

Aim of the study: Bone is a common site of metastasis in patients with breast cancer. Skeletal complications associated with bone metastasis are commonly treated with bisphosphonates. However, there are a number of side-effects associated with these, such as renal failure, hypocalcemia and osteonecrosis of the jaw. We aimed to determine the effects of ibandronic and zoledronic acid on serum creatinine (SCr), calcium (Ca), phosphorus (P), alkaline phosphatase (ALP) and estimated glomerular filtration rates (eGFR). The objective was to determine the safety of these bisphosphonates, especially zoledronic acid.

Material and methods: Forty-one patients diagnosed with breast cancer (all with bone metastasis) were enrolled. We retrospectively evaluated bisphosphonate type, duration of treatment, infusion time and the parameters SCr, Ca, P, ALP and eGFR.

Results: Nineteen patients were included in the zoledronic acid group and 22 in the ibandronic acid group. Mean age in the ibandronic acid group was 53.27 ± 11.01 , and 53.26 ± 9.98 in the zoledronic acid group. Median duration of administration in the ibandronic acid group was 11 (7-37) months, and 10 (7-57) months in the zoledronic acid group. SCr levels did not change significantly during the study period. Pre- and post-treatment Ca levels were also unchanged, but serum ALP levels in the ibandronic acid group and P levels in the zoledronic acid decreased after the final administration; eGFR was unchanged by the end of the study.

Conclusions: Zoledronic and ibandronic acid are safe modalities in the treatment of skeletal events in breast cancer patients with bone metastasis.

Key words: breast neoplasms, ibandronic acid, zoledronic acid, renal safety, creatinine.

Effects of zoledronic acid and ibandronic acid on renal functions and calcium, phosphorus and alkaline phosphatase levels in breast cancer patients with bone metastases: a retrospective analysis

Evren Fidan, Bulent Yildiz, Halil Kavgaci, Feyyaz Ozdemir, Fazil Aydin

Departments of Medical Oncology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey

Introduction

Bone is a common site of metastasis in patients with breast cancer [1]. Skeletal complications such as bone pain, pathological fractures, hypercalcemia of malignancy and spinal cord compression may occur in association with bone metastasis [2]. Bisphosphonates are agents that prevent osteoclast mediated bone destruction and are used in the standard treatment of skeletal related events [3].

Ibandronic and zoledronic acid are highly effective bisphosphonates [4]. Both contain nitrogen, and nitrogen-containing bisphosphonates have greater side-effects, including renal failure, hypocalcemia and osteonecrosis of the jaw [5]. Previous studies on the effect of bisphosphonates on renal safety have reported that renal toxicity may occur during treatment with zoledronic acid, but renal toxicity associated with ibandronic acid is so low as to be equivalent to placebos [4, 6].

The aim of this study was to evaluate the effects of zoledronic acid and ibandronic acid on renal functions, in addition to evaluating the pre- and post-treatment levels of serum calcium (Ca), phosphorus (P) and alkaline phosphatase (ALP) and especially the safety of zoledronic acid.

Material and methods

Patients were selected from those applying to the Karadeniz Technical University, Medical Faculty, Medical Oncology Clinic, in Turkey. Breast cancer patients with bone metastasis were selected and their data investigated retrospectively. Patients receiving bisphosphonates for more than 6 months were included in the analysis. Age, bisphosphonate type, duration of treatment and infusion time were noted. Patients with hypertension, diabetes mellitus or renal failure were excluded. Patients' serum biochemical parameters prior to the first administration and after the last were noted. In particular, creatinine, corrected serum Ca, P and ALP levels were recorded. Estimated glomerular filtration rates (eGFRs) were calculated according to age, gender, weight and creatinine levels using the Cockcroft-Gault formula [7].

Conformance of data obtained by measurement with normal distribution was investigated in each group using the Kolmogorov-Smirnov test. Our data did conform to normal distribution. Student's *t* test was used to compare data between groups. The paired *t* test was used to compare data in each group. Data obtained by measurement were expressed as arithmetic mean \pm standard deviation. Significance was set at $p < 0.05$.

Table 1. Comparison of ibandronic and zoledronic acid

	Ibandronic acid			Zoledronic acid		
	before treatment	after the last treatment	P value	before treatment	after the last treatment	P value
Ca (mg/dl)	9.54 ±0.83	8.47 ±2.35	0.088	7.98 ±3.58	8.11 ±2.99	0.87
P (mg/dl)	2.99 ±1.16	3.12 ±0.79	0.72	3.92 ±0.74	3.31 ±0.85	0.018
ALP (U/l)	214.05 ±101.40	167.21 ±104.60	0.049	252.60 ±208.08	177.40 ±195.56	0.17
Cr (mg/dl)	0.71 ±0.16	0.69 ±0.22	0.44	0.77 ±0.23	0.83 ±0.23	0.26
eGFR (ml/min)	102.48 ±29.7	110.25 ±36.03	0.22	94.23 ±28.9	92.73 ±38.2	0.69

Ca – calcium; P – phosphorous; ALP – alkaline phosphatase; Cr – creatinine; eGFR – Cockcroft-Gault

Table 2. Patient group classification according to the cumulative risk scale

	Ibandronic acid	Zoledronic acid	P value
Baseline Cr (mg/dl)	0.71 ±0.16	0.77 ±0.23	0.81
Last Cr (mg/dl)	0.69 ±0.22	0.83 ±0.23	0.082
Baseline eGFR (ml/min)	102.48 ±29.7	94.23 ±28.9	0.40
Last eGFR (ml/min)	110.25 ±36.03	92.73 ±38.2	0.15

Cr – creatinine; eGFR – Cockcroft-Gault

Results

Nineteen patients receiving zoledronic acid and 22 receiving ibandronic acid were selected on the basis of the inclusion criteria. Findings were analyzed retrospectively. Mean age was 53.27 ±11.01 years in the ibandronic acid group and 53.26 ±9.98 in the zoledronic acid group. There was no statistically significant difference between the groups in terms of age ($p = 0.50$). Patients receiving bisphosphonates for more than 6 months were included in the study. Median duration of use was 11 [mean 14.27 ±8.69 (7-38)] months in the ibandronic acid group and 10 [16.40 ±15.18 (7-57)] months in the zoledronic acid group. There were no differences between the groups in terms of duration of treatment ($p = 0.67$). Both agents were administered every 4 weeks. Zoledronic acid was administered in doses of 4 mg in 15 min, while ibandronic acid was administered in 6 mg doses with an infusion time of 15 min. Five patients in the ibandronic acid group and eight in the zoledronic acid group were receiving endocrine therapy. No statistically significant difference was determined in the groups' pre- and post-treatment creatinine levels. No statistically significant difference was determined between the groups in terms of final serum creatinine (SCr) levels. There was also no statistically significant difference in levels of serum Ca from the beginning to the final treatment. In the ibandronic acid group serum ALP levels decreased significantly ($p < 0.05$), and serum P levels in the zoledronic acid group decreased after the final administration ($p < 0.05$). eGFR was unchanged by the end of the study in both groups.

Discussion

Lower levels of renal complication are determined when bisphosphonates are used in appropriate doses and infusion

times [8]. Preclinical studies have shown that toxicity may change depending on renal accumulation [4]. Clinical studies with zoledronic acid have reported renal failure requiring dialysis or resulting in death [9]. The renal toxicity of zoledronic acid has not been fully established, but it may be related to high doses and administration time [6]. In addition, toxic acute tubular necrosis and collapsing focal segmental glomerulosclerosis have been implicated in the mechanism of renal impairment. One analysis comparing zoledronic acid and pamidronate determined that zoledronic acid established a 17% decrease in skeletal related events and had a similar renal safety level to that of pamidronate [10]. One series involving double blinded phase III studies determined that zoledronic acid reduced skeletal mediated events 20% more compared to pamidronate and had a similar level of renal safety. Ibandronic acid was determined to be more effective than placebo. It has also been determined to have similar safety in terms of side-effects [11]. One study of oral ibandronate in 44 patients determined a mean follow-up duration of 18.5 months, with no impairment in renal function [12]. Renal toxicity associated with ibandronic acid was so low as to be equivalent to placebos [4]. Ibandronic acid is thought to have less effect on renal function than zoledronic acid. This may be associated with binding to the plasma proteins and its half-life [8]. In this study we used bisphosphonates in appropriate doses and infusion times, so Cr levels and eGFR did not change by the end of the study. Decreased levels of serum ALP and P may be associated with decreased bone turnover.

Median use and median infusion times were similar in our study. SCr levels prior to first use and after the last dose did not change in either group. No renal failure was detected. No symptomatic hypocalcemia or osteonecrosis of the jaw were observed.

Finally, evaluation of renal functions showed that zoledronic acid is as safe as ibandronic acid. No renal dysfunction was determined during the study. However, renal disorders should be borne in mind in at-risk patients when initiating bisphosphonate therapy or changing from one bisphosphonate to another. Consideration should be given to multiple myeloma, diabetes mellitus, hypertension, advanced age and drug use that might affect renal functions. Renal functions must be evaluated and proper attention paid to sufficient hydration. Due to the small sample size involved here, this observation needs to be confirmed using larger cohorts, ideally in prospective studies.

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Address for correspondence:

Evren Fidan MD
Karadeniz Teknik Üniversitesi,
Tıp Fakültesi
Tibbi Onkoloji Bilim Dalı
61080, Trabzon, Türkiye
tel. +90-462-3775023
mob. +90-533-3449466
fax +90-462-3775023
e-mail: evrenfidan@yahoo.com

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