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Long-Term Safety of Intravenous Ibandronic Acid for Up to 4 Years in Metastatic Breast Cancer

An Open-Label Trial

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Abstract

Background and objective: Despite their widespread use in metastatic bone disease, some bisphosphonate drugs are associated with adverse events (AEs), particularly renal toxicity, adding to treatment burdens and increasing healthcare costs. Ibandronic acid is a single-nitrogen bisphosphonate with high efficacy against bone events and metastatic bone pain, and a renal safety profile comparable to that of placebo. In this study, the safety of ibandronic acid was examined over a period of 4 years.

Patients and methods: During an initial 96-week period, breast cancer patients with bone metastases were randomised in double-blind fashion to placebo or ibandronic acid 6mg administered by intravenous infusion over 1–2 hours every 3–4 weeks as part of a previously reported phase III trial (MF 4265 study). All patients completing the phase III trial were offered open-label active treatment for a further 96 weeks (extension phase). A total of 62 patients received ibandronic acid 6mg in this extension phase and were classified according to their initial treatment (placebo/ibandronic acid 6mg [placebo/6mg] and ibandronic acid 6mg/ibandronic acid 6mg [6mg/6mg] groups). Safety was assessed by AE reports and clinical laboratory evaluations.

Results: During the 4-year study, most patients experienced at least one AE, with malignancy progression being most commonly reported. However, fewer treatment-related AEs were reported in the extension phase (placebo/6mg: 6.3% [1/16]; 6mg/6mg: 13.0% [6/46]) than in the initial phase of the study (placebo: 56.3% [9/16]; 6mg: 67.4% [31/46]). Serious AEs were mainly due to malignancy progression. There were no clinically relevant renal AEs, and in both groups, serum creatinine levels were similar for up to 4 years.

Conclusion: This 96-week open-label safety extension of a phase III, placebo-controlled trial demonstrates that long-term use of intravenous ibandronic acid is well tolerated.

Introduction

Bisphosphonates have become the standard treatment for metastatic bone disease.[1] These drugs are given either intravenously or orally. Intravenous administration has advantages over the oral route (e.g. assured compliance, total bioavailability and the avoidance of gastrointestinal adverse events). However, reports of renal function deterioration with intravenous pamidronic acid and zoledronic acid have increased in recent years,[2-12] leading to a recommendation for regular patient observation and renal function monitoring before each infusion.[13] This, together with management of drug-related adverse events, adds both to the treatment burden of patients with advanced cancer and to the healthcare resources needed for bisphosphonate therapy.[14]

Ibandronic acid is a single nitrogen-containing bisphosphonate with higher comparative protein binding and a shorter comparative renal tissue half-life than other bisphosphonates.[15,16] Ibandronic acid has demonstrated efficacy for the prevention of skeletal events in patients with breast cancer and bone metastases. In a phase III trial (MF 4265 study), the recommended clinical dose of intravenous ibandronic acid (6mg every 3–4 weeks) significantly prevented skeletal events and reduced metastatic bone pain over 2 years.[17] Ibandronic acid was also well tolerated, with an adverse event profile comparable to that of placebo. In particular, the incidence of renal adverse events was low (4.0%) and similar to placebo (4.5%). Because bisphosphonate therapy is usually continued for the rest of the patient's life (which may be several years), long-term drug safety and tolerability are of paramount importance to patients and physicians. This paper reports the results of an extension phase of the MF 4265 study,[17] providing an assessment of the tolerability of intravenous ibandronic acid in breast cancer patients with metastatic bone disease for up to 4 years of treatment.

Patients and Methods

Patients

Patients entering the initial phase III trial (MF 4265)[17] were women with histologically confirmed breast cancer and radiologically confirmed bone metastases. Patients had to have a WHO performance status of ≤2, to be ≥18 years of age, and to have given written informed consent. At the end of the 96-week phase III trial, every patient could continue active treatment, within 4 weeks of receiving the last dose in the trial.

Patients were excluded from the trial if they were pregnant or breast-feeding; had impaired renal function (serum creatinine >3 mg/dL), Paget's disease of the bone, primary hyperparathyroidism or a history of aspirin-sensitive asthma; or had received an aminoglycoside antibacterial within 4 weeks before the start of the trial.

Trial Design

In the phase III trial (MF 4265), a total of 466 patients were randomised to receive placebo (n = 158) or ibandronic acid 2mg (n = 154) by intravenous bolus injection, or ibandronic acid 6mg (n = 154) by intravenous infusion over 1–2 hours.[17] Treatment was given every 3–4 weeks for up to 96 weeks. Randomisation was carried out by the investigators according to a predetermined randomisation list. The study was blinded with respect to placebo or ibandronic acid, but the dose was open label because of differences in the mode of delivery. All patients received standard antineoplastic treatment (i.e. cytostatic drugs or hormonal therapy). In comparison with placebo and with ibandronic acid 2mg, ibandronic acid 6mg significantly reduced the skeletal morbidity period rate and was therefore chosen for further clinical development.

Once the placebo-controlled period of the phase III trial had ended, all patients were offered continuation of active treatment (ibandronic acid 2mg or ibandronic acid 6mg) for a further 96 weeks (or until withdrawal). Ibandronic acid 2mg was also used in the extension phase, since at the beginning of this phase only a small proportion of all patients had finished the initial phase III trial and the superiority of the 6mg dose was not obvious at that point. Those patients given placebo in the phase III study and wishing to enter the extension phase were assigned by the investigator to active treatment. There were no restrictions on concomitant medications (except those specified as exclusion criteria). Here we report only the results of patients given ibandronic acid 6mg, as this is the recommended clinical dose.

This trial was conducted in accordance with the local medicines legislation, the principles of the Declaration of Helsinki, and the Guidelines on Good Clinical Practice at the time the trial began.

Trial Outcomes

The objective of the 96-week extension phase of the trial was to determine the long-term safety and tolerability of intravenous ibandronic acid. Safety was assessed by adverse event (AE) reports and clinical laboratory evaluations.

AEs were recorded throughout the phase III trial and extension phase, and for up to 28 days after the last dose of trial treatment. An AE was defined as any undesired, noxious or pathological change in a patient indicated by signs, symptoms and/or laboratory changes that occurred with treatment, whether considered related to treatment or not. The investigator determined the cause of each AE. An AE was considered serious if it was fatal or acutely life-threatening, required inpatient care (or prolonged existing hospital stay), resulted in persistent or significant disability or incapacity, or resulted in malignancy or congenital malformation/anomaly.

AEs are reported for all patients who entered the 96-week extension phase of the trial and are divided into those in the initial study (years 1–2), and those in the extension phase (years 3–4).

Laboratory measurements were made every 4 weeks up to week 12, and then every 12 weeks. They included haematology parameters (haemoglobin, platelets, leucocyte and lymphocyte counts) and blood chemistry parameters (calcium [adjusted for albumin concentration], alkaline phosphatase, AST, γ-glutamyltransferase, creatinine and albumin).

Data Analysis

The safety population included all patients who received at least one dose of trial treatment in the extension study and had at least one follow-up assessment. Laboratory values were assessed by examining absolute changes from baseline in the original randomised trial, according to criteria from the National Cancer Institute.[18] Deterioration in renal function was defined as an increase in serum creatinine of 0.5 mg/dL from baseline if the baseline was <1.4 mg/dL, an increase of 1.0 mg/dL from baseline if the baseline was ≥1.4 mg/dL, or an increase of twice the baseline value.

Results

Demographics

Sixty-two patients received ibandronic acid 6mg by intravenous infusion in the 96-week extension phase of the phase III trial (figure 1). Twenty-six

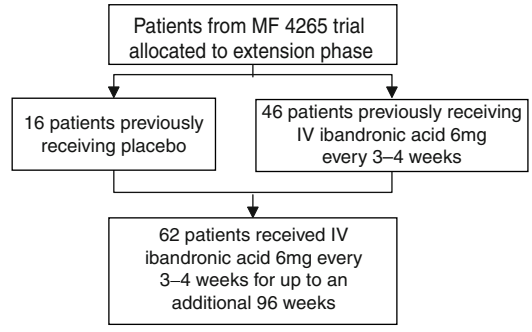

Fig. 1. Flow diagram of the disposition of the study population included in the 96-week open-label safety extension of the MF 4265 trial.[17] The initial study MF 4265 was a randomised, double-blind study that compared two doses of ibandronic acid (2mg, n = 154 and 6mg, n = 154) with placebo (n = 158). **IV** = intravenous.

percent of patients (n = 16) had received placebo for 2 years in the initial trial (placebo/6mg group). The remaining patients (74%, n = 46) were treated with ibandronic acid 6mg in both the placebo-controlled and extension phases of the study (6mg/6mg group). The mean age of patients was 55 years in the placebo/6mg group (range 39–68 years) and 56 years in the 6mg/6mg group (range 36–75 years).

Safety Parameters

All 62 patients were evaluated for safety parameters. Most patients had at least one AE over the 4-year period (initial trial: placebo/6mg 100% [n = 16/16], 6mg/6mg 95.7% [n = 44/46]; extension trial: placebo/6mg 68.8% [n = 11/16], 6mg/6mg 80.4% [n = 37/46]). Malignancy progression was the most common AE. Table I summarises the percentage of patients with AEs in the initial and extension phases. The median treatment duration for patients given placebo in the first 2 years followed by ibandronic acid 6mg was 28.5 months (range 20.0–40.0 months, n = 16). For those patients given ibandronic acid in both study phases the median treatment duration was 29.5 months (range 21.0–41.0 months, n = 46).

Overall, nine patients died in the extension phase, but no death was considered related to treatment. The most common AE leading to death was malignancy progression. This affected 6/46 patients in the 6mg/6mg group; one patient died as a result of cancer progression (asthenia) [n = 1/46] and a second as a result of pulmonary embolus (n = 1/46). One patient in the placebo/6mg group (n = 16) died as a result of leg thrombosis.

Treatment-related AEs were reported by seven patients during the extension phase (placebo/6mg: 6.3% [n = 1/16]; 6mg/6mg: 13.0% [n = 6/46]), compared with 40 patients in the initial study period (placebo/6mg: 56.3% [n = 9/16]; 6mg/6mg: 67.4% [n = 31/46]) [table II]. During the extension phase these treatment-related AEs included headache (n = 1/16) in the placebo/6mg group, and bone disorder, joint disorder, muscle cramps, chills, gastroenteritis, breast pain, rash and dyspnoea (all

Table I. Summary of patients experiencing adverse events (AEs) during the initial study (years 1–2) and extension phase (years 3–4)

	Initial study phase [no. of patients (%)]		Extension phase [no. of patients (%)]	
	placebo/6mg (n = 16)	6mg/6mg (n = 46)	placebo/6mg (n = 16)	6mg/6mg (n = 46)
At least one AE	16 (100)	44 (95.7)	11 (68.8)	37 (80.4)
Treatment-related AEs	9 (56.3)	31 (67.4)	1 (6.3)	6 (13.0)
Serious AEs	5 (31.3)	12 (26.1)	3 (18.8)	13 (28.3)
AEs leading to withdrawal			2 (12.5)	4 (8.7)
AEs leading to death			1 (6.3)	8 (11.4)

placebo/6mg = placebo/ibandronic acid 6mg group; **6mg/6mg** = ibandronic acid 6mg/ibandronic acid 6mg group.

Table II. Treatment-related adverse events with intravenous ibandronic acid that occurred during the initial study (years 1–2) and extension phase (years 3–4)

	Initial study phase [no. of patients (%)]		Extension phase [no. of patients (%)]	
	placebo/6mg (n = 16)	6mg/6mg (n = 46)	placebo/6mg (n = 16)	6mg/6mg (n = 46)
All body systems	9 (56.3)	31 (67.4)	1 (6.3)	6 (13.0)
Body as a whole	1 (6.3)	8 (17.4)		1 (2.2)
Cardiovascular system		2 (4.3)		
Digestive system	2 (12.5)	11 (23.9)		1 (2.2)
Haematological and lymphatic system	2 (12.5)	1 (2.2)		
Injection site reactions	1 (6.3)	1 (2.2)		
Metabolic and nutritional disorders	2 (12.5)	9 (19.6)		
Musculoskeletal system	1 (6.3)	8 (17.4)		3 (6.5)
Nervous system	3 (18.8)	8 (17.4)	1 (6.3)	
Respiratory system	1 (6.3)	7 (15.2)		1 (2.2)
Skin and appendages	2 (12.5)	4 (8.7)		2 (4.3)
Urogenital system	1 (6.3)	2 (4.3)		

placebo/6mg = placebo/ibandronic acid 6mg group; **6mg/6mg** = ibandronic acid 6mg/ibandronic acid 6mg group.

n = 1/46) in the 6mg/6mg group. All treatment-related AEs were either mild or moderate (table II).

Thirty-three patients experienced serious AEs (initial trial: placebo/6mg 31.3% [n = 5/16], 6mg/6mg 26.1% [n = 12/46]; extension trial: placebo/6mg 18.8% [n = 3/16], 6mg/6mg 28.3% [n = 13/46]). The most common serious AE was malignancy progression, reported by 13 patients (initial trial: placebo/6mg 12.5% [n = 2/16], 6mg/6mg 4.3% [n = 2/46]; extension trial: 6mg/6mg 19.6% [n = 9/46]). No serious AE was considered related to treatment.

In the extension phase, 12.5% of patients (n = 2/16) in the placebo/6mg group and 8.7% of patients (n = 4/46) in the 6mg/6mg group withdrew because of AEs. Approximately 6% of patients withdrew because of progression of the underlying disease (n = 1/16 in the placebo/6mg group and n = 3/46 in the 6mg/6mg group). Other AEs leading to withdrawal were leg thrombosis in the placebo/6mg group (n = 1/16) and arrhythmia in the 6mg/6mg group (n = 1/46). No renal AEs led to withdrawal.

Renal safety parameters were as expected for this population of patients with stage IV breast cancer and bone metastases. Median changes in serum creatinine from baseline in the initial phase to last value in the extension phase were similar in both groups. In the placebo/6mg group, median serum creatinine levels changed from 0.85 at baseline to 0.90 mg/dL at endpoint; in the 6mg/6mg group the corresponding change was from 0.91 to 0.90 mg/dL (figure 2). At 96 weeks, the median change in serum creatinine from baseline was from 0.85 to 0.87 mg/dL in the placebo/6mg group and from 0.91 to 0.90 mg/dL in the 6mg/6mg group (p = 0.918 from baseline to last available value in all extension study patients). The maximum individual increase from baseline was 1.33 mg/dL in the 6mg/6mg group, and 0.55 mg/dL in the placebo/6mg group. At 4 years, both groups had a median serum creatinine that was within 0.1 mg/dL of baseline values (figure 2). In the initial study phase, renal deterioration was observed in no patients in the placebo/6mg group and in 2% of patients (n = 1/46) in the 6mg/6mg group (maximum serum creatinine = 1.52 mg/dL). In the follow-up

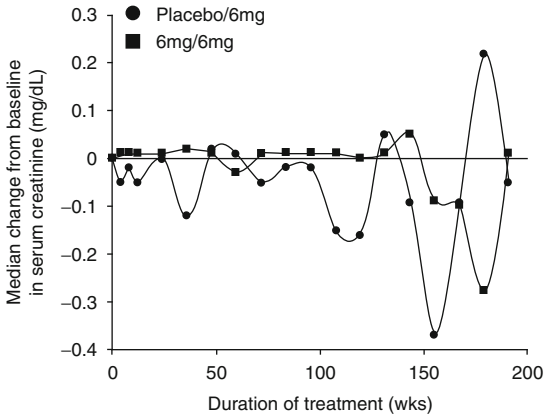

Fig. 2. Median change in serum creatinine from baseline (before initial randomisation). **placebo/6mg** = placebo/ibandronic acid 6mg group; **6mg/6mg** = ibandronic acid 6mg/ibandronic acid 6mg group.

phase, 6% of patients (n = 1/16) had renal deterioration in the placebo/6mg group, compared with 9% of patients (n = 4/46) in the 6mg/6mg group (maximum serum creatinine = 3.20 mg/dL). The small patient numbers in years 3–4 may have contributed to the increased variability of median serum creatinine changes from baseline seen in the latter phase of this study.

Discussion

This 4-year safety assessment supports the findings of the initial 2-year placebo-controlled phase III trial[17] and shows that long-term use of intravenous ibandronic acid 6mg is well tolerated. Fewer AEs overall were experienced in the extension phase compared with the initial phase III study; this was true for patients receiving placebo/6mg and 6mg/6mg. Treatment-related AEs were also fewer in both groups during the extension phase compared with the initial study. Serious AEs were essentially due to malignancy progression. It is difficult to compare the two groups accurately, because of non-randomisation of patients to study groups in the extension phase and the discrepancy in the number of patients in each group (placebo/6mg group n = 16; 6mg/6mg group n = 46). The very low incidence of treatment-related AEs in either of these study groups is a good indication of long-term ibandronic acid safety.

No treatment-related renal AEs were reported, and serum creatinine levels were similar for up to 4 years in both groups. This suggests that, compared with other intravenous bisphosphonates,[2-12] ibandronic acid has a more favourable renal safety profile.

The renal safety of high- or loading-dose intravenous ibandronic acid for severe metastatic bone pain has also been demonstrated in open-label studies, in which ibandronic acid 6mg was infused over 1 hour on three consecutive days,[19] and ibandronic acid 4mg was infused over 2 hours on four consecutive days.[20] Randomised, controlled trials of loading-dose ibandronic acid for the treatment of metastatic bone pain are underway.

Preclinical data help to explain the renal safety of ibandronic acid. Its shorter tissue terminal half-life (24 days) as compared with zoledronic acid (150–200 days) probably prevents accumulation of ibandronic acid in the kidneys and cumulative renal toxicity after long-term intermittent administration.[15,16] Another possible explanation for the renal safety of ibandronic acid is its high protein binding in comparison with other bisphosphonates (Center for Drug Evaluation and Research [CDER] New and Generic Drug Approval 1998–2003). High levels of protein binding limit bisphosphonate entry into kidney tubule cells and prevent the development of high, toxic levels of active bisphosphonate within the cell.

There are few data in the literature on the long-term renal safety of intravenous bisphosphonates. Two retrospective reviews that specifically evaluated the long-term safety of bisphosphonates (>24 months) suggested that prolonged treatment is well tolerated.[21,22] However, increases in serum creatinine were seen in both retrospective studies, with notable grade 1 increases observed in 12% of patients in the study by Guarneri et al.[22] The clinical implications of bisphosphonate tolerability are important, particularly given the potential impact of drug-related renal impairment on patients and healthcare resources. The absence of long-term safety issues suggests that intravenous ibandronic acid will not add to the toxicity burden of other anti-

cancer therapies. Ibandronic acid may also reduce healthcare resource use and costs arising from safety monitoring and management of drug-related AEs (particularly renal toxicity).[23]

An oral formulation of ibandronic acid is also available. In phase III trials in breast cancer patients with bone metastases, oral ibandronic acid 50 mg/day reduced skeletal morbidity to a similar and statistically significant extent as demonstrated in the intravenous ibandronic acid trial.[24] An extension phase of the oral ibandronic acid trials, using the same methodology as reported here, showed that oral ibandronic acid 50 mg/day was also well tolerated for up to 4 years of treatment, with good gastrointestinal tolerability.[25] Intravenous and oral ibandronic acid therefore represent important new treatment options for the management of metastatic bone disease. While oral ibandronic acid is convenient for long-term treatment at home, intravenous ibandronic acid may be particularly suitable in the hospital setting for patients receiving concomitant intravenous chemotherapy.

Conclusion

This 96-week open-label safety extension of a phase III, placebo-controlled trial shows that intravenous ibandronic acid is generally well tolerated for up to 4 years.

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