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Efficacy and Safety of Denosumab Versus Zoledronic acid in Suppressing Bone Metastases of Breast Cancer

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ABSTRACT

Background: 60% of patients with metastatic breast cancer will eventually develop bone metastases during course of disease, bone targeting agents either bisphosphonates or denosumab, through different mechanisms of action, these bone-specific agents block osteoclast function and reduce the risk of skeletal-related events.

Objectives: This study aimed to compare monoclonal antibody against receptor activator of nuclear factor _ B (RANK) ligand (denosumab), with zoledronic acid in response, toxicity related to treatment and progression skeletal-related events free survival in boney metastatic breast cancer.

Patients and Methods: Patients were assigned to receive either subcutaneous denosumab for six months or intravenous zoledronic acid for six months. The primary end point was difference in response and toxicity between bone targeting agents. The secondary end point was comparing skeletal progression survival analysis and the response in both.

Results: Denosumab was not superior to zoledronic acid in delaying skeletal progression survival (log rank test P value: 0.119). Disease progression and rates of adverse events were similar between groups. An excess of renal toxicity occurred with zoledronic acid (P value 0.004), while hypocalcemia occurred more frequently with denosumab (P value 0.004).

Conclusions: Denosumab was similar to zoledronic acid in delaying skeletal progression survival in bone metastatic breast cancer (BMBC) and was generally well tolerated. With the convenience of a subcutaneous injection and no requirement for renal monitoring, denosumab represents a potential treatment option for patients with bone metastases. While due to severe hypocalcemia with denosumab, zoledronic acid represent a good treatment option for metastatic patients.

Keywords: Breast cancer, Zoledronic acid, Denosumab.

INTRODUCTION

Breast cancer is the most prevalent malignancy and the foremost cause of cancer related death in women worldwide [(1)]. Also is the most common malignancy in women in the United States and is second only to lung cancer as a cause of death. The American Cancer Society has estimated that 279,100 Americans will be diagnosed with breast cancer and 42,690 die of disease in the united states in 2020 [(2)].

Despite the achievements in the management of this tumor, breast cancer remains an incurable disease when it is diagnosed, or it has progressed, towards advanced stages [(3)]. Metastatic breast cancer (MBC) is estimated that at least 154.000 people in U.S have metastatic breast cancer [(4)]. The median overall survival (OS) of patients with MBC ranges from 2 to 3 years, with a 27% overall 5-year relative survival rate [(5)]. The most common sites of distant metastasis include bones, lungs, liver, and brain [(6)]. Bone metastases are common in advanced breast cancer; bone is affected in more than 70% of patients with MBC [(7)]. Bone metastases not only considerably reduce the OS but also the health-related quality of life due to pain, fatigue, and skeletal-related events (SREs) [(8)].

Several therapeutic strategies to specifically target this condition (e.g., bone-modifying agents) are available [(9)]. Bisphosphonates and RANK/RANKL inhibitors represent the foremost agents for the clinical management of patients with bone metastasis [(10)]. Bisphosphonates have a dual role in decreasing bone resorption by exerting an apoptotic effect on osteoclasts and increasing mineralization by inhibiting osteoclast activity [(11)], Zoledronic acid (ZOL) is a nitrogen-containing bisphosphonate and potent osteoclast inhibitor. The administration of these agents may reduce the risk of SREs and skeletal morbidity rate [(12)]. Either intravenous or oral administration of bisphosphonates significantly reduced the absolute risk of SREs by 14% (RR 0.86, 95% CI 0.78–0.95) when compared to placebo [(13)]. Denosumab is a fully human monoclonal antibody, targets the receptor activator of nuclear factor-kappa B (RANK) ligand. This drug inhibits the RANKL/RANK signaling mediated bone resorption, suppressing bone turnover and leading to the reduction of SRE risk [(14)].

The objective of our prospective study was to evaluate zoledronic acid in comparison to denosumab in skeletal related events (SREs) progression free survival in bone metastatic breast cancer and also in toxicity.

PATIENTS AND METHODS

81 female breast cancer patients with radiological evidence of newly diagnosed bone metastases were admitted to our Medical Oncology Department, South Egypt Cancer Institute, Assiut University. Eligible criteria of patients were age ≥18 years with

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histologically confirmed breast adenocarcinoma, recent radiographic (bone scan, or magnetic resonance imaging) evidence of at least one bone metastasis.
Excluded from the study, patients having more than one cancer (second primary malignancy), pregnant patients and also patients with serious concomitant disorders that would compromise the patient's ability to complete the study.

Study design:

Prospective, single center trial carried out in Medical Oncology Department, South Egypt Cancer Institute, Assiut University, starting from 2019 to 2021, 81 patients fulfilled the inclusion criteria. Patients were randomly assigned to receive either an intravenous infusion on 15 minutes of zoledronic acid 4 mg (group 1: N=41), or a subcutaneous injection of denosumab 120 mg every 4 weeks (group 2: N=40). All regimens received under normal renal function tests and normal calcium level.

All patients included in this study were subjected to baseline evaluation with full history taking, complete clinical examination**,** staging, complete laboratory investigations (complete blood count, liver function test, renal function test and calcium level), imaging studies (CXR, Abdominal ultrasound and bilateral Sonomammography), bone scan and local MRI on boney metastatic site.

Follow up evaluation after 6 months on bone supporting agents with clinical evaluation included assessment of performance status according to the World Health Organization (WHO)[(15)] criteria, bone pain evaluation according to the Radiation Therapy Oncology Group (RTOG)[(16)], pain score scale and recording of concomitant treatments (analgesics, anti-cancer therapy). Skeletal-related events, including pathological fractures, hypercalcemia, neurologic abnormalities due to spinal cord compression and need for bone irradiation, were also recorded. Bone scan and MRI on boney metastatic site and the response interpreted according to the response evaluation criteria in solid tumors (RECIST) criteria.

Ethical consent:

An approval of the study was obtained from Assiut University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of the operation. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis:

All statistical calculations was done using SPSS (statistical package for the social science; SPSS Inc., Chicago, IL, USA) version 21. Data were statistically described in terms of mean ± standard deviation (± SD), or median and range when not normally distributed and frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables was done using Mann Whitney U test because the data were not normally distributed. Comparison of paired quantitative variables was done by Wilcoxon signed rank test because the data were not normally distributed. For comparing categorical data, Chi square (χ^2) test was used. Exact test was used instead when the expected frequency is less than 5. Odds ratio (OR) with 95% confidence interval (CI) and logistic regression was calculated to measure the different independent factors. Kaplan-Meier's method with log rank test, Cox regression method for univariate or multivariate overall and progression free survival analysis were used to assess the associations among different clinicopathological indices and patients outcome. P-value is always 2 tailed set significant when ≤ 0.05 level.

RESULTS

Baseline characteristics of breast cancer (BC) cases according to the bone targeting agent received (n=81):

Demographic characteristics of the enrolled patients showed that there was no statistically significant difference between both groups (P value > 0.05) regarding age, menopausal state, laterality, pathological type, grading, TNM staging, hormonal state, sites of metastases and baseline bone scan findings (Table 1).

Table (1): Baseline characteristics of BC cases according to the bone targeting agent received (n=81)

Variable name	Zoledronic acid (n=41)		Denosumab (n=40)		P value
Age (years), mean ± SD	51.05 ± 10.87		49.95 ± 12.53		0.674
Median (range)	50 (25 – 73)		50 (25 – 75)		
Menopausal status					0.904
Pre-menopausal	19	(46.3)	18	(45.0)	
Post-menopausal	22	(53.7)	22	(55.0)	
Tumor laterality					0.563
Right	14	(34.1)	18	(45.0)	
Left	25	(61.0)	21	(52.5)	
Bilateral	2	(4.9)	1	(2.5)	
Type of surgery					0.821
MRM	26	(63.4)	27	(67.5)	
BCS	4	(9.8)	2	(5.0)	
No surgery	11	(26.8)	11	(27.5)	
Pathological type					0.261
IDC	32	(78.0)	39	(97.5)	
ILC	9	(22.0)	1	(2.5)	
Tumor grade					0.749
Grade I, II	31	(75.6)	29	(72.5)	
Grade III, V	10	(24.4)	11	(27.5)	
Tumor size					0.921
T1-T2	23	(56.1)	22	(55.0)	
T3-T24	18	(43.9)	18	(45.0)	
Lymph node status					0.201
Negative	5	(12.2)	1	(2.5)	
Positive	36	(87.8)	39	(97.5)	
Luminal A					0.565
No	19	(46.3)	16	(40.0)	
Yes	22	(53.7)	24	(60.0)	
Luminal B					0.712
No	38	(92.7)	36	(90.0)	
Yes	3	(7.3)	4	(10.0)	
Her2neu overexpression					0.494
No	41	(100.0)	39	(97.5)	
Yes	0	(0.0)	1	(2.5)	
Triple negative					0.271
No	25	(61.0)	29	(72.5)	
Yes	16	(39.0)	11	(27.5)	
Ki67 (%)					0.228
<15	8	(19.5)	1	(2.5)	
≥15	33	(80.5)	39	(97.5)	
Site of Metastasis					0.441
Bone only	16	(39.0)	19	(47.5)	
Bone + Visceral	25	(61.0)	21	(52.5)	
Baseline bone scan					0.150
One site	25	(61.0)	18	(45.0)	
> one site	16	(39.0)	22	(55.0)	

Tumor-related treatment (Radiotherapy, Chemotherapy or Hormonal), their response and outcome according to the bone targeting agent:

According to treatment received, 20 patients (48.8%) received chemotherapy and 20 (48.8%) received hormonal therapy in zoledronic acid group, 15 patients (37.5%) received chemotherapy and 23 (57.5%) received hormonal therapy in denosumab group (P value: 0.520). During the study period, 30 out of 41 patients (73.2%) required bone irradiation in zoledronic acid group and 20 patients in denosumab group (50%) required bone irradiation (P value: 0.148). In evaluation of bone disease outcome according to bone scan, bone disease showed a regression or remained stable in 21 of the 41 patients (51.2%) in zoledronic acid group, while 20 patients (48.8%) experienced bone disease progression. While in denosumab group, bone disease showed a regression or remained stable in 20 of the 40 patients (50%), while 20 patients (50%) experienced bone disease progression (P value: 0.226).

Table (2): Tumor related treatment (Radiotherapy, Chemotherapy or Hormonal) ,their response and outcome according to the bone targeting agent

Variable name	Zoledronic acid (n=41)		Denosumab (n=40)		P value
Current treatment					0.520
• Chemotherapy	20	(48.8%)	15	(37.5%)	
• Hormonal therapy	20	(48.8%)	23	(57.5%)	
• No treatment	1	(2.4%)	2	(5.0%)	
Radiotherapy					0.148
• Yes	30	(73.2%)	20	(50.0%)	
• No	11	(26.8%)	20	(50.0%)	
Response					0.226
• Regression	8	(19.5%)	16	(40.0%)	
• Stationary	13	(31.7%)	4	(10.0%)	
• Progression	20	(48.8%)	20	(50.0%)	

Treatment-related toxicity (Zoledronic acid or Denosumab):

Concerning toxicity related to treatment after receiving zoledronic acid or denosumab for 6 months in studied patients in this study (table 3 & figure 1), there were statistically significant differences between both groups in hypocalcemia (**P value: 0.03**) as denosumab more commonly caused hypocalcemia, 10 patients (25%)of denosumab group versus only 3 cases (7.3%) had hypocalcemia after receiving zoledronic acid. Regarding renal toxicity, there was statistically significant difference between both groups (**P value: 0.004**) as zoledronic acid more commonly caused renal toxicity than denosumab (19.5% versus 7.5%). In other toxicities related to bone supporting agent, there was no statistically significant difference between both groups as regards allergy and osteoporosis (P value > 0.05).

Table (3): Toxicity related treatment (Zoledronic acid or Denosumab)

Toxicity	Zoledronic acid (n=41)		Denosumab (n=40)		P value
• Allergy	8	(19.5)	2	(5.0)	0.088
• Hypocalcaemia	3	(7.3)	10	(25.0)	**0.030***
• Osteoporosis	3	(7.3)	7	(17.5)	0.194
• Renal toxicity	8	(19.5)	3	(7.5)	**0.004***

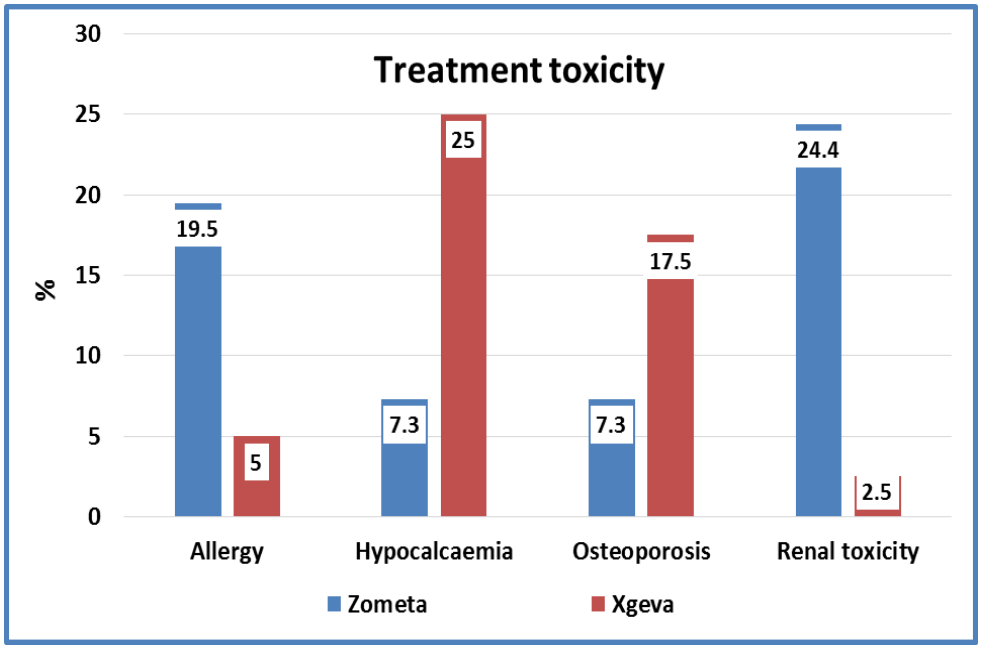

Figure (1): Bar graph showing the difference in treatment toxicity among BC cases according to the bone targeting agent.

Skeletal progression free survival analysis according to the bone targeting agent (n=81):
Table (4) showed progression free survival that is defined as the time from randomization till 6 months after finishing of bone supporting agent. The median time to bone disease progression in patients receiving denosumab (10 months) compared to those received zoledronic acid (11 months) showed no significant difference between both groups. the corresponding Kaplan-Meier curves for bone disease progression were shown in figure **(2**) (log rank test **p 0.119**).

Table (4): Skeletal-related event progression free survival analysis according to the bone targeting agent (n=81)

Bone targeting agent	Median				Log Rank (Mantel-Cox) p-value
	Estimate (months)	Std. Error	95% Confidence Interval		
Zoledronic acid	11.000	0.445	10.128	11.872	
Denosumab	10.000	2.335	5.423	14.577	0.119
Overall	11.000	0.588	8.847	11.153	

Skeletal PFS	Estimate ± SE		P-value
	Zometa	Xgeva	
At 1 year	30.5±10.0%	30.2±12.4%	0.119

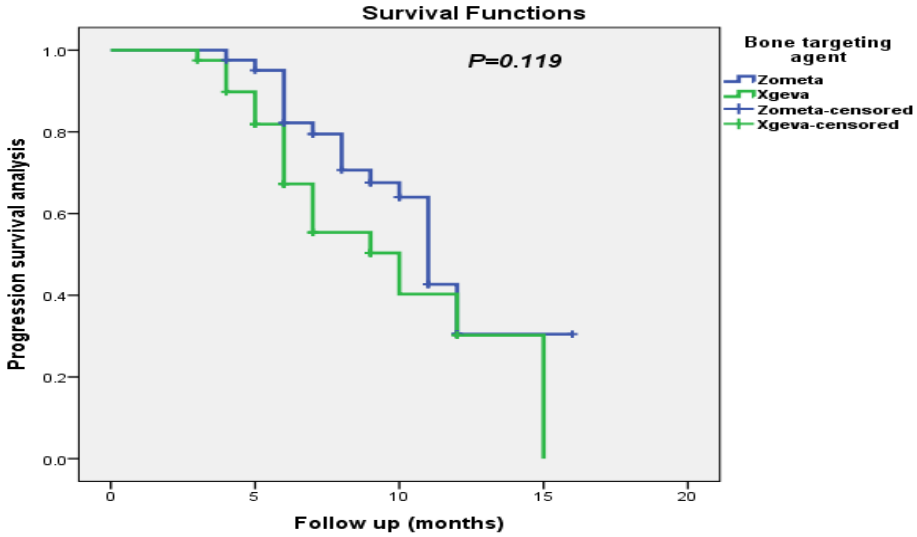

Figure (2): Kaplan-Meier's curve showing skeletal PFS according to bone targeting agent.

DISCUSSION

Bone metastases are common in advanced breast cancer where bone is affected in more than 70% of patients with MBC [7]. Bone metastases not only considerably reduce the OS but also the health-related quality of life due to pain, fatigue, and skeletal-related events (SREs) [8]. Several therapeutic strategies to specifically target this condition (e.g., bone-modifying agents) are available [9], Bisphosphonates and RANK/RANKL inhibitors represent the foremost agents for the clinical management of patients with bone metastasis [10]**.** Bisphosphonates have a dual role in decreasing bone resorption by exerting an apoptotic effect on osteoclasts and increasing mineralization by inhibiting osteoclast activity [11]. Denosumab inhibits the RANKL/RANK signaling mediated bone resorption, suppressing bone turnover and leading to the reduction of SRE risk [14]**.**

In our prospective study, 81 patients were randomly assigned to receive either an intravenous infusion on 15 minutes of zoledronic acid 4 mg (group 1: N=41), or a subcutaneous injection of denosumab 120 mg every 4 weeks (group 2: N=40). All regimens received under normal renal function tests and normal calcium level. When comparing a fully human monoclonal antibody against RANK ligand (denosumab) with zoledronic acid in skeletal progression free survival at 1year in bone metastatic breast cancer patients, we found that 30.5% of patients had progression in zoledronic acid group that closely near to the percentage of denosumab group, which was 30.2% (Kaplan-Meier curves, p value :0.119). This is in accordance with **Nakai *et al.*** [17] who directly compared denosumab with zoledronic acid and demonstrated that no significant differences were observed in overall survival and disease progression. Also, **Jiang *et al.*** [18], regarding overall survival and time to disease progression, both showed no differences between denosumab and ZA. But, this is in discordance with clinical trials done by **Stopeck *et al.*** [19] who directly compared denosumab with zoledronic acid and demonstrated that denosumab was superior in terms of reducing bone turnover and pain as well as preventing SREs. Also **Henry *et al.*** [20] concluded that denosumab was significantly superior to ZA in delaying time to first-and-subsequent SREs. Zoledronic acid showed that nephrotoxicity related to treatment showed statistically significant difference in relation to denosumab **(P value: 0.004),** 8 cases in zoledronic acid group (24.4%) versus only 3 cases (7.5%) had renal toxicity after receiving denosumab. Renal toxicity was defined as increased blood creatinine and blood urea, oliguria, renal impairment, proteinuria, decreased creatinine clearance, acute renal failure and chronic renal failure. This agrees with **Stopeck *et al.*** [19] who compared both bone supporting agents in safety and found that zoledronic acid was more commonly to cause renal toxicity. Therefore, denosumab represents a valid therapeutic option for patients with bone metastases suffering from chronic renal impairment**.** Also **Wang *et al.*** [21] who compared denosumab and ZA effect on renal functioning. It is well believed that ZA is associated with clinically significant nephrotoxicity than denosumab**.** However, this disagrees with **Jiang *et al.*** [18] who showed no differences between denosumab and ZA in overall AE or serious AEs.

The intravenous bisphosphonates are not metabolized, not interact with or affect the P450 enzyme system, and are excreted unchanged by the kidneys by glomerular filtration, without a significant component of tubular secretion [22]. As a result, impaired renal function reduces bisphosphonate excretion and can lead to excessive serum (and bone) levels with resultant toxicity so nephrotoxicity has been shown to be associated with zoledronic acid therapy and increases with extended treatment. To minimize this risk, zoledronic acid is contraindicated for patients with creatinine clearance 60 ml/min. Its dose is adjusted for baseline renal function [23]. Decline in glomerular filtration rate (GFR), coupled with decreased renal blood flow, leads to reduced drug clearance and increased concentration of drugs in the renal medulla [24]**.**

There were statistically significant differences between both groups in hypocalcemia (P value: 0.03) as denosumab more commonly causes hypocalcemia. 25% of patients of denosumab group versus only 3 cases (7.3%) had hypocalcaemia after receiving zoledronic acid. This is in agreement with **Qi *et al.*** [25] and **Peddi *et al.*** [26] who found that denosumab contributes to lower SRE rates compared to the bisphosphonate zolendronic acid (ZA), but the incidence of high-grade hypocalcaemia was 5.2 and 2.0 % respectively. Also, in accordance with **Raje *et al.*** [27]**,** probably due to its higher antiresorptive potency over ZA, denosumab was associated with higher incidence of hypocalcemia. In addition, prevention of denosumab-induced hypocalcaemia was necessary via close monitoring of calcium, vitamin D, magnesium, phosphate, and kidney function.

CONCLUSION

We concluded that denosumab is more effective and safe versus zoledronic acid in bone metastatic breast cancer. There is no significant difference in response and skeletal progression free survival. Denosumab can be used as an alternative option for BMBC with renal impairment.

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