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Evaluation of Safety of Zoledronic Acid (3 Months Regimen) versus Zoledronic Acid (1 Month Regimen) Regarding the Treatment of Bone Metastasis

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Abstract

Background: Zoledronic acid, a third-generation amino bisphosphonate, reduces the incidence of skeletal-related events and pain in patients with bone metastases. The optimal dosing interval for zoledronic acid is uncertain.

Aim: To determine whether the Zoledronic acid 12 weeks regimen was equal to the Zoledronic acid 4 weeks regimen for safety profile with bone metastasis or not.

Patients and Methods: The study is a randomized, clinical trial that was conducted at the Clinical Oncology Department, Zagazig university hospitals in the period from December 2017 to December 2019. Patients with bone metastasis were enrolled in the study. Patients were randomized to receive zoledronic acid every 12 weeks (n = 54) group A vs. every 4 weeks (n = 54) group B for 2 years. Both groups were compared regarding the safety of Zoledronic acid.

Results: The studied groups A and B were matched regarding age and sex distribution. All patients in both groups had pre-treatment normal serum creatinine and serum calcium levels. There was no significant difference between group A and group B regarding post-treatment serum calcium and serum creatinine (p-value=0.243and 0.489) respectively. All patients in both groups did not have osteonecrosis of the jaw.

Conclusion: Zoledronic acid every 12 weeks regimen was equal to zoledronic acid every 4 weeks regimen for safety profile in patients with bone metastasis.

Keywords: Zoledronic Acid; Safety; Bone Metastasis

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Introduction

Bone is the third most frequent site of metastasis, behind lung and liver. Prostate and breast cancer are responsible for the majority of the skeletal metastases (up to 70%) [1]. Moreover, the bone disease is the most frequent disease-defining clinical feature of multiple myeloma, with 90% of patients developing bone lesions throughout their disease [2]. The overall incidence of bone metastasis is not known [3]. The relative incidence of bone metastasis by type of tumor, in patients with advanced metastatic disease, is 65-75% in BC; 65-75% in the prostate; 60% in the thyroid; 30-40% in the lung; 40% in bladder; 20-25% in renal cell carcinoma and 14-45% in melanoma [4]. The major skeletal complications of bone metastatic disease including cancer-induced bone pain, hypercalcemia, pathological fractures, and spinal cord compression, all of which may profoundly impair a patient's quality of life [5]. Patients with Metastatic bone disease are generally treated with surgery, radiation therapy, chemotherapy, hormonal therapy according to primary tumor type [6]. Zoledronic acid, a third-generation is given to patients with bone metastasis to decrease skeletal-related events such as bone fractures, spinal cord compression, radiation to bone, or bone surgery and pain. It slows the breakdown of bones, increases bone density, and decreases the amount of calcium being released by the bones into the blood. The optimal dosing interval for the drug has not been established [7].

It has serious side effects that include kidney problems, low blood calcium, and osteonecrosis of the jaw [8]. So, the present study was conducted to evaluate whether Zoledronic acid every 12 weeks regimen was equal to zoledronic acid every 4 weeks regimen for safety profile with bone metastasis or not as this would result in less toxicity and more economic benefits.

Patients and Methods

The study is a randomized, clinical trial that included 108 patients with histologically proven breast cancer, prostate cancer, or multiple myeloma with at least 1 site of bone involvement. Patients were prospectively treated in Clinical Oncology Department, Zagazig university hospitals who fulfilled the eligibility criteria and who approved to join the study by written consent in the period from December 2017 to December 2019, after being informed of any expected complications. Patients were randomized to receive zoledronic acid every 12 weeks (n = 54) group A *vs.* every 4 weeks (n = 54) group B for 2 years.

Inclusion criteria

- Patients are required to have histologically proven breast cancer, prostate cancer, or multiple myeloma with at least 1 site of bone involvement
- Normal creatinine level
- Corrected serum calcium level between 8.0mg/dL o r greater and less than 11.6 mg/dL.

Exclusion criteria

- Patients with brain metastasis
- If they received prior intravenous bisphosphonates, denosumab,or bone-targeting radiopharmaceuticals.

All patients were evaluated: clinically by medical history and complete physical examination and laboratory tests by serum calcium level and serum creatinine were done. Patients were also evaluated by radiography (computed tomography scanning, magnetic resonance imaging, bone scanning and DEXA).

Evaluation of Toxicity and Severity

Incidences of osteonecrosis of the jaw and kidney dysfunction using version 3.0 of the Common Terminology Criteria for Adverse Events criteria:

- Grade 1: serum creatinine levels greater than the upper limit of normal to 1.5 times the upper limit of normal
- Grade 2: serum creatinine levels >1.5-3.0 times the upper limit of normal
- Grade 3: serum creatinine levels >3.0-6.0 times the upper limit of normal
- Grade 4: serum creatinine levels >6 times the upper limit of normal)

Statistical Analysis

All data were collected, tabulated and statistically analyzed using SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA). Continuous Quantitative variables were expressed as the mean ± SD & median (range), and categorical qualitative variables were expressed as absolute frequencies (number) & relative frequencies (percentage). Continuous data were checked for normality by using Shapiro Walk test. Mann-Whitney U test was used to compare two groups of non-normally distributed data. Categorical data were compared using Chi-square test or Fisher's exact test when appropriate. McNemar's test was used for paired categorical data. Stuart–Maxwell test (different generalization of McNemar test) was used for testing marginal homogeneity in a square table with more than two rows/columns. All tests were two sided. P-value < 0.05 was considered statistically significant (S), p-value < 0.001 was considered highly statistically significant (HS), and p-value ≥ 0.05 was considered not statistically significant (NS).

Results

There was an insignificant difference between group A and group B regarding sex distribution (p-value=0.433 and 0.634) respectively.

All patients in both groups had pre-treatment normal serum creatine and serum calcium (Table 1). There was an insignificant difference between group A and group B regarding post-treatment serum creatinine where elevated serum creatinine had occurred in 5.6% of group A versus 11.1% of group B (p-value=0.489). All patients in both groups did not have osteonecrosis of jaw (Table 2).

There was no significant change of serum calcium and creatinine in both groups except for a significant increase in serum creatinine among patients in group B where six patients (11.1%) had developed elevated serum creatinine with treatment (Tables 3 and 4).

Discussion

Among the literatures, we found only three recent clinical trials

Table 1: Comparison between group A and group B regarding pre-treatment evaluation.

Pre-treatment Evaluation	Group A (N=54)		Group B (N=54)		Test‡	p-value (Sig.)
	No.	%	No.	%		
Serum calcium						
Normal	54	100%	54	100%	0.000	1.000 (NS)
Abnormal	0	0%	0	0%		
Serum creatinine						
Normal	54	100%	54	100%	0.000	1.000 (NS)
Abnormal	0	0%	0	0%		

Where: ‡ Chi-square test; p< 0.05 is significant; Sig.: Significance.

Table 2: Comparison between group A and group B regarding post-treatment evaluation.

Post-treatment Evaluation	Group A (N=54)		Group B (N=54)		Test‡	p-value (Sig.)
	No.	%	No.	%		
Serum calcium						
Normal	54	100%	51	94.4%	3.086	0.243 (NS)
Abnormal	0	0%	3	5.6%		
Serum creatinine						
Normal	51	94.4%	48	88.9%	1.091	0.489 (NS)
Elevated (G1)	3	5.6%	6	11.1%		
ONJ						
Absent	54	100%	54	100%	0.000	1.000 (NS)
Present	0	0%	0	0%		

Where: ‡ Chi-square test; p< 0.05 is significant; Sig.: Significance.

Table 3: Treatment effect upon serum calcium.

Pre-treatment Serum Calcium	Post-treatment Serum Calcium		Total
	Normal	Abnormal	
Normal	54	0	54
	(100%)	(0%)	(100%)
Abnormal	0	0	0
	(0%)	(0%)	(0%)
Total	54	0	54
	(100%)	(0%)	(100%)
Test‡			0.000
p-value (Sig.)			1.000 (NS)
Pre-treatment Serum Calcium	**Post-treatment Serum Calcium**		**Total**
	Normal	**Abnormal**	
Normal	51	3	54
	(94.4%)	(5.6%)	(100%)
Abnormal	0	0	0
	(0%)	(0%)	(0%)
Total	51	3	54
	(94.4%)	(5.6%)	(100%)
Test‡			1.333
p-value (Sig.)			0.248 (NS)

Where: ‡ McNemar test; p< 0.05 is significant; Sig.: Significance.

Table 4: Treatment effect upon serum creatinine.

Pre-treatment Serum Creatinine	Post-treatment Serum Creatinine		Total
	Normal	Elevated (G1)	
Normal	51	3	54
	(94.4%)	(5.6%)	(100%)
Abnormal	0	0	0
	(0%)	(0%)	(0%)
Total	51	3	54
	(94.4%)	(5.6%)	(100%)
Test‡			1.333
p-value (Sig.)			0.248 (NS)
Pre-treatment Serum Creatinine	**Post-treatment Serum Creatinine**		**Total**
	Normal	**Elevated (G1)**	
Normal	48	6	54
	(88.9%)	(11.1%)	(100%)
Abnormal	0	0	0
	(0%)	(0%)	(0%)
Total	48	6	54
	(88.9%)	(11.1%)	(100%)
Test‡			4.167
p-value (Sig.)			0.041 (S)

Where: ‡ McNemar test; p< 0.05 is significant; Sig.: Significance.

that compare zoledronic acid every 12 weeks with zoledronic acid every 4 weeks in patients with bone metastasis.

The first one was Amadori D, et al. in (2013) study which enrolled patients with breast cancer who had one or more bone metastases and had completed 12-15 months of monthly treatment with zoledronic acid [9]. Patients were randomly to receive zoledronic acid 4 mg once every 12 weeks or once every 4 weeks, and followed up for at least 1 year.

Himelstein AL, et al. (2017) study included patients (n=1822) with metastatic breast cancer, metastatic prostate cancer, or multiple myeloma who had at least 1 site of bone involvement and they were randomized to receive zoledronic acid administered intravenously every 4 weeks (n = 911) vs every 12 weeks (n = 911) for 2 years [7].

Regarding Hortobagyi GN, et al. (2017) study, patients were randomized (1:1) to receive 4.0 mg of intravenous zoledronic acid every 4 or every 12 weeks with placebo for interim infusions for 1 year [10]. The study randomized 416 women (≥18 years old) with bone metastases from breast cancer who previously received 9 or more doses of zoledronic acid during the first 10 to 15 months of therapy.

Type of cancer included in the study was similar to Himelstein AL, et al. (2017) study but differ than Amadori D et al. (2013) and Hortobagyi GN, et al. (2017) studies that included only breast cancer patients [7,9,10].

The present study was open-label so neither patients nor investigators were masked to treatment allocation, also Amadori D et al. (2013) study was open-label in contrast to Himelstein AL, et al. (2017) study where allocations were concealed until patients were registered and enrolled while in Hortobagyi GN, et al. (2017) study masking of treatment allocation was done by giving every 12 weeks arm two placebo infusions [7,9,10].

We excluded patients that received prior i.v bisphosphonates while in Amadori D et al. (2013) study patients completed 12-15 months of monthly treatment with zoledronic acid, also in Hortobagyi GN, et al. (2017) study, patients were eligible if they had received zoledronic acid, pamidronate disodium, or a sequence of both for 9 doses or more during the first 10 to 15 months of treatment [9,10].

We included patients with normal serum creatinine according to reference of our laboratory report; patients with serum creatinine less than 1.3 mg/dL were included in contrast to Hortobagyi GN, et al. (2017) patients who had a serum creatinine level higher than 3.0 mg/dL were excluded [9].

In our study, there was an insignificant difference between patients received zoledronic acid every 12 weeks and patients received zoledronic acid every 4 weeks regarding sex distribution where male constituted 37% versus 44.4% respectively (p-value=0.433), in agreement with Himelstein AL, et al. (2017) where male constituted 47% of patients received zoledronic acid every 12 weeks versus 45.4% of patients received zoledronic acid every 4 weeks [7].

In our study, thirty patients in each group had breast cancer, fifteen patients in each group had prostate cancer and the remaining nine patients in each group had multiple myeloma (p-value=1.000) in agreement with Himelstein AL, et al. (2017) study [7].

In our study, all patients in both groups had pre-treatment normal serum creatinine in disagreement with Hortobagyi GN, et al. (2017) where 94.6% of patients received zoledronic acid every 12 weeks had normal serum creatinine versus 98% of patients received zoledronic acid every 4 weeks.

In our study, elevated serum creatinine occurred in 5.6% of patients received zoledronic acid every 12 weeks versus 11.1% of patients received zoledronic acid every 4 weeks, in disagreement with Himelstein AL, et al. (2017) where 15.5% of patients received zoledronic acid every 12 weeks had increased creatinine level *vs.* 19.9% of patients received zoledronic acid every 4 weeks because we included only patients with normal serum creatinine level, while Himelstein AL, et al. (2017) included patients with elevated serum creatinine if they had creatinine clearance of 30 mL/min or greater using the Cockroft and Gault formula and Zoledronic acid doses were administered even if creatinine levels had not decreased to levels within 10% of baseline [7].

In the current study, no patient in both arms had developed osteonecrosis of jaw in disagreement with Himelstein AL, et al.

(2017) where 1% of patients received zoledronic acid every 12 weeks had developed osteonecrosis of jaw versus 2% of patients received zoledronic acid every 4 weeks owing to the shorter duration of treatment in our study (24 months *vs*. 37-48 months in previous studies) and our practice of sending patients for dental treatment and clearance prior to initiating bisphosphonate therapy.

Conclusion

Our study revealed that zoledronic acid every 12 weeks regimen was equal to zoledronic acid every 4 weeks regimen for safety profile with bone metastasis from breast cancer, prostate cancer, and multiple myeloma. So, it also achieves more economic benefits.

Limitations

This study also has several limitations: small sample size of the study, heterogeneous group of patients that had a different natural history and different treatments. Finally, the study was open-label, which could potentially bias reporting of skeletal-related events.

Recommendations

This longer interval of zeledronic acid administration (every 12 weeks) is recommended as an acceptable treatment option for treatment of bone metastasis due to breast cancer, prostate cancer, or multiple myeloma.

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