bone disease due to breast cancer, with AE profiles similar to placebo. The long-term tolerability of bisphosphonate therapy is crucial given the

Table 3
Most common treatment-related AEs with oral ibandronate versus placebo (MF 4414/4434)

	Placebo ($n=277$) %	Ibandronate 50 mg ($n=286$) (%)
Patients reporting at least one event	17.7	26.6
Body as a whole		
Abdominal pain	0.7	2.1
GI events		
Dyspepsia	4.7	7.0
Nausea	1.4	3.5
Oesophagitis	0.7	2.1
Diarrhoea	1.4	1.4
Metabolic and nutritional disorders		
Hypocalcaemia	5.1	9.4

chronic nature of metastatic bone disease management. As improvements in cancer therapies increase survival duration, patients with metastatic bone disease may well receive bisphosphonate therapy for a number of years.

In a phase III trial, infusion of i.v. zoledronic acid 4 mg over 15 min and i.v. pamidronate infused over 2 h every 3–4 weeks led to elevated creatinine levels (defined by increases of 0.5 mg/dL if baseline <1.4 mg/dL or 1.0 mg/dL if baseline $\geqslant 1.4$ mg/dL; or an increase of twice the baseline value) in 8–9% of patients [11]. In a retrospective study conducted in a US cancer clinic, when zoledronic acid 4 mg was infused over 15 min, 23% of patients with bone metastases from multiple myeloma, breast, prostate or lung cancer had raised serum creatinine levels [17]. These incidences are considerably higher than reported for i.v. ibandronate 6 mg (1.4%) or oral ibandronate 50 mg (2.2%) in the phase III trials reported here.

Occasionally, infusion of zoledronic acid and pamidronate at recommended doses (4 mg infused over 15 min, 90 mg infused over >2 h) has been shown to cause severe renal toxicity, resulting in acute renal failure and drug discontinuation [18,19]. Regular patient observation is essential, with renal function monitoring prior to each dose [20], as stated in product labelling [21]. Such monitoring is time-consuming for patients and hospital staff, and may add to the overall cost of care. The absence of evidence for long-term renal safety concerns suggests that i.v. ibandronate 6 mg provides a well-tolerated alternative to other i.v. bisphosphonates. In addition, ibandronate may offer a viable treatment option for patients with existing renal function impairment [21]. The need for constant safety monitoring should be lower with i.v. ibandronate than existing i.v. agents, reducing patient visit time and hospital resource use. Inpatient or outpatient clinic visits for bisphosphonate therapy would no longer be required if the oral ibandronate formulation (which also has no related renal safety issues) was prescribed.

Oral ibandronate 50 mg/day also has a favourable GI tolerability profile, with an incidence of GI side effects that is similar to placebo. In contrast, a 2-year study of 1069 breast cancer patients with bone metastases showed a significantly higher incidence of diarrhoea with oral clodronate 1600 mg/day (16.6%) versus placebo (7.4%, $P<0.001$) [10]. Although it is difficult to compare results between trials, upper GI events occurred in 22% of patients receiving clodronate in this study [9], compared with an incidence of approximately 7% with oral ibandronate in phase III trials. The GI tolerability of oral ibandronate may help to ensure daily adherence to treatment (and therefore optimal drug efficacy), particularly if taken at home without close medical supervision.

5. Conclusion

Available data suggest that ibandronate is well-tolerated in metastatic bone disease. There were no significant renal or GI safety concerns with ibandronate at recommended doses in phase III clinical studies. These data suggest that ibandronate is suitable for the long-term care of patients with skeletal metastases. Further trials to directly compare the safety of ibandronate and other bisphosphonates are underway.

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References

1. Coleman RE, Rubens RD. The clinical course of bone metastases from breast cancer. *Br J Cancer* 1987, **55**, 61–66.
2. Coleman RE. Skeletal complications of malignancy. *Cancer* 1997, **80**(Suppl. 8), 1588–1594.
3. Diel IJ, Solomayer E-F, Bastert G. Treatment of metastatic bone disease in breast cancer: bisphosphonates. *Clin Breast Cancer* 2000, **1**, 43–51.
4. Janjan N. Bone metastases: approaches to management. *Semin Oncol* 2001, **28**(Suppl. 11), 28–34.
5. 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.
6. Pavlakis N, Stockler M. Bisphosphonates for breast cancer. *Cochrane Database Syst Rev* 2002, **1**, CD003474.
7. Body JJ, Bartl R, Burckhardt P, *et al*. Current use of bisphosphonates in oncology. *J Clin Oncol* 1998, **16**, 3890–3899.
8. Hurst M, Noble S. Clodronate. A review of its use in breast cancer. *Drugs Aging* 1999, **15**, 143–167.
9. Powles T, Paterson S, Kanis J, *et al*. Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer. *J Clin Oncol* 2002, **20**, 3219–3224.
10. Body JJ. Dosing regimens and main adverse events of bisphosphonates. *Semin Oncol* 2001, **28**, 49–53.
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. Adami S, Zamberlan N. Adverse effects of bisphosphonates. A comparative review. *Drug Saf* 1996, **14**, 158–170.
13. Bounameaux HM, Schifferli J, Montani JP, *et al*. Renal failure associated with intravenous disphosphonates. *Lancet* 1983, **1**, 471.
14. Body JJ, Diel IJ, Lichinitser MR, *et al*. Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. *Ann Oncol* 2003, **14**, 1399–1405.
15. Diel IJ, Body JJ, Tripathy D, Bergstrom B. Oral daily ibandronate in women with metastatic breast cancer: a pooled safety analysis. *Proc ASCO* 2003, **22**, 47 (abstr. 186).
16. Body JJ. Reducing skeletal complications and bone pain with intravenous ibandronate for metastatic bone disease. *EJC Supplements* 2004, **2**(5), this issue (doi: 10.1016/j.ejcsup.2004.01.002).

17. Johnson KB, Gable P, Kaime EM, *et al*. Significant deterioration in renal function with the new bisphosphonate, zoledronic acid. *Proc ASCO* 2003, **22**, 738 (abstr 2968).
18. Markowitz GS, Fine PL, Stack JI, *et al*. Toxic acute tubular necrosis following treatment with zoledronate (Zometa). *Kidney Int* 2003, **64**, 281–289.
19. Banerjee D, Asif A, Striker L, *et al*. Short-term, high-dose pamidronate-induced acute tubular necrosis: the postulated mechanisms of bisphosphonate nephrotoxicity. *Am J Kidney Dis* 2003, **41**, E18.
20. Kloth DD, McDermott RS, Rogatko A, Langer CJ. Impact of zoledronic acid (Zol) on renal function in patients (pts) with cancer: as constant monitoring necessary? *Proc ASCO* 2003, **22**, 755 (abstr 3036).
21. Zometa®. Prescribing Information. Novartis.