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Bone modifying agents: incidence and risk factors of adverse reactions in bone metastasis

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ABSTRACT

Background: Bone-targeted agents such as Zoledronic Acid (ZA) and Denosumab (DE) are essential in preventing skeletal-related events in cancer patients with bone metastasis. Both drugs carry risks of adverse events (AEs), including electrolyte disorder, nephrotoxicity, and osteonecrosis of the jaw. *Aim*: To compare the safety profiles of ZA and DE and identify risk factors associated with AEs in cancer patients with bone metastasis. *Methodology*: A retrospective cohort study was conducted from August 1, 2021, to August 1, 2023, at the Cancer Care and Research Centre. Adult patients with solid tumors and confirmed bone metastasis who received either ZA or DE were included. Patients taking these agents for other indications were excluded. Data from electronic health records, lab results, and medication charts were analyzed. Univariate analysis was used to assess AE risk factors. *Results*: A total of 250 patients were included (ZA=125, DE=125). The incidence of AEs was higher in the ZA group. Calcium disorder occurred in both groups. Comorbidities were significantly associated with increased AE risk (p<0.001). DE showed a better safety profile. *Conclusion*: Denosumab was linked to fewer AEs than Zoledronic Acid. Comorbidities increased AE risk, highlighting the need for preventive strategies.

KEYWORDS

solid tumor, bone-targeted agents, calcium disorder, incidence, comorbidity

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1. INTRODUCTION

Bone metastasis can lead to complications and increased morbidity, and eventually to skeletal-related events “SREs” associated with high incidence of fracture, bone pain, spinal cord compression, hypercalcemia of malignancy, palliative radiation to the bone, and palliative bone surgery [1].

Bone-targeted agents (BTAs) are used to prevent SRES and improve the patient’s quality of life, BTAs such as bisphosphonates and the monoclonal antibodies. Bisphosphonate work by inhibiting the metabolism and apoptosis of osteoclast. Denosumab (DE) is a subcutaneous full human mono-

clonal antibody immunoglobulin G2 isotype drug with affinity for nuclear factor-kappa ligand (RANKL) working by inhibiting (RANKL) [2].

The risks which are common with ZA and DE are osteonecrosis of jaw (ONJ), electrolyte disorder (hypocalcaemia, hypercalcemia, hypophosphatemia, hypokalaemia, and hypomagnesemia), and nephrotoxicity [3].

There are certain factors that might affect patient's risk of developing these adverse reactions, for example hypocalcaemia can be linked with vitamin D deficiency, and for other rare events like osteonecrosis of jaw (ONJ), infections could play a role in the occurrence [4]. Other disorders like diabetes and rheumatoid arthritis and other chronic disorders could also play a role in enhancing the inflammation and changes in immune cell function [5].

Here in the leading cancer centre in Sultanate of Oman both Zoledronic Acid (ZA) and Denosumab (DE) are used in the treatment-plan of SREs associated with bone metastasis in patients with solid tumours. The purpose of this study is to investigate the incidence of adverse reactions with BTAs (Zoledronic Acid and Denosumab) in Omani population. Moreover, we aim to identify risk factors for the development of adverse reactions.

2. METHODOLOGY

2.1. Study design

This retrospective cohort study reviewed all the patient's (250) electronic medical records, laboratory results, and their medication charts for the period between August 2021-August 2023. The protocol of the study was approved by the Ethic Committee of college of pharmacy and the Institutional Review Board & Ethic Committee of Sultan Qaboos Comprehensive Cancer Care and Research Centre.

2.2. Inclusion and exclusion criteria

We included all adult cancer patients (18 years and above) who were diagnosed with bone metastasis secondary to a solid tumour and were receiving bone-targeting agents (BTAs), either zoledronic acid or Denosumab. Zoledronic acid dose used was 4 mg and administrated intravenously over at least 15 minutes every 3 to 4 weeks, or every 3 months, while denosumab was administrated subcutaneously at a dose of 120 mg dose every 3 to 4 weeks or every 3 months. Our exclusion criteria included patients who were receiving BTAs for other medical conditions such as osteoporosis, osteopenia, and as adjuvant agents for non-metastatic breast cancer.

2.3. Study variables

All patient characteristics like gender, age, weight, height, and BMI were included. Clinical characteristics were reported by oncologists involving solid tumour type, presence and time of bone metastasis, and medical history of patients. Moreover, Laboratory readings were done at each visit to the centre.

2.4. Statistical analysis

Descriptive statistics were used to summarize all the parameters of patients. We used means, standard deviation and frequency (percentage) to represent the data. We further tested the association between the variables using univariate analysis like the chi-square. Multivariate analysis was also used like MANOVA test to compare the means between the electrolyte's levels, and Binary logistic was used to further test the predictors effect on the adverse events. Statistical graphs and tables were used to represent the data. P-values were two-tailed of a value <0.05. We preformed all statistical tests and data analysis using SPSS 26.

3. RESULTS

Baseline Characteristics: A total of 250 patients met the inclusion criteria and were enrolled in the study, with an equal distribution between the two groups (ZA=125; DE=125). Patients were followed for six treatment cycles with either zoledronic acid or denosumab.

The majority were female (87.6%), while male patients accounted for 12.4%. The mean age was 59.2 years in the ZA group and 54.6 years in the DE group.

Breast cancer was the most common primary tumor (81.6%), followed by prostate cancer (5.6%), colon cancer (6%), non-small cell lung cancer (1.6%), gastric cancer (1.2%), and other advanced cancers (4%).

All patients received calcium and vitamin D supplementation, except for two individuals.

Baseline characteristics were comparable between the ZA and DE groups, as detailed in Table 1.

Incidence of Electrolytes Disorder: The incidence of hypocalcaemia was higher among patients taking denosumab vs zoledronic acid (28.8% vs. 14.4%, p=0.04), while the incidence of hypercalcemia was found out to be slightly higher

with denosumab vs zoledronic acid (18.4% vs. 12%, *p*=0.03). The higher incidence of hypocalcemia with denosumab may influence treatment decisions and requires close monitoring during therapy.

Table 1. Baseline characteristics of patients.

Demographics		
Characteristics n (%)	Denosumab (N=125)	Zoledronic-Acid (N=125)
Female	107 (85.6%)	112 (89.6%)
Male	18(14.4%)	13 (10.4%)
Mean age (year)/ SD	54.6 years/+-10.8	59.2 years/+-13
Mean weight (kg)/SD	70.4 kg/+-15	78.8kg/+-17.1
Mean height (cm)/SD	158.8 cm/+-7.4	157.2cm/+-8
Diagnosis n (%)		
Breast cancer	100 (80%)	104 (83.2%)
Prostate cancer	9 (7.2%)	5(4%)
Non-Small Cell Lung Cancer (NSCLC)	3 (2.4%)	1(0.8%)
Colon cancer	5 (4%)	10 (8%)
Gastric cancer	1 (0.8%)	2(1.6%)
Other advanced cancer	7 (5.6%)	3 (2.4%)

Sub-group analysis of adverse reaction**:** The association between the adverse reaction and presence of comorbidity were tested by using chi-square test. Out of 250 patients, 75 patients experienced adverse reaction with the presence of comorbidity. The fisher's exact test was calculated, and *p*-value was found out to be <0.001.

Analysis of calcium levels with MANOVA**:** Calcium level readings were measured for six cycle, and MANOVA test was used to compare the means of the calcium levels in regard to the time for three cycles. There were differences in cycle 1 to cycle 3, calcium levels dropped significantly (p<0.001).

3. DISCUSSION

Identical findings were reported in a clinical trial study between DE and ZA reporting a higher incidence of hypocalcaemia among the DE group vs the ZA group due to its higher antiresorptive effect (3.1% vs 1.3%) [6].

There were few articles comparing the safety profile between ZA and DE. One meta-analysis article that reviewed 13 randomized clinical trials discovered that the incidence of adverse events was lower with DE group vs ZA group (86.3% vs 87.6%, OR= 0.84, 95% CI: 0.75-0.94, p-0.003). [7] Certain risk factors play a role in the development of the adverse events, such as the presence of comorbidity. Additionally, a retrospective study analysed the risk factors associated with hypocalcaemia and found that vitamin D deficiency was associated with a higher risk of hypocalcaemia, whereas calcium and vitamin D supplementation reduced the risk (*p*=0.01, and *p*=0.03, respectively) [8].

MANOVA was used to compare the means of the calcium levels and showed significant differences between the means of the calcium readings from cycle 1 to cycle 3. The starting calcium levels from cycle 1 mean was 2.3 mmol/ L, and the calcium levels from cycle 3 mean was 2.1 mmol/L. Our study had multiple limitations, first of all it was conducted retrospectively in a single-centre and focused only on solid-tumour cancer types, plus the follow-up period was short and not enough for long-term side effects of these medications.

4. CONCLUSION

This study was well focused on the safety profile of ZA and DE, and it emphasizes the importance of frequent monitoring of calcium levels for the management of side effects including the administration of calcium and Vitamin D supplements especially with DE patients.

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CONFLICT OF INTEREST STATEMENT
The author declares no conflicts of interest.

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