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The Efficacy of Denosumab versus Zoledronic Acid in Preventing Skeletal Related Events in Cancer Patients with Bone Metastasis

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Abstract

Background: This study compared the effect of denosumab in delaying or preventing the skeletal related events (SREs) versus zoledronic acid in patients with advanced cancer with bone metastases.

Patients and methods: Patients classified into two groups, the first group (no=50 patients) received intravenous zoledronic acid 4mg every 4 weeks and the second group (no=50 patients) received subcutaneous denosumab 120mg every 4 weeks. The primary end point was time to first on-study SRE (defined as radiation to bone, surgery to bone, spinal cord compression, and pathologic fracture) and the second end point was time to first and subsequent on-study SRE (defined as an event occurred ≥21 days after the previous SRE) .

Results: Denosumab resulted in delaying time to first on-study SRE compared to zoledronic acid (26% versus 36%, 95% confidence interval [CI], 0.82 to 1.44; P<0.04). The median time to first on-study SRE was 21.9 month for denosumab versus 18.1 month for zoledronic acid (P<0.04). Denosumab reduced the subsequent on-study SREs (10% versus 16%, p<0.04). There is a significant difference between patients without SREs in both groups (64% versus 48%) at the end of study (P<0.04). Denosumab was found to be safer than zoledronic acid as regarding renal toxicity (2% versus 10%, P<0.04).

Conclusion: Denosumab was more efficacious in delaying and preventing the SREs in patients with advanced cancer with bone metastases compared to zoledronic acid. Therefore denosumab improved the quality of life (QOL) of patients.

Keywords: Denosumab, Zoledronic acid, SRES, bone metastases, cancer

Introduction

The third site of cancer metastases, after lung and liver is bone [1]. Up to 70% of the skeletal metastases are due to breast and prostate cancer [2]. Patients with bone metastases or multiple myeloma frequently experience increased osteoclast activity resulting in osteoclast-mediated bone destruction, bone pain, hypercalcemia and skeletal-related events (SREs) this includes, pathological fracture, spinal cord compression, and radiation or surgery to the bone [3- 8]. These complications are associated with increased morbidity and

decreased quality of life of patients [9- 11]. Patients with cancer and bone metastases experience an SRE every 3- 6 month, in the clinical trials and when the patients develop a first SRE, the chance of having a second SRE increased [5, 12].

The microenvironment of healthy bone consisted of osteoblasts, osteoclasts and other cells as osteocytes and mineralized bone matrix. This microenvironment is constantly in dynamic state. The growth of tumor cells within this environment leads to disruption of its balance leading to bone destruction and bone resorption [13, 14].

Inside the bone, the metastatic tumor cells release cytokines and growth factors that induce osteoblasts to secrete receptor activator of nuclear factor kappa-B ligand (RANKL), an important mediator of osteoclast function, formation, and survival. Osteoclast activity, resulting in bone destruction and releasing growth factors that may increase proliferation of tumor cells thus a vicious cycle of tumor growth and bone destruction will develop resulting in SERs [15, 16].

The goal of treatment of cancer patients with bone metastases is focused mainly on palliation of pain, prevention of SREs and improvement of the quality of life. This can be achieved through the use of analgesics, radiation or surgery to bone, chemotherapy, and bone-targeting agents [17]. The bisphosphonates zoledronic acid is frequently used to delay or prevent SREs in cancer patients with bone metastasis [18-26]. Zoledronic acid is excreted through the kidneys so it may be associated with adverse events (AE) nephrotoxicity and renal failure in some patients, this may need dose adjustment or drug withholding [27- 30]. Other limitations to zoledronic acid include the route of its administration (intravenous) and some adverse events (AE) as acute flu-like syndrome and osteonecrosis of the jaw [27].

Denozumab is a fully human monoclonal antibody with high affinity and specificity for human RANKL, therefor inhibiting osteoclast function and bone destruction [30-33]. Denosumab was approved by the FDA for the prevention of SREs in patients with bone metastasis [34].

This present study was conducted to compare Denozumab with zolidronic acid in delaying or preventing the SREs in patients with advanced cancer and bone metastasis.

Patients and methods

Study population

This randomized clinical study included patients' ≥ 18 years old with histologically confirmed solid tumor and had radiological evidence of at least one bone metastasis by x-ray or computed tomography (CT) or magnetic resonance imaging (MRI) or bone scan. Patients had adequate renal function and had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2.

Study design

This prospective phase III clinical randomized study was conducted at the Clinical Oncology Department of Assiut University Hospital from 2014 to 2017. The Ethics Committee of Faculty of Medicine, Assiut University approved this protocol before data collection. Patients provided written informed consent before treatment. Patients were randomly classified into two groups, the first group received zoledronic acid (Zometa) 4 mg as an intravenous infusion over 15 minutes every 4 weeks and the second group received denosumab (XGEVA) as 120mg subcutaneous injection every 4 weeks.

The primary end point was time to first on-study SRE and the secondary endpoint was time to first-and-subsequent on-study SREs. The time to SREs was defined as the time from diagnosis of bone metastases, as confirmed on imaging, to the first occurrence of SREs.Subsequent SRE was

defined as an event occurred ≥21 days after the previous SRE. Routine chemistry was done at baseline and every 4 weeks. Skeletal surveys done at baseline and every 12 weeks. As in previous trials, development of new bone metastases was not included in the definition of SREs [21, 35, 36].

Statistical analysis

Continuous and categorical variables were summarized using the descriptive statistics. Kaplan-Meier method was used to estimate time to first on-study SRE. Andersen-Gill model was used to estimate time to first-and-subsequent on study SRE. X^2 test was used to calculate the P values. P values less than 0.05 was considered significant.

Results

A total of 100 patients were enrolled in this study, patients were classified into two groups. The first group (no=50 patients) received zoledronic acid and the second group (no=50 patients) received denosumab. Patients' demographic data were summarized in Table 1.

Table 1: Demographic characteristics of patients and tumor.

Character	Zoledronic acid (no.50)	Denosumab (no.50)
Sex no. (%)		
Female	37(74)	39(78)
Male	13(26)	11(22)
Mean age± standard deviation(SD)	52.7±9.1	54.6±10.2
Type of tumor no. (%)		
Breast	30(60)	32(64)
Non-small cell lung(NSCL)	7(14)	4(8)
Renal cell carcinoma	3(6)	6(12)
prostate	8(16)	7(14)
Non-Hodgkin lymphoma	2(4)	1(2)
ECOG status no. (%)		
0	19(38)	14(28)
1	27(54)	30(60)
2	4(8)	6(12)
Location of bone metastasis no. (%)		
Axial only	26(52)	22(44)
Appendicular only	7(14)	9(18)
Axial and Appendicular	17(34)	19(38)
Prior SRE	27(54)	25(50)
Presence of visceral metastasis, no. (%)		
Yes	37(74)	31(62)
No	13(26)	19(38)
Prior treatment		
Chemotherapy	42(84)	40(80)
Radiotherapy	27(54)	29(58)
Surgery	26(52)	20(40)
Hormonal therapy	17(34)	19(38)

Table 2: Incidence of SREs among patients group.		
	Zoledronic acid no. (%)	**Denosumab**
Type of SREs		
Radiation to bone	21(42)	13(26)
Surgery to bone	5(10)	3(6)
Spinal cord compression	9(18)	7(14)
Pathologic fracture	3(6)	5(10)

The mean age in patients received zoledronic acid was 52.7±9.1 and was 54.6±10.2 in patients received denosumab. Advanced breast cancer was the most common tumor in both groups (60% versus 64%); followed by prostate cancer (16% versus 14%). 54% of patients in the first group had SRE before the beginning of the study versus 50% in the second group.

Denosumab administration resulted in prolonging the time to first on-study SRE compared to zoledronic acid (95% confidence interval [CI], 0.82 to 1.44; P<0.04) figure 1. The median time to first on-study SRE was 21.9 month for denosumab versus 18.1 month for zoledronic acid (P<0.04).

During the period of study 18 (36%) patients had first on-study SRE in zoledronic acid group versus 13(26%) patients in denosumab group (P<0.04). In zoledronic acid arm 8(16%) patients developed subsequent on-study SRE versus 5(10%) patients in denosumab arm (P<0.04) figure 2. The most common SRE in both groups was radiation to bone (42% versus 26%) Table 2. There is a significant difference between patients without SREs on-study in the denosumab arm (64%) compared with patients without SREs on-study in the zoledronic acid arm (48%) at the end of study (P<0.04).

As regarding the toxicity of therapy, few patients in both groups had elevated serum creatinine level but no dose adjustment or drug withholding was needed, 5(10%) patients in zoledronic acid versus 1(2%) patient in denosumab arm (P<0.04), no incidence of occurrence of osteonecrosis of the jaw in the patients of both groups.

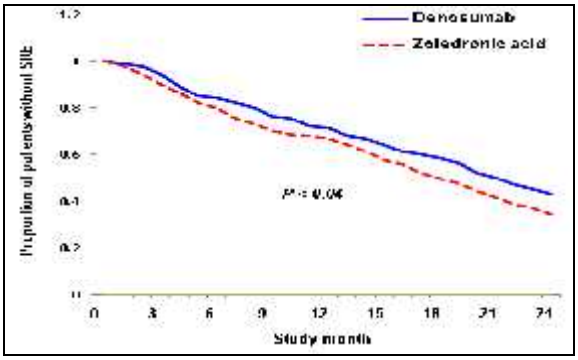

Figure 1: Kaplan-Meier estimate of time to first on-study skeletal-related events (SREs).

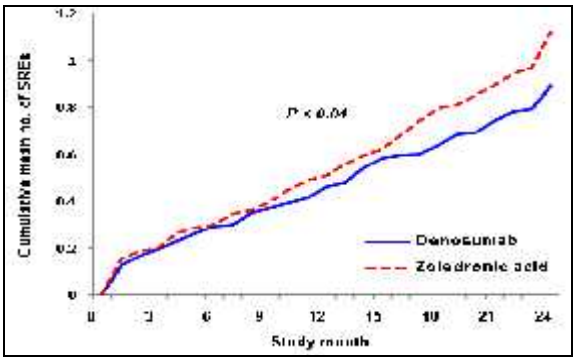

Figure 2: Time to first and subsequent on-study skeletal-related events (SREs).

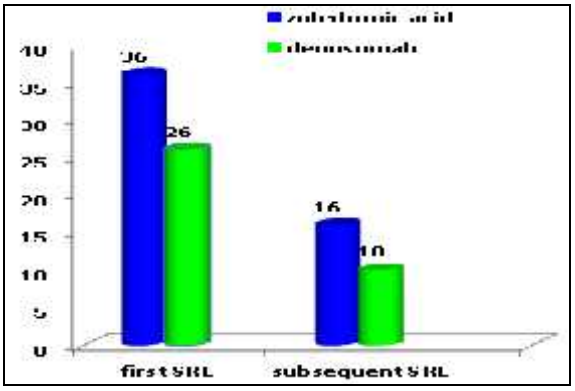

Figure 3: Incidence of first on- study SRE and subsequent on-study SRE.

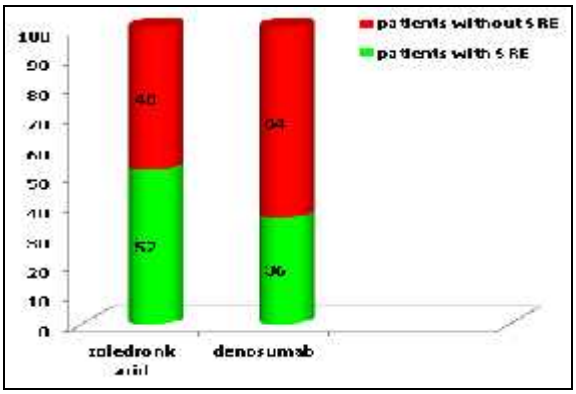

Figure 4: Patients with SRE on-study and patients without SRE on-study.

Discussion

In cancer patients with advanced stage, bone is a common site of metastasis. The most common tumors that spread to bones are breast, prostate, and lung [1, 3, 15]. Bone resorption resulted from bone metastasis increases the risk of SREs [1, 3, 5, 15]. Bone-targeting agents reduce the risk of developing SREs associated with bone metastases [25, 26, 30-33]. Intravenous bisphosphonates zoledronic acid is effective in delaying and preventing SREs, however SREs still occur in large number of patients treated with zoledronic acid [18, 19]. Zoledronic acid has been associated with some AE as acute flu-like syndrome, nephrotoxicity, and osteonecrosis of the jaw [35]. Therefore, other bone-targeting agents are required. Denosumab differs in mechanism of action as it is a fully human monoclonal antibody against RANKL so prevent osteoclast-mediated bone destruction [34].

In this prospective phase III study administration of subcutaneous 120mg of denosumab every 4 weeks was superior to intravenous infusion of 4mg of zoledronic acid every 4 weeks in delaying and preventing the incidence of SREs in patients with advanced cancer to bone. Denosumab reduced the incidence of first on-study SRE and first-and-subsequent on-study SREs. These results are consistent with the previous trials [30, 32, 37-40]. In denosumab group the less frequent need for radiation to bone provides an objective measure of pain control and subsequently improves the quality of life (QOL) of patients. As regarding toxicity, zoledronic acid was associated with some AE as renal toxicity compared to denosumab. Denosumab does not require renal function monitoring or dose adjustment or drug withholding in case of renal impairment. 10% of patients treated with zoledronic acid had increased serum creatinine compared with 2% in the denosumab arm, these results are consistent with the results reported in other studies [41]. The subcutaneous administration of denosumab provided convenience for patients and eliminated the need for intravenous administration of zoledronic acid over 15 minutes. These finding are similar to that reported in the previous studies [42,43].

Conclusion

Denosumab was more efficacious in delaying and preventing the SREs than zoledronic acid. Moreover denosumab reduced the need for radiation to bone, reduced the risk of renal toxicity, and improved the QOL of patients. Subcutaneous administration of denosumab was more convenient than the intravenous administration of zoledronic acid.

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