Original article

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Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases

J.-J. Body[1]*, I. J. Diel[2], M. R. Lichinitser[3], E. D. Kreuser[4], W. Dornoff[5], V. A. Gorbunova[6], M. Budde[7] & B. Bergström[8]
On behalf of the MF 4265 Study Group[8]†

[1]*Université Libre de Bruxelles, Institut Jules Bordet, Brussels, Belgium;* [2]*Department of Obstetrics and Gynaecology, University Hospital, Heidelberg, Germany;* [3]*Department of Clinical Chemotherapy, Cancer Research Center, Moscow, Russia;* [4]*Krankenhaus der Barmherzigen Brueder, Onkologische Ambulanz, Regensburg;* [5]*Mutterhaus der Borromaeerinnen, Trier, Germany;* [6]*Cancer Research Center, Department of Chemotherapy, Moscow, Russia;* [7]*F. Hoffmann-La Roche Ltd, Basel, Switzerland;* [8]*F. Hoffmann-La Roche Inc., Nutley, NJ, USA*

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Background: This phase III study compared the efficacy of the new potent bisphosphonate, ibandronate, with placebo as intravenous (i.v.) therapy in metastatic bone disease due to breast cancer.

Patients and methods: A total of 466 patients were randomised to receive placebo (n = 158), or 2 mg (n = 154) or 6 mg (n = 154) ibandronate every 3–4 weeks for up to 2 years. The primary efficacy parameter was the number of 12-week periods with new bone complications, expressed as the skeletal morbidity period rate (SMPR). Bone pain, analgesic use and safety were evaluated monthly.

Results: SMPR was lower in both ibandronate groups compared with the placebo group; the difference was statistically significant for the ibandronate 6 mg group (P = 0.004 versus placebo). Consistent with the SMPR, ibandronate 6 mg significantly reduced the number of new bone events (by 38%) and increased time to first new bone event. Patients on ibandronate 6 mg also experienced decreased bone pain scores and analgesic use. Treatment with ibandronate was well tolerated.

Conclusions: These results indicate that 6 mg i.v. ibandronate is effective and safe in the treatment of bone metastases from breast cancer.

Key words: bisphosphonate, bone metastases, breast cancer, ibandronate, pain, radiotherapy

Introduction

Bone is the most common site of metastasis in patients with breast cancer, affecting up to 90% of women with advanced disease [1, 2]. Patients with bone metastases are at increased risk of further skeletal complications, which cause considerable morbidity including pain, impaired mobility, hypercalcemia of malignancy and pathological fractures (spinal vertebral compression) [3].

The majority of bone metastases from breast cancer are osteolytic, causing elevated bone resorption [4]. Inhibitors of bone resorption, particularly bisphosphonates, have therefore been extensively used for treatment of metastatic breast cancer [5]. While the exact mechanism of action of bisphosphonates on bone resorption remains unclear, they are thought to act through inhibition of osteoclast activity and possibly osteoclast differentiation [6, 7]. Bisphosphonate use may also result in a decrease in tumour burden by rendering the bone microenvironment a less favourable site for the growth of tumour cells [8–10]. Intravenous (i.v.) pamidronate became established as a standard treatment for bone metastases due to breast cancer, notably based on the results of two randomised, placebo-controlled clinical trials in patients with metastatic breast cancer being treated with either chemotherapy [11] or hormonal therapy [12]. Pamidronate was effective in reducing skeletal morbidity in patients receiving both types of treatment, although there were substantial differences between the two studies in terms of the extent of the effect, and the number and types of skeletal events that were reduced by pamidronate treatment. The discrepancies may have been due to differences in the patient populations.

Ibandronate is a third-generation bisphosphonate that is 50–100 times more potent than pamidronate in animal studies. Ibandronate markedly inhibits bone resorption and is effective in the treatment of tumour-induced hypercalcaemia [13]. It is currently being evaluated in both i.v. and oral formulations for the treatment of bone metastases in patients with breast cancer. The aim of the present study was to evaluate the efficacy and safety of i.v. ibandronate in the treatment of skeletal complications in women with breast cancer and bone metastases. Unlike previous studies of bisphosphonates in breast cancer, the patient population in this trial was not selected for variables such as the regimen used in cancer treatment (hormonal or chemotherapy), the presence or

**Correspondence to:* Professor J.-J. Body, Institut Jules Bordet, Department of Medicine, 1 Rue Heger Bordet, 1000 Brussels, Belgium.
Tel: +32-254-1-3303; Fax: +32-254-1-3310; E-mail: jj.body@bordet.be
†Members of the MF 4265 Study Group are listed in the Acknowledgements.

absence of any visceral metastases and the size of the lytic lesion. The mixed population thus obtained is likely to be more representative of the patient population for whom bisphosphonate treatment is indicated, since the recommended criterion for bisphosphonate use in patients with breast cancer is the diagnosis of bone metastases, irrespective of these other variables [14, 15].

Patients and methods

Study design

This was a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase III study.

Inclusion criteria

Women aged ≥18 years with histologically confirmed breast cancer and bone metastases demonstrated by X-ray and/or computed tomography and/or nuclear magnetic resonance scan with a World Health Organization (WHO) performance status ≤2 were included in the study. The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was received by local ethics committees and all patients gave written informed consent.

Exclusion criteria

Patients were excluded if they had a life expectancy <60 weeks, were pregnant or had received bisphosphonate or gallium nitrate treatment within the past 6 months, any investigational drug or aminoglycoside antibiotic within the past 30 days, or previous high-dose chemotherapy (dose intensity >3 times standard therapy). Patients were also excluded if they had hypercalcaemia or hypocalcaemia (albumin-corrected serum calcium >2.7 mM or <2 mM), serum creatinine >3 mg/dl, Paget's disease of bone, primary hyperparathyroidism, aspirin-sensitive asthma, or known liver or brain metastases.

Treatment

Each patient was randomised to receive either placebo or ibandronate 2 mg by i.v. bolus injection, or placebo or 6 mg ibandronate by i.v. infusion over 1–2 h. The study was thus blinded with respect to placebo or ibandronate treatment, but the dose was open-label due to differences in the mode of delivery. Each study arm received either injection or infusion of ibandronate or placebo on day 0. Subsequent treatments were administered at 3- or 4-weekly intervals for a minimum of 60 weeks and a maximum of 96 weeks. Patients were limited to a maximum of 24 treatments during the study. Owing to the severe nature of the underlying disease, there were no restrictions on concomitant medication. All concomitant medication was documented throughout the study.

Baseline assessments

Baseline assessments included: confirmation of inclusion and exclusion criteria, laboratory tests, urine tests, WHO performance status, recording of concomitant medication and radiotherapy, and assessment of bone pain and analgesic consumption.

Efficacy assessments

The primary efficacy parameter was the number of 12-week periods with new skeletal complications (bone events), allowing for the time the patient spent on study. This was expressed as the skeletal morbidity period rate (SMPR), calculated as the number of periods with new bone complications divided by the total observation time in periods. Bone events were defined as any of: vertebral fractures; pathological non-vertebral fractures; radiotherapy for bone complications (uncontrolled bone pain or impending fractures); or surgery for bone complications (fractures or impending fractures). The SMPR was used rather than the simple skeletal morbidity rate (number of events divided by time on study) since skeletal complications occurring close together are often likely to be related, rather than distinct, events. All skeletal complications occurring within a single 12-week period were considered as a single occurrence, avoiding double or triple counting of the same event. However, the SMPR calculation does not fully allow for time on study, since patients who withdrew or died very early, without experiencing a complication, would receive the same score (zero) as patients who completed 96 weeks on study without experiencing any skeletal complications. In a study on metastatic breast cancer, where patients may be very ill and a high proportion of withdrawals would be expected, the influence of early withdrawals on SMPR may be substantial. To avoid this the SMPR was calculated using a 'revised event ratio' method, as follows:

$$\text{SMPR} = \frac{\text{number of periods with new skeletal events} + 1}{\text{number of 12-week periods on study} + 0.5} \quad (1)$$

The revised event ratio calculation avoids the occurrence of zero in the numerator of the fraction, thus ensuring that sufficient weighting is given to the time spent on study when calculating the number of periods with bone events [16]. Thus for patients with zero bone events, the SMPR ratio is lower the longer the time spent on study.

The assessment of vertebral fractures identified on spine radiographs was performed morphometrically [17].

Confirmatory analyses of the primary efficacy point included the proportion of patients with new bone events and the time to first new bone event. Secondary efficacy parameters included assessment of bone pain, analgesic consumption, WHO performance status, patient survival and markers of bone turnover.

Adverse events

Adverse events were monitored throughout the study and graded according to WHO criteria.

Statistics

The global null hypothesis was tested at the two-sided α-level of 5% using the non-parametric Jonckheere–Terpstra method [18, 19]. If the global hypothesis was rejected, pairwise comparisons between treatments were performed using the Wilcoxon rank sum method maintaining an overall two-sided α-level of 5% and following a closed-test procedure. The primary and secondary efficacy analyses were conducted on the intention-to-treat population. The placebo groups (injection and infusion) were combined for all efficacy and safety analyses.

Results

Patient demographics

A total of 466 patients were randomised to treatment (158 to placebo, 154 to ibandronate 2 mg and 154 to ibandronate 6 mg). Patient demographics are shown in Table 1. No major differences were observed between groups in terms of characteristics at baseline.

Most patients (n = 283) were receiving concomitant hormonal therapy at baseline, and 110 patients were receiving chemotherapy, while 69 patients received neither hormonal therapy nor chemotherapy. There were no differences between the treatment groups with regard to the type and number of concomitant medications taken during the study.

Table 1. Patient characteristics at baseline

	Placebo (n = 158)	Ibandronate 2 mg (n = 154)	Ibandronate 6 mg (n = 154)
Mean age, years (SD)	54.5 (11.5)	55.3 (10.9)	56.1 (11.4)
Mean time from breast cancer diagnosis to bone metastases, months (SD)	46.0 (59.0)[a]	54.7 (50.2)[b]	48.7 (56.9)[c]
Mean time from bone metastases to study entry, months (SD)	17.4 (21.6)	17.3 (21.8)	15.4 (19.0)
Bone metastases only, *n* (%)	105 (66.5)	101 (65.6)	106 (68.8)
Lung metastases, *n* (%)	18 (11.4)	23 (14.9)	9 (5.8)
Other metastases,[d] *n* (%)	35 (22.2)	36 (23.4)	26 (16.9)
Vertebral fractures, *n* (%)	46 (29.1)	49 (31.8)	49 (31.8)
Non-vertebral fractures, *n* (%)	28 (17.7)	31 (20.1)	33 (21.4)
Line of tumour treatment,[e] *n* (%)			
1st	25 (15.8)	31 (20.1)	34 (22.1)
2nd	49 (31.0)	38 (24.7)	36 (23.4)
3rd	34 (21.5)	36 (23.4)	33 (21.4)
≥4th	40 (25.3)	44 (28.6)	43 (27.9)
Radiotherapy, *n* (%)	53 (33.5)	48 (31.2)	43 (27.9)
Bone pain score, *n* (%)			
None	26 (16.5)	30 (19.5)	21 (13.6)
Mild	51 (32.3)	60 (39.2)	51 (33.1)
Moderate	51 (32.3)	42 (27.3)	49 (32.2)
Severe	23 (14.6)	16 (11.0)	22 (14.3)
Intolerable	0 (0.0)	1 (0.7)	2 (1.3)
WHO performance status, *n* (%)			
0	27 (17.1)	41 (26.6)	32 (20.8)
1	91 (57.6)	89 (57.8)	84 (54.5)
2	36 (22.8)	23 (14.9)	36 (23.4)
3	3 (1.9)	1 (0.6)	2 (1.3)
4	1 (0.6)	0 (0.0)	0 (0.0)

[a]n = 149; [b]n = 146; [c]n = 145.

[d]Except liver and brain metastases (exclusion criteria).

[e]Includes chemotherapy and hormonal therapy.

n, number of patients.

Treatment administration and duration

A total of 249 patients (53% of all patients randomised to treatment) completed 60 weeks of study treatment (58% ibandronate 6 mg; 57% ibandronate 2 mg; 45% placebo), while 187 patients (40%) completed 96 weeks (43% ibandronate 6 mg; 47% ibandronate 2 mg; 31% placebo). The median time on study (time from randomisation to study termination) was markedly longer for patients in both ibandronate groups (18.1 months) compared with placebo (13.1 months) (Figure 1).

Adverse clinical events, death and refusal of treatment were the main reasons for withdrawal (Table 2).

Primary efficacy outcomes

Skeletal morbidity period rate. Patients receiving ibandronate 6 mg had a 20% reduction in the frequency of 12-week periods with bone events (SMPR) compared with the placebo group (1.19 versus 1.48 periods with events per patient year; $P = 0.004$). An 11% reduction in the SMPR for the ibandronate 2 mg treatment versus placebo was also observed, although this was not statistically significant (1.31 versus 1.48; $P = 0.152$) (Table 3).

Among the individual components of the primary end point, the SMPR for vertebral fractures and events requiring radiotherapy were both significantly lower in the 2 mg and 6 mg ibandronate treatment groups compared with placebo (global P value 0.023 for vertebral fractures and 0.012 for events requiring radiotherapy). For bone events requiring surgery, the SMPR was lower in both ibandronate groups than placebo, with the global test P value just above the 5% significance level ($P = 0.06$) (Table 3).

Analysis of the unadjusted SMPR confirmed the sensitivity of the revised event ratio method. The mean unadjusted SMPR for

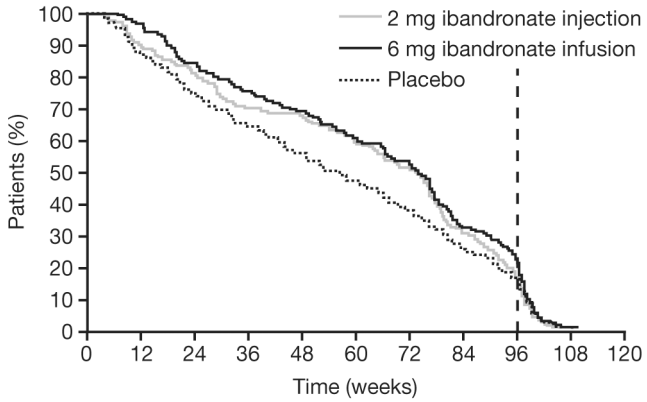

Figure 1. Kaplan–Meier estimates of the time to study termination.

all new bone events was significantly reduced in the 6 mg group compared with placebo (26% reduction; $P = 0.019$), whereas the treatment difference between the 2 mg group and placebo was not statistically significant (10% reduction; $P = 0.638$). Only the ratio for 'events requiring radiotherapy' in the 6 mg treatment group approached statistical significance at the 5% level ($P = 0.057$).

New bone events

The mean number of new bone events per patient was significantly lower in the ibandronate 6 mg treatment group (2.65 events per patient) than in the ibandronate 2 mg (4.24 events per patient) or placebo (3.64 events per patient) groups ($P = 0.032$ for 6 mg ibandronate versus placebo) (Table 4). This appeared to be primarily due to a reduction in new bone events requiring radiotherapy. The number of 12-week periods with at least one new bone event was ~20% lower in the ibandronate 6 mg group (145 periods) than in either the placebo (181 periods) or 2 mg (193 periods) groups ($P = 0.09$ for ibandronate 6 mg versus placebo). The proportion of patients who did not experience any new bone events during the study was higher in the ibandronate 6 mg group (49%) than in the ibandronate 2 mg (38%) or placebo (38%) group, although this did not reach statistical significance ($P = 0.052$).

Time to first new bone event

The median time from treatment randomisation to a first new bone event was greater for patients treated with ibandronate 6 mg (50.6 weeks) than for patients treated with either ibandronate 2 mg or placebo (44.6 and 33.1 weeks, respectively) (Figure 2). The difference in median time was significant ($P = 0.018$) between the ibandronate 6 mg and placebo treatment groups.

Secondary efficacy outcomes

Bone pain. Patients in the ibandronate 6 mg group showed a significantly improved bone pain score over time compared with the placebo and ibandronate 2 mg groups (Figure 3). Furthermore, patients treated with placebo and the 2 mg dose experienced a transient decrease, then an increase, in pain score. The 6 mg patient group experienced a rapid initial decrease in pain score that remained below baseline score throughout the study. Analgesic use was lower in both ibandronate groups than in the placebo group, indicating that the improvement in pain was not due to increasing use of analgesics [20].

Safety

Four randomised patients did not receive any study medication and so 462 patients were included in the safety evaluation. Exposure to treatment was different between the groups, with patients in the 6 mg and 2 mg groups spending more time on study drug (median time from first intake of medication to 28 days after last intake) than the placebo group (18.4 and 19 months versus 13.2 months). At least one adverse event was experienced by the majority of patients during the study (up to 28 days after last drug administration) (93% ibandronate 6 mg, 99% ibandronate 2 mg, 99% placebo). The majority of adverse events were related to the underlying disease, with malignancy progression the most common adverse event observed, and recorded by a similar percentage of patients in all three groups. There were no major differences in adverse events between treatment groups. More patients in the placebo group experienced leukopenia, while the incidence of flu-like syndrome and arthralgia was slightly higher in the two ibandronate groups.

More than 50% of patients in all three treatment groups experienced serious adverse events, with more than 98% considered unrelated to treatment. The proportion of patients experiencing serious adverse events was higher in the placebo group (63%) than the 6 mg (53%) or 2 mg (58%) ibandronate groups. The most

Table 2. Primary reason for premature withdrawal from the study

	Placebo [*n* (%)]	Ibandronate 2 mg [*n* (%)]	Ibandronate 6 mg [*n* (%)]
Adverse event	46 (29)	41 (27)	38 (25)
Death	25 (16)	16 (10)	23 (15)
Refused treatment	21 (18)	12 (8)	14 (9)
Lost to follow-up	5 (3)	5 (3)	3 (2)
Protocol violation	3 (2)	4 (3)	1 (1)
Inappropriate enrolment	1 (1)	0 (0)	1 (1)
Other reasons	8 (5)	4 (3)	8 (5)
Total	109 (69)	82 (53)	88 (57)

Table 3. Mean SMPR at last available efficacy date per patient year (revised event ratio method)

	Placebo (n = 158)	Ibandronate 2 mg (n = 154)	Ibandronate 6 mg (n = 154)	P value[a]
All new bone events	1.48	1.31	1.19	0.004
		P = 0.152[b]	P = 0.004[b]	
Vertebral fractures	0.82	0.70	0.71	0.023
		P = 0.028[b]	P = 0.023[b]	
Non-vertebral fractures	0.81	0.70	0.72	0.421
		P = 0.235[b]	P = 0.396[b]	
Events requiring radiotherapy	1.09	0.95	0.91	0.012
		P = 0.062[b]	P = 0.011[b]	
Events requiring surgery	0.62	0.50	0.56	0.060
		P = 0.013[b]	P = 0.075[b]	

[a]Global comparison between treatments using Jonckheere–Terpstra test.
[b]Pairwise comparisons versus placebo using Wilcoxon rank sum test. Not adjusted for multiplicity.
SMPR, skeletal morbidity period rate.

Table 4. Total number of skeletal complications (events) per patient and proportion of patients with events

	Placebo (n = 158)	Ibandronate 2 mg (n = 154)	Ibandronate 6 mg (n = 154)	P value
Mean events per patient (n)	3.64	4.24	2.65	0.032[a]
		P = 0.905[b]	P = 0.025	
Patients with events (%)	62.0	62.3	50.6	0.062[c]
		P = 1.000[d]	P = 0.052[d]	

[a]Global comparison between treatments using Jonckheere–Terpstra test.
[b]Pairwise comparisons versus placebo using Wilcoxon rank sum test.
[c]Global comparison between treatments using exact Pearson χ^2-test for 2×3 table.
[d]Pairwise comparisons between active treatment groups and placebo using exact Pearson χ^2-test for 2×2 table.

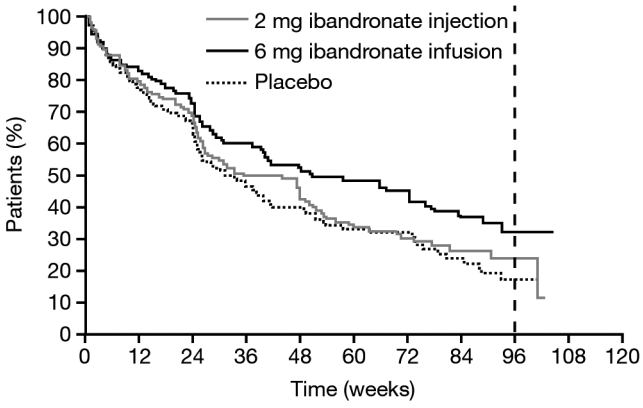

Figure 2. Time to first new bone event.

common serious adverse event was malignancy progression, which also occurred more frequently in the placebo group (40%) than in the 6 mg (53%) or 2 mg (58%) ibandronate groups. Only three patients experienced serious adverse events that were considered to be related to treatment; one in the ibandronate 2 mg group (asthenia and hydronephrosis) and two in the ibandronate 6 mg group (one with bone pain and one with lung oedema).

There was no evidence of renal toxicity associated with ibandronate treatment: the incidence of renal adverse events was low and did not differ between placebo and ibandronate groups. The percentage of patients with increased creatinine levels (300 mM) was low and was similar between treatment groups (2.6% ibandronate 6 mg, 0.7% ibandronate 2 mg, 1.3% placebo). No patient withdrew from the study due to renal adverse events.

A total of 34 patients died during the study (up to 28 days following the last dose of study drug). Of these, 15 were in the placebo group, 11 in the 2 mg and eight in the 6 mg ibandronate groups. Death was most commonly due to malignancy progression, and no death was considered to be related to study treatment.

Discussion

This study demonstrates that i.v. ibandronate treatment is effective in reducing the incidence of new skeletal complications in women with breast cancer and bone metastases. A beneficial

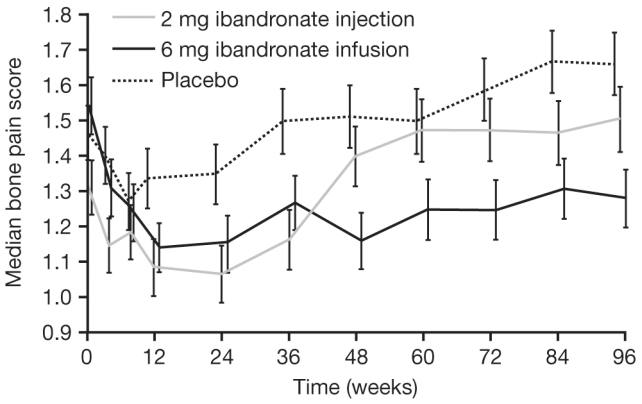

Figure 3. Median bone pain score.

effect of 6 mg ibandronate was observed on the SMPR (the number of 12-week periods with new bone events, allowing for time on study), as well as the overall number of periods with new bone events, the proportion of patients with new bone events and the time to occurrence of the first new bone event. Within the individual components of the primary end point, the most marked effect was seen on the incidence of vertebral fractures and radiotherapy for bone events. Although it is possible that restricted availability of radiotherapy could have biased the results, this form of treatment was available at all of the study centres.

Previous studies have demonstrated efficacy of i.v. bisphosphonates in reducing the incidence of new bone events [11, 12, 15]. Unlike the present study, however, these trials were in selected patient populations. In addition, the primary end point was the skeletal morbidity rate, which, unlike the SMPR used in our study, may increase the likelihood of 'multiple counting' of related events. Overall skeletal morbidity in the placebo group was lower in the current study than seen in the earlier studies using pamidronate [11, 12]. This may have been partly related to differences in methodology between the studies. In the pamidronate studies, all skeletal-related events were recorded separately. In contrast, in the current study, only one skeletal-related event could count within a given 12-week period; an event such as fracture that subsequently led to surgery and/or radiation only contributed once to the analysis. In addition, the patient population in the current study may have had less advanced metastatic disease at baseline: 45% of patients in the placebo group and ~58% in each of the ibandronate groups completed 60 weeks on the study, whereas in the two pamidronate studies only 26% of patients on placebo and 31% of patients on treatment completed the full 48 weeks of study [15]. The proportion of patients who did not experience any new bone events was 49% in the ibandronate 6 mg group and 47% in the pamidronate trials. Furthermore, ibandronate 6 mg reduced and maintained bone pain scores below baseline during the 96-week study phase. This contrasts favourably with the studies of pamidronate, where pain scores were not maintained below baseline throughout the whole of the study period [11, 12]. In our study, the median time from randomisation to first new bone event with ibandronate 6 mg was 50.6 weeks, whereas the median time from randomisation to first new bone event in the pamidronate trials was 50.8 weeks [11, 12]. Our results suggest that ibandronate is at least as effective as pamidronate in patients with breast cancer and bone metastases. Importantly, ibandronate was associated with additional clinical benefits on bone pain scores. The efficacy of ibandronate shown here was thus achieved in a patient population representative of those for whom bisphosphonate treatment is clinically recommended—that is, all patients with breast cancer and bone metastases, irrespective of the size of lytic lesion, mode of cancer treatment or presence of other metastases. American Society of Clinical Oncology guidelines recommend use of bisphosphonates as soon as bone metastases are diagnosed [14].

A separate analysis of secondary efficacy parameters from the study by Diel et al. [20] has shown that ibandronate 6 mg significantly improved quality of life compared with placebo. In addition, treatment with ibandronate significantly improved survival in the subpopulation of patients with bone and visceral metastases.

In terms of safety, although the majority of patients experienced serious adverse events, these were overwhelmingly related to the underlying disease, with less than 2% considered to be related to treatment. Differences between the ibandronate and placebo groups were small, and there was no evidence of renal toxicity of ibandronate. Adverse effects on renal function can occur with i.v. administration of currently available bisphosphonates. For example, the 8 mg dose of zoledronate was withdrawn from all clinical trials because of concerns over renal safety [21]. Moreover, in a phase III trial of zoledronate and pamidronate in patients with bone metastases from breast cancer, the 5-min infusion time for zoledronate was increased to 15 min to limit the amount of renal impairment [22]. Before the amendment, 13.2% of patients experienced deterioration of renal function, whereas 8.8% of patients still experienced elevated serum creatinine levels when the infusion time was increased. After the 15-min infusion amendment the incidence of renal impairment was similar between zoledronate (8.8%) and pamidronate (8.2%). In the present study, the proportion of patients with increased creatinine levels was similar between groups (2.6% ibandronate 6 mg versus 1.3% placebo). Although the definitions of renal dysfunction vary between studies, our results suggest that ibandronate has a more favourable renal safety profile than other bisphosphonates. Comparative trials are warranted.

The uneven withdrawal rate between the treatment and placebo groups is an important factor in interpretation of these data. The higher withdrawal rate for the placebo group meant that these patients had less time on study and therefore less opportunity to experience a skeletal-related event. This factor would be expected to favour placebo, but patients treated with ibandronate experienced fewer skeletal-related events overall.

Both doses of ibandronate demonstrated some efficacy, but the 6 mg dose appeared more effective without increased toxicity. These data therefore indicate that i.v. ibandronate 6 mg is an effective and well-tolerated treatment for patients with breast cancer and bone metastases.

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