A Retrospective Analysis of Denosumab for the Treatment of Bone Metastases in Chinese Patients With Breast Cancer

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ABSTRACT

BACKGROUND: Denosumab entered the Chinese market for the first time in 2020. Since it is a short period of time, there is a lack of data on its effectiveness and safety in Chinese people. The objective of this study was to evaluate the effectiveness and safety of denosumab in delaying skeletal-related events (SREs) in patients with breast cancer metastatic to bone.

METHODS: The study retrospectively analyzed data from breast cancer patients with bone metastases (BM) who were treated with denosumab in the First Affiliated Hospital of Nanjing Medical University from September 2020 to January 2022. The primary endpoint was SRE incidence at 1 year after receiving denosumab treatment. The secondary endpoints included time to first on-study SRE and safety. Descriptive analysis was utilized to display clinicopathological features. The Kaplan-Meier method was used to estimate the median time to first on-study SRE in total population and subgroups. Logistic regression analysis and χ^2 test were employed to determine the potential factors influencing the occurrence of SREs.

RESULTS: Fifty breast cancer patients with BM were enrolled in our study, and 54.0% of the patients had 5 or more metastatic bone lesions. After a median follow-up of 17.00 months, 24% of the patients developed SREs at 1 year after receiving denosumab treatment, and the median time to first on-study SREs was not reached. Five or more metastatic bone lesions were an independent risk factor for SRE occurrence (odds ratio = 6.06, 95% CI: 1.09-33.54, $P = .039$). The adverse events (AEs) associated with denosumab mainly included hypocalcemia (68.0%), periodontitis (28.0%), and myalgia (14.0%). Only 3 cases of grade III/IV AEs were reported, and no serious AEs occurred.

CONCLUSION: Denosumab was effective and well tolerated in Chinese breast cancer patients with BM.

KEYWORDS: Breast cancer, denosumab, bone-modifying agents, skeletal related events, bone metastasis

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Introduction

Bone is a common site of metastasis in patients with breast cancer, and studies have shown that bone metastases (BM) can occur in 55% to 75% of patients with advanced breast cancer.[1] Skeletal-related events (SREs) are the sum of a series of bone complications due to disease progression in malignant tumor patients with BM, including pathological fractures, surgery to bone, radiotherapy to bone, and spinal cord compression.[2] Yan reported that most BM from breast cancer were osteolytic, which predisposes to the occurrence of SREs.[3] The incidence of SREs can be as high as 64% without the administration of bone-modifying agents (BMAs).[4] Compared with breast cancer patients who did not experience SREs, those with SREs had a shorter median survival time.[5]

To reduce the risk of SREs in patients with BM, European Society of Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), and Chinese Society of Clinical Oncology (CSCO) guidelines jointly recommend initiating treatment with BMA immediately after diagnosis of BM and continuing BMA throughout the course of the disease. Currently available BMA included bisphosphonates (BPs) and denosumab. BPs are effective at preventing SREs for the treatment of BM in patients with breast cancer. Despite the BP therapy, SREs still occur in a large portion of patients. Moreover, renal toxicity and acute-phase reactions arise frequently after BP treatment, which may further complicate management of patients.[6]

Denosumab is a fully human monoclonal antibody that specifically binds to the receptor activator of nuclear factor-κB ligand (RANKL), impeding osteoclast maturation and activation and inhibiting bone resorption.[7] A randomized, double-blind, active controlled study has shown that denosumab was superior to zoledronate in delaying SREs in patients with breast cancer metastatic to bone and was generally well tolerated.[8] Both domestic and international guidelines consistently recommend denosumab with high-level evidence for the treatment of BM in patients with breast cancer.[9-11]

In China, denosumab has only been clinically accessible since May 2020, meanwhile it is more expensive than BPs and not covered by medical insurance. Therefore, denosumab has not been widely used in breast cancer patients with BM. The effectiveness and safety of denosumab in Chinese patients with breast cancer metastatic to bone needs further investigation. This study aims to observe the clinical effect and adverse events (AEs) of denosumab for the treatment of BM in patients with breast cancer and to explore the potential clinicopathological factors affecting its effectiveness.

Patients and Methods

Patient inclusion criteria

Patients who met the following conditions were enrolled in this retrospective study: (1) age ⩾ 18 years; (2) histologically or cytologically confirmed breast cancer with radiological imaging suggestive of at least 1 bone metastasis; (3) adequate organ function; (4) Eastern Cooperative Oncology Group score ⩽ 2; (5) complete medical recordings, including treatment regimens, effectiveness assessment, and AEs.

Study design

This study enrolled breast cancer patients with BM treated with denosumab in the First Affiliated Hospital of Nanjing Medical University from September 2020 to January 2022. All patients received denosumab treatment, 120 mg subcutaneously, once per cycle every 28 days. The demographic information, clinicopathology features, and combined antitumor regimen, radiographical, and laboratory examination were retrospectively collected.

Study endpoints

The primary endpoint of this study was SRE incidence at 1 year after receiving denosumab treatment. SREs were defined as pathological fracture, bone surgery, bone radiotherapy, and spinal cord compression. The secondary endpoint was the time to first on-study SRE, defined as the time from initiation of denosumab treatment to the occurrence of first on-study SRE. AEs were recorded as safety endpoints according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE 5.0).

Statistical analysis

A χ^2 test was used to perform 1-way analysis of factors that may influence the occurrence of SREs after 1 year treatment of denosumab. Logistic regression analysis was employed to perform a multifactorial analysis of factors that may influence the occurrence of SREs. The median time to first on-study SRE was analyzed using the Kaplan-Meier method. Factors with $P < .5$ in a single-factor analysis or factors clinically meaningful were included in a multifactor analysis. All P values and confidence intervals were tested by a 2-sided test, and $P < .05$ was considered statistically significant. These statistical data were performed using SPSS Statistics 26.0 software (SPSS Inc, Chicago, IL, USA)

Results

Patient characteristics

Fifty patients were enrolled in our study. The median age of patients was 54 years, ranging from 30 to 74 years. Eighty percent of patients (40/50) had a body mass index ⩽ 24, and 76.0% (38/50) were postmenopausal. Forty percent (20/50) of patients were hormone receptor (HR)-positive human epidermal growth factor receptor 2 (HER2)-negative, 38.0% (19/50) were HER2-positive, and 22.0% (11/50) were triple-negative. Patients with BM alone accounted for 16% (8/50), and those with visceral metastases accounted for 64.0% (32/50). Fifty-four percent (27/50) of patients had 5 or more metastatic bone lesions. All patients received concurrent antitumor therapy, 68.0% (34/50) of patients received chemotherapy, 72.0% (36/50) received targeted therapy, and 18.0% (9/50) received endocrine therapy. Of the enrolled patients, 70.0% (35/50) had previous history of SREs, and 14% (7/50) had received prior treatment of BPs. Sixty-six percent (33/50) of patients initiated denosumab therapy within 3 months after the diagnosis of BM. The baseline characteristics of the patients are shown in Table 1.

Clinical effectiveness

With denosumab treatment, SREs incidence was 14% (7/50) at 6 months and 24% (12/50) at 1 year in breast cancer patients with BM, including 5 cases of pathological fracture, 3 cases of spinal cord compression, 3 cases of bone radiotherapy, and 1 case of bone surgery. See Table 2.

After 1 year of treatment with denosumab, 23.7% of postmenopausal patients and 25.0% of premenopausal patients developed SREs. The incidence of SREs in HR-positive HER2-negative, HER2-positive, and triple-negative breast cancer patients was 30.0%, 15.8%, and 27.3%, respectively. SREs occurred in 12.5% of patients with BM alone and 26.2% of those with non-BM alone. The incidence of SREs was 8.7% in patients with less than 5 metastatic bone lesions and 37.0% in patients with 5 or more metastatic bone lesions. See Table 3.

At a median follow-up of 17.00 months, the median time to first on-study SREs had not been reached. Survival analysis is shown in Figure 1.

Analysis of relevant factors affecting the denosumab effectiveness

Univariate analysis of factors influencing SRE incidence after denosumab treatment. χ^2 Univariate analysis showed that SRE incidence was significantly increased in patients with ⩾5 metastatic bone lesions compared with patients with <5 metastatic bone lesions after 1-year application of denosumab ($\chi^2 = 5.469$,

Table 1. Clinicopathological characteristics of patients.

CHARACTERISTICS	PATIENTS (N = 50)	
	NO.	%
Age, years		
Median (range)	54 (30-74)	
BMI		
⩽24	40	80.0
>24	10	20.0
Menstrual status		
Postmenopausal	38	76.0
Premenopausal	12	24.0
ECOG status		
0-1	35	70.0
2	15	30.0
Molecular type		
HR-positive HER2-negative	20	40.0
HER2-positive	19	38.0
Triple negative	11	22.0
BM alone	8	16.0
Visceral metastases	32	64.0
Number of metastatic bone lesions		
⩾5	27	54.0
<5	23	46.0
Combined antitumor regimen		
Chemotherapy	34	68.0
Targeted	36	72.0
Endocrine therapy	9	18.0
Prior SREs	35	70.0
Initial BMA		
BPs	7	14.0
Denosumab	43	86.0
Time interval between BM diagnosis and denosumab initiation		
⩽3 months	33	66.0
>3 months	17	34.0

Abbreviations: BM, bone metastases; BMA, bone-modifying agents; BMI, body mass index; BPs, bisphosphonates; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; SREs, skeletal-related events.
The number of metastatic bone lesions was calculated at the time of initiation of denosumab therapy.

$P = .019$). In contrast, age, menstrual status, molecular subtype of breast cancer, metastatic sites, combined antitumor regimen, prior history of SREs, initial BMA, time interval between BM diagnosis and denosumab initiation, and actual denosumab dosing interval showed no significant influence on SRE occurrence after denosumab treatment. χ^2 Test univariate analysis is shown in Table 3.

Table 2. The incidence and distribution of SREs after denosumab treatment.

CLINICAL EFFECTIVENESS	PATIENTS (N = 50)	
	NO.	%
Therapeutic effect		
Incidence of SREs after 6 months administration	7	14.0
Incidence of SREs after 1 year administration	12	24.0
1-Year SREs distribution		
Pathological fractures	5	10.0
Spinal cord compression	3	6.0
Bone surgery	1	2.0
Bone radiotherapy	3	6.0
Time to first on-study SREs, months		
Median (95% confidence interval)	Not reached	
Follow-up time, months		
Median (range)	17.00 (16.00-18.00)	

Abbreviation: SREs, skeletal-related events.

Multifactor analysis affecting SRE incidence after denosumab treatment. The logistics multifactorial analysis showed that patients with ⩾5 metastatic bone lesions had a significantly higher risk of developing SREs than those with <5 metastatic bone lesions after 1-year application of denosumab (odds ratio [OR] = 6.06, 95% CI: 1.09-33.54, $P = .039$), whereas metastatic sites, initial BMA, and time interval between BM diagnosis and denosumab initiation showed no significant influence on SRE occurrence after denosumab treatment. The logistic multifactorial analysis is shown in Table 4.

Safety

The most common AEs associated with denosumab in our study were hypocalcemia (68.0%), followed by periodontitis (28.0%). Other AEs included myalgia (14.0%), abnormal renal function (10.0%), arthralgia (4.0%), and osteonecrosis of the jaw (4.0%), all of which were mainly of grade I-II. Grade III or greater AEs included periodontitis and hypocalcemia, with the incidence of 4% and 2%, respectively. There were no denosumab-related serious adverse events and deaths, as detailed in Table 5.

Discussion

As a kind of severe skeletal complication, SREs contribute to a substantial deterioration in quality of life for breast cancer patients

Table 3. χ^2 Univariate analysis.

FACTORS	NO. OF CASES (%)	NO. OF SRE CASES (%)	χ^2 VALUE	*P* VALUE
Age			0.521	.411
⩽50 years old	19 (28.0)	6 (31.6)		
>50 years old	31 (62.0)	6 (19.4)		
Menstrual status			0.000	1.000
Premenopausal	12 (24.0)	3 (25.0)		
Postmenopausal	38 (76.0)	9 (23.7)		
Molecular subtype			1.251	.632
HR-positive HER2-negative	20 (40.0)	6 (30.0)		
HER2-positive	19 (38.0)	3 (15.8)		
Triple negative	11 (22.0)	3 (27.3)		
BM alone			0.144	.704
No	42 (84.0)	11 (26.2)		
Yes	8 (16.0)	1 (12.5)		
Visceral metastases			0.663	.416
No	18 (36.0)	6 (33.3)		
Yes	32 (64.0)	6 (18.8)		
Number of metastatic bones lesions			5.469	.019
<5	23 (46.0)	2 (8.7)		
⩾5	27 (54.0)	10 (37.0)		
Combined antitumor regimen			1.890	.366
Chemotherapy	34 (68.0)	9 (26.5)		
Targeted therapy	36 (72.0)	8 (22.2)		
Endocrine therapy	9 (18.0)	4 (44.4)		
Prior SREs			0.005	.942
No	15 (30.0)	3 (20.0)		
Yes	35 (70.0)	9 (25.7)		
Initial BMA			0.612	.434
Denosumab	43 (86.0)	9 (20.9)		
BPs	7 (14.0)	3 (42.9)		
Time interval between BM diagnosis and denosumab initiation			0.985	.321
⩽3 months	33 (66.0)	6 (18.2)		
>3 months	17 (34.0)	6 (35.3)		
Actual dosing interval			0.035	.852
⩽28 days	28 (56.0)	7 (25.0)		
>28 days	22 (44.0)	5 (22.7)		

Abbreviations: BM, bone metastases; BMA, bone-modifying agents; BPs, bisphosphonates; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; SRE, skeletal-related event.

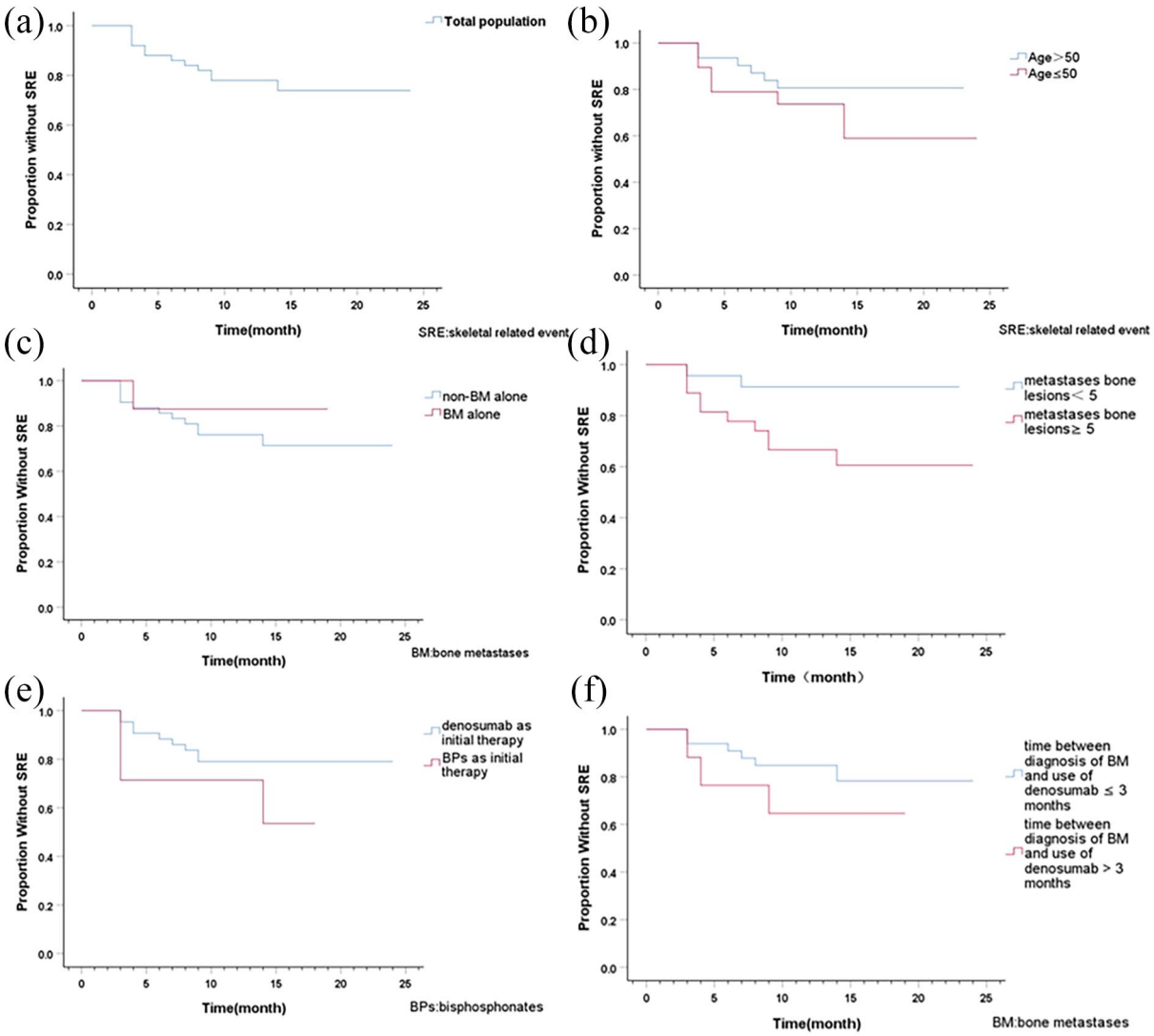

Figure 1. Kaplan-Meier curve of time to first on-study SRE. (A) In the total population. (B) Age ⩽ 50 years vs > 50 years. (C) BM alone vs nonbone metastasis alone. (D) Metastatic bone lesions < 5 vs ⩾ 5. (E) Denosumab vs BPs as initial therapy. (F) Time interval between bone metastasis diagnosis and denosumab initiation > 3 months vs ⩽ 3 months.
BM indicates bone metastases; BPs, bisphosphonates; SRE, skeletal-related event.

with BM. BMA can effectively reduce the occurrence of SREs in patients with breast cancer.[12] Denosumab, a monoclonal antibody targeting RANKL, has been recommended for the treatment of BM in patients with breast cancer by multiple guidelines, including the NCCN, ESMO, and CSCO guidelines.[9-11]

However, denosumab has only been clinically accessible since May 2020 and has not been covered by medical insurance in China. Therefore, the activity and safety data of denosumab in Chinese patients with breast cancer metastatic to bone are quite limited. To our knowledge, this research is the first real-world study conducted in Chinese breast cancer patients with BM. Our findings further consolidate the activity and safety of denosumab in Chinese populations and provide primary data for the real-world application of denosumab in patients with breast cancer metastatic to bone.

Study 136[13] compared the efficacy of zoledronate and denosumab in breast cancer patients with BM. It showed that more than half of the patients in the zoledronate group had already experienced their first on-study SREs at 27 months, while most patients in the denosumab group had not yet experienced their first SREs, suggesting that denosumab was superior to zoledronate in delaying SREs in patients with breast cancer metastatic to bone.

In Study 136, the SRE incidence was approximately 23.0% at 6 months and 30.0% at 1 year in the denosumab group. In our study, the SRE incidence at 6 months and 1 year after denosumab administration was 14.0% and 24%, respectively, showing a lower SRE occurrence rate than that in Study 136. This may be due to the great improvement in imaging technology and antitumor strategy for breast cancer in recent years. The

Table 4. Logistics multifactor analysis.

FACTORS	REGRESSION COEFFICIENT	STANDARD ERROR	WALD χ^2 VALUE	*P* VALUE	OR VALUE	95% CI
Age (≤50 vs >50 years)	−0.50	0.74	0.46	.500	0.61	0.14-2.58
BM alone (no vs yes)	−0.80	1.19	0.45	.501	0.45	0.04-4.62
Number of metastatic bone lesions (<5 vs ≥5)	1.80	0.87	4.25	.039	6.06	1.09-33.54
Initial BMA (denosumab vs BPs)	0.92	0.96	0.93	.335	2.51	0.39-16.38
Time interval between BM diagnosis and denosumab initiation (≤3 vs >3 months)	0.78	0.75	1.08	.298	2.17	0.50-9.39

Abbreviations: BM, bone metastases; BMA, bone-modifying agents; BPs, bisphosphonates; CI, confidence interval; OR, odds ratio.

Table 5. Adverse effects.

ADVERSE EFFECTS	I	II	III	IV	ALL GRADES		GRADE III/IV	
					NO.	(%)	NO.	(%)
Hypocalcemia	26	7	-	1	34	68.00	1	2.00
Periodontitis	7	5	2	-	14	28.00	2	4.00
Myalgia	5	2	-	-	7	14.00	-	-
Abnormal renal function	3	2	-	-	5	10.00	-	-
Arthralgia	2	-	-	-	2	4.00	-	-
Osteonecrosis of the jaw	1	1	-	-	2	4.00	-	-
Injection site pain	1	-	-	-	1	2.00	-	-
Fever	-	-	-	-	-	-	-	-
Serious adverse events	-	-	-	-	-	-	-	-

BM could be detected at early stages and then treated with various highly effective agents, leading to a decreased development of SREs. In addition, the incidence of SREs varies among different subtypes of breast cancer. Neither Study 136 nor our current study has defined patients with specified subtypes of breast cancer; therefore, subgroup proportion imbalance in baseline would also lead to the intrinsic difference in SRE incidence. Study 136 also showed that SRE incidence in the zoledronate group was approximately 25.0% at 6 months and 33.0% at 1 year, indicating a higher occurrence rate than that after denosumab treatment both in Study 136 and our study, further demonstrating denosumab's superior effectiveness in preventing SREs in breast cancer patients with BM.

To explore the potential factors affecting the effectiveness of denosumab in this study, we performed a χ^2 univariate analysis and a logistic multivariate analysis. Both analyses showed the incidence of SREs was significantly increased in patients with ≥5 metastatic bone lesions compared with that in patients with <5 metastatic bone lesions after 1 year of denosumab application (OR, 6.06, 95% CI: 1.09-33.54, *P* = .039). In the study by Chen et al.,[14] they obtained similar results, showing that breast cancer patients with ≥5 metastatic bone lesions had a shorter time to develop SREs (HR = 1.698, *P* = .02). These data alerted us to pay more attention to the patients with multiple metastatic bone lesions and urge them to follow regular treatment and examination.

Our study showed that the incidence of SREs in patients with and without previous SREs after 1 year of treatment with denosumab was 25.7% and 20.0%, respectively, indicating a higher risk of SREs in patients with a prior SRE history. This result was in accordance with the study by Bhowmik et al., which retrospectively studied the incidence of SREs in patients with solid tumors[15] and found that patients with previous SREs had a significantly increased risk of subsequent SREs. Lipton et al. performed a combined analysis of 3 pivotal phase III clinical trials applying BMA to malignant tumor patients with BM, also demonstrating that the SRE incidence is higher in patients with previous SREs,[16] underlining the importance of early diagnosis and treatment of BM.

A Swedish retrospective study investigated the optimal regimen of BMA in patients with metastatic cancer.[17] Compared with continuing the zoledronate therapy, switching the strategy

from zoledronate to denosumab significantly reduced the risk of SREs by 53% (HR = 0.47, 95% CI: 0.25-0.88, $P = .019$). Our study showed a lower SRE incidence with denosumab as the initial bone-modifying therapy than with BPs as the initial bone-modifying therapy (20.9% vs 42.9%). Although a statistically significant difference was not reached, which may be attributed to the short follow-up period and insufficient sample size in this study, long-term follow-up and a larger sample size are needed to further confirm this finding.

Kettle and Patel[18] retrospectively analyzed the feasibility of extending the dosing interval of denosumab in patients with primary bone tumors and metastatic cancer and showed that SRE incidence was significantly lower with a standard dosing interval of 28 days than with a longer dosing interval. In our study, the SRE incidence was found to differ with different dosing intervals, but the difference between standard and deviated interval was small (25.0% vs 22.7%) and not statistically significant. The majority of our patients had a good compliance. Although some patients did prolong their dosing interval, the delay was not too much, with a median dosing interval of only 47 days.

Our study showed a low incidence of myalgia (14% in our study vs 20.0% in Study 136) and arthralgia (4% in our study vs. 24.5% in Study 136) after denosumab therapy, probably because this study was retrospective and some of these AEs were not reported and recorded, resulting in an underestimation of the incidence of AEs. Most of the patients suspended treatment because of severe hypocalcemia and periodontitis. The incidence of hypocalcemia (68% in our study vs 5.5% in Study 136) and periodontitis (28% in our study vs 5.6% in Study 136) were obviously higher in our study than those in prior large studies. The reasons may be as follows: With respect to hypocalcemia, Study 136 strongly recommended daily calcium and vitamin D supplementation for patients participating in the study, whereas in our study, a considerable proportion of patients failed to follow the advice to take calcium and vitamin D routinely. Moreover, 76% of our patients were postmenopausal, further aggravating the risk of hypocalcemia. Regarding periodontitis, Study 136 excluded patients with previous unhealed dental or oral surgery, whereas our study did not rule out these patients. However, most hypocalcemia and periodontitis AEs were mild and manageable, and the grade III/IV hypocalcemia and periodontitis accounted only 2% and 4%, respectively.

The limitations of this study include a single-center retrospective analysis and a small number of enrolled cases. Our study lacks sufficient power to conclude the superior efficacy and safety of denosumab versus traditional BPs. Multicenter randomized controlled trials in larger cohorts are needed to further confirm the superiority of denosumab in efficacy and safety compared with BPs. Besides, due to the relatively short follow-up time, it is unable to observe patients' compliance to long-term denosumab treatment.

Conclusions

Denosumab was active and well tolerated in Chinese breast cancer patients with BM, especially in those with multiple metastatic bone lesions. This limited small study confirms the effective and safe real-world use of denosumab in patients with breast cancer metastatic to bone and states that it is comparable to that seen in clinical trials. Further validation in a large-scale real-world population is warranted.

Author Contributions

Wei Li completed data processing, article writing, proofreading, and revision. Xinyu Wu mainly was involved in article ideas and data guidance. Heng Yu, Zekai Zhu, and Wenjie Li completed data collection, data processing, and first-draft writing. Xiang Huang was mainly involved in article design, supervision, and revision of article. All authors read and approved the final. All authors approved the final version of manuscript for submission.

Ethical Approval

Approval was granted by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (approval no: 2022-SR-494). This was a retrospective study, so informed consent was not required by the board.

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