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Oral daily ibandronate: an effective and convenient therapy for skeletal complications in metastatic breast cancer

D. Tripathy

University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-8852, USA

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Abstract

Bisphosphonate therapy reduces the relative risk of skeletal-related events in metastatic bone disease and is widely used in the long-term management of this condition. The efficacy of oral ibandronate, a third-generation high potency aminobisphosphonate, has been evaluated in patients with bone metastases from breast cancer. In a phase III trial (MF 4434), daily treatment with ibandronate 50 mg over 96 weeks significantly reduced the number of 12-week periods with new bone complications (the skeletal morbidity period rate [SMPR]) compared with placebo ($P = 0.037$). These results were supported by a protocol-specified pooled analysis of this trial and another study of identical design (MF 4414), which demonstrated that overall SMPR and SMPR for bone radiotherapy were significantly reduced versus placebo ($P = 0.004$). The pooled analysis also revealed that oral ibandronate rapidly reduced and maintained bone pain below baseline over 2 years of treatment ($P = 0.001$ versus placebo) and significantly improved patient quality of life ($P = 0.03$). Oral ibandronate is therefore an effective bisphosphonate for the management of metastatic bone disease, and offers a convenient alternative to intravenous (i.v.) bisphosphonate therapy.

1. Introduction

Metastatic bone disease affects a significant proportion of women with advanced breast cancer [1], and causes severe pain, impaired mobility, and pathological fractures [2,3]. Because of their effectiveness against skeletal complications [4–11], bisphosphonates have been used in the treatment of metastatic bone disease for a number of years. Infused agents tend to be preferred over available oral agents (e.g. clodronate), because they are perceived as being more effective. However, i.v. bisphosphonate therapy has its limitations, with adverse events including renal complications, infusion-associated reaction, the inconvenience of regular hospital visits for bisphosphonate therapy, and the health care cost implications of administration and patient monitoring [11–14].

Oral administration of bisphosphonates would overcome the issue of infusion-related side effects, and offer long-term maintenance therapy at home. Yet available oral bisphosphonate therapy (clodronate) has gastrointestinal side effects [15,16], with multiple daily doses and large tablet size that may reduce compliance therapy. Ibandronate is a high-potency amino-bisphosphonate that has been developed in i.v. and oral formulations. A placebo-controlled randomised phase III trial demonstrated that infusion of i.v. ibandronate (6 mg) every 3–4 weeks is highly effective in reducing skeletal complications in patients with metastatic bone disease due to breast cancer [17,18]. The effect of oral ibandronate on the incidence of skeletal events has been investigated in two multicentre, randomised, double-blind placebo-controlled pivotal phase III studies over 96 weeks of treatment [19]. The findings of one of these studies (MF 4434) and the pooled results from both trials are summarised here. Safety data for oral ibandronate are presented elsewhere within this supplement [20].

2. Phase III trial of oral ibandronate

In this trial (MF 4434), 191 patients were randomised to once-daily treatment with oral ibandronate (50 mg) ($n = 148$) or placebo ($n = 143$). The primary efficacy endpoint was the skeletal morbidity period rate (SMPR), defined as the number of 12-week periods with new bone complications (vertebral and non-vertebral fractures, the need for bone radiotherapy and the need for bone surgery). Assessment of the SMPR included post-withdrawal follow-up (PWFU) data on key outcome events, which were gathered retrospectively on

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patients who withdrew prior to the 96-week study period. Additional efficacy analyses included bone pain, analgesic use and quality of life.

Oral ibandronate (50 mg) significantly reduced the incidence of new bone events, as assessed by mean SMPR ($P=0.037$ versus placebo) (Table 1). Although this study was not powered to assess subclasses of bone events, there was a statistically significant decrease in the incidence of events requiring radiotherapy with ibandronate ($P=0.005$ versus placebo). The incidence of vertebral and non-vertebral fractures and bone events requiring surgery was similar between the ibandronate and the placebo groups (Table 1). Oral ibandronate 50 mg also reduced the mean number of new bone events per subject, the mean number of measurement periods with events, and the percentage of patients with events (Table 1). A multivariate Poisson regression analysis, conducted to assess the relative risk of new bone events and including PWFU data, revealed a highly significant relative risk reduction with ibandronate compared with placebo (39%, $P=0.0005$).

From baseline to study endpoint, bone pain score increased by +0.21 in the placebo group, compared with a slight increase of +0.03 in the 50 mg group ($P=0.201$). Mean analgesic use was lower in the ibandronate 50 mg group than with placebo (0.73 versus 0.96), which approached statistical significance ($P=0.074$). Although ibandronate led to a lesser deterioration in quality of life scores over time, there were no significant differences between the ibandronate group and placebo (mean change from baseline −15 versus −32, $P=0.42$).

3. Pooled analysis of two phase III trials of oral ibandronate

In the pre-planned and protocol-specified pooled analysis of the two phase III trials with identical design (MF 4434/MF 4414), 286 patients received oral ibandronate 50 mg/day and 277 patients received placebo. Analysis of SMPR and Poisson regression of skeletal-related events included PWFU data, and excluded data from the first 12 weeks of the study as prespecified in the analysis plan for the pooled dataset. There was a clear treatment benefit for oral ibandronate for mean SMPR and bone events requiring radiotherapy, with significant reductions in the mean number of new bone events and the mean number of measurement periods with events, compared with placebo (Table 2). Poisson regression analysis indicated that ibandronate 50 mg reduced the relative risk of skeletal events by 38% ($P=0.0001$ versus placebo).

Mean bone pain score increased with placebo from baseline to endpoint (+0.20), in contrast to a reduction of −0.10 in the ibandronate group ($P=0.001$). While bone pain levels in the placebo group increased progressively, they remained below baseline throughout the 2-year study period with ibandronate (Fig. 1). In addition, analgesic use scores were significantly higher in the placebo group than in the ibandronate group (0.85 versus 0.60, $P=0.019$).

As expected for a patient population with advanced malignant disease, quality of life scores decreased in the course of the study. However, the reduction in total score was significantly greater in the placebo group (−26.8) than with ibandronate (−8.3, $P=0.032$).

4. Discussion

The results of these studies demonstrate that oral ibandronate effectively reduces the incidence of new skeletal events in women with breast cancer and bone metastases. Within the individual components of the SMPR, the most marked effect of ibandronate treatment was observed on the need for bone radiotherapy, which is considered to be one of the most clinically relevant measures of bone metastases. The reduction in

Table 1
Mean SMPR and individual components of the SMPR including PWFU data: MF 4434 and pooled oral dataset

	MF 4434		Pooled dataset MF 4414/MF 4434[a]	
	Placebo ($n=143$)	Ibandronate 50 mg ($n=148$)	Placebo ($n=268$)	Ibandronate 50 mg ($n=276$)
All new bone events (SMPR)	1.20	0.98 $P=0.037$	1.18	0.95 $P=0.004$
Vertebral fractures	0.51	0.52 $P=0.739$	0.63	0.58 $P=0.093$
Non-vertebral fractures	0.52	0.54 $P=0.890$	0.61	0.60 $P=0.246$
Events requiring radiotherapy	0.99	0.77 $P=0.005$	0.98	0.73 $P<0.001$
Events requiring surgery	0.44	0.43 $P=0.644$	0.53	0.47 $P=0.037$

P-value versus placebo.
[a] Excluding events occurring during the first 12 weeks of the treatment

Table 2
Supportive analyses of new bone events including PWFU data: MF 4434 and pooled oral dataset

	MF 4434		Pooled dataset MF 4414/MF 4434[a]	
	Placebo ($n=143$)	Ibandronate 50 mg ($n=148$)	Placebo ($n=268$)	Ibandronate 50 mg ($n=276$)
Mean number of events per patient	2.23	1.43 $P=0.014$	1.85	1.15 $P=0.008$
Mean number of measurement periods with events per patient	1.27	0.84 $P=0.014$	0.99	0.71 $P=0.015$
Total number of periods with events	182	125 $P=0.014$	N/A	N/A
Percentage of patients with events	61.5	52.0 $P=0.102$	52.2%	45.3% $P=0.122$

P-value versus placebo. N/A Not assessed.
[a] Excluding events occurring during the first 12 weeks of the treatment.

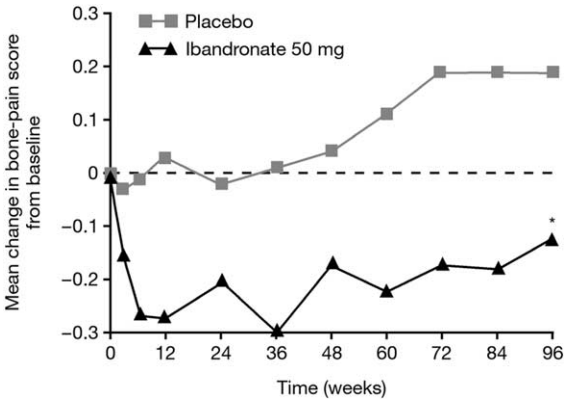

Fig. 1. Change in bone pain scores over 2 years of treatment: pooled oral dataset (*$P=0.001$).

SMPR for need for radiotherapy with ibandronate was highly statistically significant, even though the studies were not powered for this or other individual components (vertebral fractures, non-vertebral fractures, need for bone surgery) of the primary endpoint (overall SMPR), which supports the strength of the treatment effect.

In MF 4434 and the pooled oral trials, Poisson regression analysis showed a 38% reduction in the relative risk of skeletal events with ibandronate 50 mg versus placebo. This value is comparable to that seen with i.v. ibandronate 6 mg in a phase III trial (40%)[21]. Direct comparative trials are being conducted to compare oral ibandronate with other bisphosphonates in patients with bone metastases from breast cancer and other tumour types.

Bone pain scores with oral ibandronate remained lower than with placebo throughout the trial period in the pooled analysis. Although reductions in bone pain from skeletal metastases were observed in clinical studies of other bisphosphonates [22–25], ibandronate is the only bisphosphonate shown to maintain bone pain reductions below baseline for 2 years [22]. The mean decrease in bone pain scores from baseline to endpoint was highly statistically significant, and was not due to increased analgesic use (this was actually lower with ibandronate 50 mg than with placebo). Quality of life also significantly improved with oral ibandronate, an effect not reported over 2 years of treatment with other bisphosphonates for metastatic bone disease.

In addition to its efficacy benefits, the availability of oral ibandronate would improve treatment convenience with long-term, at-home dosing. The absence of frequent hospital trips would help maintain patients' normal life activities. This is of considerable value in the palliative care setting, where survival time is limited. Oral ibandronate also offers dosing simplicity, with a once-daily regimen, a small tablet size and a 30-min pre-food fasting period. Ease of dosing is important in real-life settings, where complex regimens are likely to diminish compliance and compromise drug efficacy.

5. Conclusion

Oral ibandronate 50 mg is an effective treatment for the skeletal complications and symptoms of metastatic bone disease, with efficacy to i.v. bisphosphonates. With added treatment convenience, the availability of oral ibandronate will improve therapeutic choice in metastatic bone disease.

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