Long-Term Renal Safety Profile of Ibandronate 6 mg Infused over 15 Minutes

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Key Words
Breast cancer · Ibandronate · Renal safety · Bone metastasis

Summary
Background: In an earlier study, intravenous (i.v.) ibandronate 6 mg administered every 3–4 weeks had a similarly good renal safety profile whether infused over 15 or 60 min in women with breast cancer and bone metastases. This current study focuses on the renal safety of the extended use of ibandronate. Patients and Methods: Patients completing the original study could choose to enter a follow-up phase and continue (or switch) to receive ibandronate 6 mg by 15-min i.v. infusion every 3–4 weeks. The primary endpoint was the percentage of patients with a serum creatinine increase of ≥44.2 μmol/l (= 0.5 mg/dl) from core baseline. Results: Fourteen patients entered the follow-up phase and received a median of 16 infusions (range: 9–24). No patient reached the primary endpoint. Most adverse events were mild to moderate in intensity. None of the 6 reported treatment-related adverse events was considered severe or reported as a serious adverse event. Conclusions: Ibandronate was well tolerated when administered as a 6-mg i.v. infusion over 15 min every 3–4 weeks during the follow-up phase to the earlier core study. No evidence of any treatment-related deterioration in renal function was noted, and no new or unexpected adverse events occurred.

Schlüsselwörter
Brustkrebs · Ibandronat · Nierensicherheit · Knochenmetastasen

Zusammenfassung
**Introduction**

Bisphosphonates are standard treatment to prevent skeletal complications of bone metastases [1, 2]. In patients with metastatic breast cancer, the American Society of Clinical Oncology guidelines recommend starting bisphosphonates at the time of diagnosis of radiologically confirmed bone metastases, and to continue this treatment until there is a substantial decline in performance status [3]. Ibandronate, a nitrogen-containing bisphosphonate, is indicated for the prevention of skeletal-related events in patients with breast cancer and bone metastases [4]. Studies of ibandronate 6 mg intravenous (i.v.) have demonstrated significantly reduced skeletal morbidity period rates (number of 12-week periods with new bone events) compared with placebo (p = 0.004), decreases in bone pain scores and analgesic use, and an improved quality of life [5–7]. Some nitrogen-containing bisphosphonates are associated with an increased risk of renal toxicity, especially after rapid i.v. infusion [8–13]. In two double-blind, randomized phase III studies comparing zoledronic acid with denosumab, renal failure was reported in 2.5% of patients with breast cancer [14] and in 2.8% of patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma [15] receiving zoledronic acid. A study of the effect on renal function of repeated 15-min infusions of ibandronate 6 mg in women with breast cancer and bone metastases was completed in 10 centers in Austria, 7 centers in Switzerland, and 1 center in Germany [16]. Patients received ibandronate 6 mg i.v. either as a 15-min infusion (n = 102) or a 60-min infusion (n = 28) every 3 or 4 weeks for 6 months. The 60-min arm was regarded as the control arm. The results showed that ibandronate administered over 15 min was well tolerated with a safety profile consistent with that of the 60-min infusion. No evidence for any treatment-related deterioration in renal function was seen, as assessed by the change from baseline in serum creatinine, calculated creatinine clearance, or in the urinary excretion of markers of glomerular and tubular function. After the completion of the 6-month core trial, patients enrolled in the Swiss centers were given the option to enter a follow-up phase until reimbursement. Patients could choose either to continue treatment with the 15-min infusion of i.v. ibandronate every 3 or 4 weeks or to switch to oral ibandronate (50 mg tablets daily). The objective of the follow-up phase was to continue to investigate the safety and tolerability of 15-min i.v. ibandronate infusions, with special focus on nephrotoxicity. Patients opting for oral ibandronate were not followed after the final visit of the core trial. To date, this is the first published long-term prospective study of ibandronate with a primary endpoint of renal safety.

**Patients and Methods**

**Study Design**

A prospective, multicenter, open-label study was conducted for a total of 18 months between September 2004 and February 2006 at 2 centers in Switzerland.

**Inclusion and Exclusion Criteria**

Eligible women were aged ≥ 18 years with histologically or cytologically confirmed breast cancer and at least one osteolytic, mixed or blastic bone metastasis confirmed by X-ray, computed tomography, or magnetic resonance imaging, and had completed the 6-month treatment phase of the core trial. Exclusion criteria for the core study were as reported previously [16]. The study was conducted in accordance with the Declaration of Helsinki (1996) with ethical approval from local ethics committees and patients’ written informed consent.

**Treatment**

Ibandronate 6 mg i.v. infusions were administered over 15 min every 3 or 4 weeks. A time window of ± 7 days and a change of schedule were permitted. In contrast to the core trial, but as occurs in clinical practice, unrestricted use of concomitant treatment was allowed. Medications known to be nephrotoxic could be used with caution.

**Assessments**

Blood samples for the assessment of serum creatinine and calculated creatinine clearance (Cockcroft-Gault formula) were taken at each study visit (visits 8–14). Routine urinalysis laboratory tests (α-2-macroglobulin, immunoglobulin G, transferrin, albumin, α-1-microglobulin, retinol-binding protein, total protein, creatinine, monoclonal free light chains (Bence-Jones protein), and dipstick results of erythrocytes, leukocytes, and nitrite) were performed at each scheduled visit, and vital signs (blood pressure, pulse, weight, body mass index, and body temperature) were assessed at visits 12 and 14. Blood and urine tests were performed at a central laboratory, but, unlike in the core phase of the trial, the results were not required before the next infusion. Adverse events (AEs) were monitored throughout the study.

**Endpoints**

As in the core study, the primary endpoint was the percentage of patients with a serum creatinine increase of ≥ 44.2 μmol/l (= 0.5 mg/dl) from baseline.

**Statistical Analysis**

Continuous data were summarized by mean, standard deviation, median, and range (minimum, maximum). Categorical data were presented using absolute and relative frequencies.

**Results**

Two of 7 Swiss centers participated in the follow-up phase. These 2 sites had enrolled 27 patients in the core study (15-min arm: 23 patients; 60-min arm: 4 patients). Of the 22/27 patients who completed the 6-month core trial, 14 were enrolled into the follow-up phase, 13 of the 14 patients continued with the 15-min i.v. infusion to which they had been randomized at study entry, and 1 patient switched from the 60-min i.v. infusion arm to the ibandronate 15-min i.v. infusion (fig. 1). 6 patients decided to continue treatment with ibandronate tablets. Two patients continued with 15-min i.v. infusions of ibandronate outside the follow-up phase, because their health insurance provided reimbursement. The median number of infusions was 16 (range: 9–24); 8 patients (56%) received ≥ 16 infusions (2 patients (14%) received 23 infusions and a further 2 patients (14%) received 24 infusions).
Renal Function
None of the 14 patients included in the follow-up phase met the criteria for an increase from baseline in serum creatinine of ≥ 44.2 µmol/l. No obvious relationship between the number of ibandronate infusions and either serum creatinine levels or the change from baseline in serum creatinine was observed; both remained relatively stable throughout the core study and follow-up period (fig. 2). For patients enrolled in the follow-up phase, the mean baseline serum creatinine value was 59.4 ± 10.6 µmol/l, and the mean baseline calculated creatinine clearance was 93.5 ± 28.5 ml/min (fig. 3). No clinically relevant change from baseline in either parameter was observed over the course of the trial: changes of between 1.3 and –10.6 µmol/l for mean serum creatinine values and between 17.3 and –1.8 ml/min for calculated creatinine clearance were observed (fig. 3). No clinically relevant urinalysis findings were noted during the follow-up phase.

Adverse Events
All 14 patients reported at least 1 AE during the follow-up phase. Arthralgia and nausea were reported by 5 patients (36%) and were the most commonly reported AEs. Fatigue was reported by 4 patients (29%), and bone pain, paresthesia, nasopharyngitis, and cough by 3 patients (21%) each. Two patients (14%) reported musculoskeletal chest pain, extremity pain, anorexia, vomiting, and toothache. The majority of AEs were mild or moderate (grade 1/2) in intensity. Four patients (29%) experienced 4 grade 3 (severe) AEs: sick sinus syndrome (also reported as a serious grade 3 AE), venous thrombosis, loss of appetite, and bone pain. Another patient (in addition to the patient with sick sinus syndrome) reported a serious AE: a mild worsening of her general condition. Neither serious AE was considered by the investigator to be related to study therapy, and both conditions improved following their treatment. Six AEs reported in 3 patients (21%) were considered by the investigator to be treatment-related although none was considered severe or reported as a serious AE. No patient died during the follow-up phase. No clinically relevant changes from baseline in vital signs were reported during the follow-up study.
Discussion

In this small population of 14 patients continuing into the follow-up phase of the earlier, open-label, prospective core study [16], there was no evidence that the 15-min infusion of 6 mg i.v. ibandronate every 3–4 weeks was associated with a deterioration in renal function. Long-term administration (approximately 12–24 months) of i.v. ibandronate 6 mg was generally well tolerated with an AE profile consistent with that of the core study. No new or unexpected AEs related to extended i.v. ibandronate treatment were noted. This follow-up study supports the conclusions from the core trial [16] and preclinical research [17] that 6 mg ibandronate administered over 15 min does not cause renal tubular cell damage, interfere with renal tubular reabsorption, or affect glomerular filtration. Thus, 6 mg i.v. ibandronate administered over 15 min offers improved convenience to patients while maintaining the good tolerability profile reported with a 60-min infusion. Although the sample size for the follow-up study was small, the results are consistent with previously conducted clinical research [18, 19] and a growing body of other evidence suggesting that ibandronate has negligible nephrotoxicity and probably a better renal safety profile than other i.v. bisphosphonates [20]. This improved renal tolerability may be linked to differences in protein binding and renal tissue half-life [17]. Ongoing experience in the use of the regimen in real-life clinical practice will add to this accumulating data.

Conclusions

Ibandronate was well tolerated when administered as a 6 mg i.v. infusion over 15 min every 3–4 weeks for the 12-month follow-up phase to the 6-month core study. No evidence for any treatment-related deterioration in renal function, as assessed by the change from baseline in serum creatinine and calculated creatinine clearance, was noted, and no new or unexpected AEs were seen. The 15-min ibandronate infusion offers patients a convenient therapeutic option.

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Conflicts of Interest

Dr. Roger von Moos is an investigator in this study, has been an advisor for Roche Ltd, Novartis and Amgen, and has received speaker honoraria from Roche Ltd, Schering Plough, and Amgen. Prof. Dr. R. Steimer has received consultancy fees from Astra Zeneca and speaker honoraria from Organon. Dr. R. Angst was an employee of Bayer Healthcare for 1.5 years until April 2009. Dr. K. Schmieding is an employee of F. Hoffmann-La Roche and holds stocks with Roche. Dr. B. Thürlimann holds stocks with Roche and has received honoraria from Roche for advisory board and educational activities. Dr. C. B. Caspar and Dr. R. Inauen have no conflicts of interest.

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