Comparison of Zoledronic Acid Every 12 Weeks versus Slandered 4 Weeks Regimen in Breast Cancer Patients with Bone Involvement

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Abstract: Purpose: The present study is to evaluate the 12 weeks interval of zoledronic acid compared to the 4 weeks regimen. **Methods**: Patients were distributed in 2 groups, for receive 4.0 mg of intrvenous zoledrnic acid every four weeks (group 1) or 12 weeks (group 2) / year. One hundred and forty patients (140) were enroled in this study on 69 patients randomlly to receive zoledrnic acid every four weeks and 71patients randomly receive zoledronic acid every 12 weeks. The primary endpoint was the proportion of patients having at least 1 SRE within 1 year after that. Secondary end points included pain, the incidences of adverse events of zoledrnic acid (osteoncrosis and renal dysfunction) and the skeletal morbidity rate. **Results***:* After 1 years of follow-up, SREs occurred in 15 (21.7%) patients in the zoledrnic acid every 4 weeks group and 16 (22.5%) patients in zoledrnic acid every 12 weeks group; (noninferiority with P= 0.910). The time to first SRE between treatment groups was not statistically significantly different (hazard ratio [HR], 1.04; 95% CI, 0.52-2.1; P = 0.903). According to pain score the 2 treatment groups was not statistic significant different (p=0.595). The mean skeletal morbidity rate (SMR) 0.46 (1.06) vs 0.50 (1.50) events per year in the every four weeks versus every 12 weeks groups (P = .85). **Conclusion:** Zoledrnic acid every 12 weeks compared with every 4 weeks did not result in an increased risk of skeletal events, seems to be noniferior and may be an acceptable treatment option.
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1. Introduction

Metastatic breast cancer to bone is a common clinical problem. [1]It hasmany debilitating skeletal-related events (SREs), that included the bone fractures, hypercalcemia, nerve compression, and severe pain[2] These skeletal complications, in turn, increase the need for palliative radiation or surgery to bone[3] limit functional independence, adversely affect the quality of life[4,5] and continue to cause morbidity of the affected patients. [6,7]

Zoledronic acid was approved for patients with metastases of bone from solid tumors. the use of zoledronic acid every three to four weeks decreases pain, compression of spinal cord, bone radiation and surgery by 25% to 40%.[1,8,9]

The bone-modifed considered the guidelines of agents in metastatic breast-cancer which were verified by American society of clinical oncology (ASCO).[10,11] These agents include BPs and new osteoclast inhibitors. These agents are recorded in bone metastases of breast cancer with bone loss. They advice to have a dental examination before BP administration with follow upcreatinine levels. Agents include zoledronic acid (ZA), pamidronate (PA) and denosumab.

Amadori et al,[12] studied patients with metastatic breast cancer to bone treated with zoledronic acid administered at 12-weeksversus 4-weeks. There was nosignificant difference as regard skeletal morbidity rate (0·26 in the 12, week group 0·22 (0·14–0·29) in 4, week group with no. Bone pain was recorded in (27%) of patients in the 12-week arm *vs* (30%) of the 4-week arm. There were no significant differences as regards to renal impairment, bony pains and osteonecrosis.

This study is to evaluate the 12 weeks interval of zoledronic acid compared to the 4 weeks regimen.

2. Patients and Methods

Pathologically proven breast cancer with at least 1 site of bone metastasis documented by plain radiograph required, CT scan, PET scan, MRI or bone scan. Age of 21 years or older, Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2, calculated creatinine clearance[13], and serum calcium level within normal ranges (between8.0 to 11.6 mg/dL).

Patients were ineligible if they had received prior intravenous bisphosphonates, denosumab, or bone-targeting radiopharmaceuticals. Patients received priorradiation to bone were excluded.

Patients were distributed in 2 groups, to receive 4.0 mg of intravenous zoledronic acid every 4 weeks (group 1) or every 12 weeks (group 2) for 1 year. This study was conducted at oncology department, Tanta

university hospitals, Egypt the period from 2014 up to June 2018. One hundred and forty patients (140) were enrolled in the study with 69 patients randomized to receive zoledronic acid every 4 weeks and 71patients randomized to receive zoledronic acid every 12 weeks.

Patients encouraged swallowing elemental calcium and vitamin D. The zoledronic acid adverse effects were assessed according to Common Terminology Criteria for Adverse Events.[14]

The primary endpoint was the proportion of patients having at least 1 SRE within 1 year after randomization, it is defined as pathological fracture, spinal cord compression, palliative radiation to bone, and surgery involving affected bone to treat pathological fractures or spinal cord compression.

Secondary end points included pain as assessed by scores ranged from score 0 (no pain) to score 10 (as bad as you can imagine), mild pain (1-4), moderate pain (5-7) and sever pain (8-10)[15], the incidences of adverse events of zoledronic acid (osteonecrosis and renal dysfunction) was assessed; (grade 1, serum creatinine levels 1.5 times greater than the upper limit of normal; grade 2, >1.5–3.0 times; grade 3, >3.0–6.0 times the upper limit of normal; grade 4, >6 times the upper limit of normal), and the skeletal morbidity rate was defined as the mean number of skeletal-related events per year. Skeletal related events were evaluated every 4 weeks for all patients. Also, Imaging reports, Pain scores, serum creatinine levels, creatinine clearance.

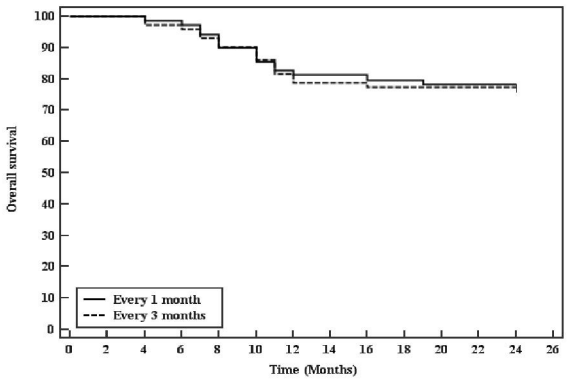

Figure (1): Kaplan Meier curve for time to first skeletal related event

3. Results

Table (1) patients characteristics

	every 4 weeks (no=69)	every 12 weeks (no=71)
Age, median (range), y	65 (26-93)	65 (33-94)
Body surface area, mean (SD), m^2	1.9 (0.3)	2.0 (0.3)
performance status, No. (%)		
0	10 (14.49%)	9 (12.68%)
1	59(85.6%)	62(87.32%)
Serum creatinine, median (IQR)	0.9 (0.7-1.0)	0.9 (0.7-1.1)

After 1 years of follow-up, SREs occurred in 15 (21.7%) patients in the zoledronic acid every 4 weeks group and 16 (22.5%) patients in the zoledronic acid every 12 weeks group; (noninferiority with P= 0.910). Table 2

Table (2): Comparison between Zomita every 1 month and Every 3 months according to SRE

	Zomita every 1 month (n= 69)	**Every 3 months (n= 71)**	**c^2**	**p**
SRE				
No	54(78.3%)	55(77.5%)	0.013	0.910
Yes	15(21.7%)	16(22.5%)		

The time to first SRE between treatment groups was not statistically significantly different (hazard ratio [HR], 1.04; 95% CI, 0.52-2.1; P = 0.903). Table 3, Figure1.

Table (3): Time to first skeletal related event

	Mean	95% CI of mean (LL-UL)	%	Log rank c^2	p	Hazard ratios (95% CI)
Every 1 month	20.913	19.473 – 22.353	78.3	0.015	0.903	1.04 (0.52 – 2.1)
Every 3 months	20.662	19.183 – 22.141	77.5			

According to pain score the 2 treatment groups was not statistically significantly different (p=0.595). Table 4

Table (4): Zomita every 1 month and Every 3 months according to pain Score

	4weeks group (n= 69)	Every 12weeks (n= 71)	c^2	p
Pain Score				
0	2(2.9%)	1(1.4%)	0.608	0.959
Mild	21(30.4%)	20(28.2%)		
Moderate	35(50.7%)	38(53.5%)		
Severe	11(15.9%)	12(16.9%)		

The mean skeletal morbidity rate (SMR) 0.46 (1.06) vs 0.50 (1.50) events per year in the every 4 weeks versus every 12 weeks groups (P = .85)

The safety profiles of the every four weeks and every 12weeks groups were compare, with only 2 patients (0.029%) in the every 4weeks group complained from renal dysfunction versus one patient (0.014) in the every 12 weeks group. These patients were excluded from the study as they didn't complete the doses. No patients experienced osteonecrosis in both groups.

4. Discussion

The clinical randomized trial in this study was included metastatic breast cancer to bone patients. The administered of zoledrnic acid every 12weeks was non. inferior to that administered every 4weeks for reducing the occur in skeletal events, (21.7%) of patients every 4weeks versus (22.5%) in every 12weeks groups). The time between treated groups with SRE was of no statistical significantly different (hazard ratio [HR], 1.04; 95% CI, 0.52-2.1; P = 0.903). The mean skeletal morbidity rate (SMR) was noninferior, 0.48 (1.08) versus 0.51 (1.51) events per year in the every 4 weeks vs every 12 weeks groups (P = .85).

Similar observations were made in OPTIMIZE-2 study[17] 44 patients (22.0%) in every four weeks group vs 47patients (23.2%) in the every 12weeks group experienced 1 or more SRE and ZOOM study[12] 31 of 209 (15%) patients in the 12week group and 33 of 216 (15%) in the 4-week group (p=0·898). The SRE was not statistical significant was differ (hazardratio [HR], 1.6; 95% CI, 0.70-160; P = 0.79). The median time to first SRE could not be calculated in ZOOM study[10] because of the low event rate. At same time, there was no statistically significant between treatment groups (P= 0.46 vs 0.50). Also SMR was not statistically significant in ZOOM study[10] (95% CI) 0·26 (0·15–0·37) in 12 week group vs 0·22 (0·14–0·29) in 4 week group.

In present study, the incidence of renal impairment of the 2 treatment arms was comparable (only 2 patients (0.02.8) in the every four weeks versus one patient (0.014) in the every 12 weeks group).

In the ZOOM study[10], Renal adverse occur in 1 patient (<1%) in the group,12-week and two patients (1%) in the group, 4-week. One patient (<1%) in the four week group had non-serious acute grade 1 renal failure. According to pain score the 2 treatment groups was not statistically significantly different in this study (p=0.595). The OPTIMIZE-2 study[17] assessed bonepain by the Brief Pain Inventory (BPI) and analgesic consumption, pain score and analgesic consumption was not statistically different between groups (P =.1) .

Ling et al [18]reorted that there were no differences in the incidence of skeletal-related events ($P = 0.80$) or grade 3/4 adverse events ($P = 0.52$) were observed between the 12-week and 4-week schedule of zoledronic acid. The 12-week arm have lower incidences osteonecrosis in jaw (0.98%) versus (1.73%) and renal impairment (1.68%) versus (2.45%) with no significant difference ($P= 0.11$); ($P = 0.15$) respectively. They claimed that zoledronic acid at 12-week intervals don't increase risk of SREs, and maybe reduce the incidence of ostonecrosis of jaw and kidney failure.

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