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ORIGINAL RESEARCH

Safety Profile and Predictors of Adverse Events of Incadronate Disodium in Treating Breast Cancer Patients with Bone Metastases: A Retrospective Study

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Purpose: Bone metastasis is a common complication in advanced breast cancer. Bisphosphonates like incadronate disodium have shown potential in reducing bone resorption and skeletal-related events. We therefore performed a retrospective study to evaluate the safety profile of incadronate disodium in breast cancer patients with bone metastases.

Patients and Methods: This retrospective study was conducted involving 84 breast cancer patients with bone metastases who received incadronate disodium treatment between February 2022 and August 2024 in our center. The primary endpoint was the incidence of dental-related issues and acute phase reactions, with an analysis of the associated risk factors. The secondary endpoint was the incidence of other adverse events. Adverse events were recorded during treatment and within 90 days post-treatment.

Results: Dental-related issues were observed in 33.3% of patients and only one (1.2%) developed medication-related osteonecrosis of the jaw. Higher risk was significantly associated with prolonged treatment duration (OR = 4.33, 95% CI:1.21–15.50), secondary bone metastases (OR = 6.3, 95% CI:1.58–25.00), and lower hemoglobin levels (OR = 4.16, 95% CI:1.31–13.2) at multivariate analysis. 26.2% patients occurred acute phase reactions. Higher medication doses (OR = 1.41, 95% CI:1.07–2.05), multiple metastatic sites (OR = 4.22, 95% CI:1.39–15.89) and lower hemoglobin levels (OR = 3.27, 95% CI:1.21–9.22) were significant in univariate analysis, but not in multivariate analysis. Rare adverse effects included renal dysfunction (1.2%) and hypocalcemia (4.76%).

Conclusion: Incadronate disodium demonstrates a favorable safety profile for treating bone metastases in breast cancer patients. Identified risk factors, such as prolonged treatment duration and lower hemoglobin levels, highlight the need for intensified dental health management and personalized treatment strategies.

Keywords: breast cancer, bone metastasis, bisphosphonate, incadronate disodium, adverse effect

Introduction

Breast cancer is one of the most common malignant tumors among women worldwide. According to the 2020 GLOBOCAN statistics, breast cancer has overtaken lung cancer to become the most common cancer in women, with approximately 2.3 million new cases globally, accounting for 24.5% of all malignant tumors in women.[1] With the widespread use of early screening and continuous improvements in treatment methods, the survival rate of breast cancer patients has increased significantly. However, among newly diagnosed breast cancer patients each year, approximately 3% to 10% have distant metastasis at the time of diagnosis.[2] About 30% of early-stage patients may progress to advanced

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breast cancer. Compared to early-stage breast cancer, the prognosis of advanced breast cancer is worse, with a 5-year survival rate of only 20% and a median overall survival time of 2 to 3 years.[3,4] Bone metastasis (BM) remains a serious clinical problem in the advanced breast cancer. The mechanism of bone metastasis is complex and mainly involves the interaction between tumor cells and the bone microenvironment, which ultimately leads to the alteration of the bone microenvironment and activation of osteoclasts, promoting bone resorption and destruction.[5] Studies have shown that approximately 70% of patients with advanced breast cancer will develop bone metastasis, which can further lead to skeletal-related events such as bone pain, fractures, spinal cord compression, and hypercalcemia, significantly affecting the patient's quality of life and survival prognosis.[6]

The use of bone-modifying agents (BMAs) to prevent bone resorption is clinically significant in many aspects of breast cancer treatment, including treating osteoporosis caused by endocrine therapy, managing bone metastasis, and potentially preventing bone metastasis. Best established agents include the bisphosphonate zoledronic acid and the receptor activator of NF-κB ligand (RANKL) antibody denosumab.[7] Bisphosphonates inhibit osteoclast activation mainly by inhibiting bone mineralization or bone resorption, thus reducing bone destruction caused by malignant tumor bone metastasis, alleviating bone pain, and decreasing the incidence of fractures.[8] They are recommended upon diagnosis of bone metastases and have been shown to alleviate bone pain and reduce fracture risk. Furthermore, the addition of bisphosphonates to standard adjuvant therapy for early-stage breast cancer can decrease bone recurrence and enhance survival rates. A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) and trials such as ABCSG-12 demonstrated that adjuvant bisphosphonate use reduces recurrence and mortality in early-stage breast cancer. However, the occurrence of side effects remains an undeniable part of the clinical application of bisphosphonates. These adverse effects can affect various systems of the body, with common manifestations including acute-phase reactions, hypocalcemia, renal toxicity, osteonecrosis of the jaw, and gastrointestinal issues.[9,10] Undoubtedly, in most cases, the benefits of anti-resorptive therapy outweigh the potential adverse events. However, the long-term use of these medications may increase the cumulative risk of adverse events. A 20-year follow-up study on breast cancer patients with bone metastases found that 2.8% of patients in the bisphosphonate group were diagnosed with medication-related osteonecrosis of the jaw (MRONJ), with a median time to diagnosis of 5.1 years.[11] Additionally, switching from zoledronic acid to denosumab increased the risk of MRONJ in patients with bone metastasis.[12]

Incadronate disodium is a third-generation bisphosphonate, which is superior to the first- and second-generation bisphosphonates for the treatment of osteoporosis, pain, fractures, and other symptoms associated with metastasis of malignant tumors. An in vitro study demonstrated that its anti-resorptive ability is 1000 times that of clodronate and 100 times that of pamidronate.[13] And it can also regulate the proliferation and apoptosis of tumor cells.[14,15] Meanwhile, it has been shown that incadronate disodium can inhibit the increase in DNA synthesis as well as tube formation of human microvascular endothelial cells, thereby exerting certain anti-angiogenic effects.[16] Although previous studies have suggested that incadronate disodium may cause fewer adverse reactions than zoledronic acid, the evidence remains limited due to small sample sizes, short follow-up periods, and incomplete event reporting. Although the efficacy of incadronate disodium has been widely recognized in clinical practice, there remains uncertainty about its safety, particularly due to the limited safety data available for long-term use and in specific patient populations, as well as the lack of systematic studies. In breast cancer patients, there are currently no detailed reports on the efficacy and related adverse events of incadronate disodium.

These issues above have raised our further concerns about the safety of incadronate disodium. Therefore, we conducted this retrospective study to evaluate the safety of incadronate disodium treatment in breast cancer patients with bone metastases, focusing on common adverse events such as dental-related problems and acute-phase reactions. Additionally, we aim to explore the associated risk factors for these adverse events to provide scientific evidence for safe clinical drug use.

Materials and Methods

Study Design

This was a single-arm, single-center retrospective study that included 106 patients with breast cancer bone metastases who received incadronate disodium treatment at the Cancer Hospital Chinese Academy of Medical Science between

February 2022 and August 2024. Eligible patients had received at least two consecutive infusions of incadronate disodium and were ≥18 years old with histologically confirmed breast cancer. All patients had at least one bone metastasis lesion confirmed by imaging (ie, X-ray, computed tomography, or bone scintigraphy) or pathology. Patients who received treatment for bone metastases from other cancers (n = 10), had fewer than two consecutive administrations of the medication (n = 6), or had no available follow-up information (n = 6) were excluded from the study. Patients with bone metastases originating from cancers other than breast cancer were excluded. Breast cancer patients with bone metastases, regardless of the presence of additional metastases to visceral organs (eg, liver, lung), were eligible for inclusion. Ultimately, a total of 84 patients met the inclusion criteria for the study (Figure 1). Incadronate disodium was administered intravenously once every 3–4 weeks at a dose of 10 mg per infusion, with each infusion lasting at least 2 hours. Physicians were allowed to adjust the dosage and infusion interval based on the patient's individual condition. Dose adjustment was primarily based on renal function, general condition, and tolerance. Specifically, patients with eGFR <60 mL/min/1.73m², ECOG performance status ≥2, or clinical frailty typically received a reduced dose of 5 mg per infusion. In principle, the discontinuation criteria for incadronate disodium are the occurrence of intolerable adverse reactions or a deterioration in the patient's physical condition assessed by the physician, making further treatment unadvisable.

Data Collection

Based on the inclusion and exclusion criteria, baseline data of eligible patients were retrieved from the hospital's electronic medical records, including age, body mass index (BMI), tumor pathology characteristics, presence of comorbid diabetes, total duration of medication, dose per administration, dosing interval, sites of metastases, timing of bone metastasis occurrence (primary or secondary), number of bone metastases at initiation (extent of disease [EOD] grade[17]), concurrent use of anti-angiogenic drugs, and clinical laboratory data at the first infusion (hemoglobin [Hb], serum albumin [Alb], serum alkaline phosphatase [ALP], serum total cholesterol [TC], serum calcium [Ca], carcinoembryonic antigen [CEA], cancer antigen 125 [CA125], and cancer antigen 15–3 [CA15-3]). Baseline blood tests, including hemoglobin, were collected to explore their potential association with treatment-related adverse events. In our study, primary bone metastases were defined as present at the initial diagnosis of breast cancer and secondary metastases developed during disease progression. Due to the long half-life of the medication, any adverse events occurring within 90 days after discontinuation of treatment were also considered to be potentially related to the medication.

Endpoints

The primary endpoint was the incidence of dental-related issues and acute phase reactions, with an analysis of the associated risk factors. The secondary endpoint was the incidence of other adverse events. Most studies on the adverse effects of bisphosphonate focus on medication-related osteonecrosis of the jaw. However, our primary concern was the occurrence of dental-related issues potentially induced by the medication, defined as newly developed symptoms such as

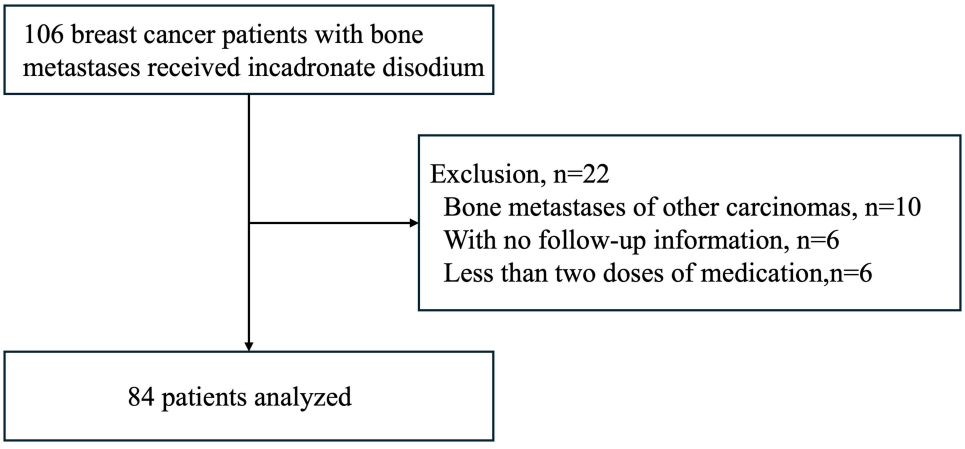

Figure 1 Study schematic.

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gingival recession or swelling, tooth sensitivity, tooth looseness, or fractures, with osteonecrosis of the jaw (MRONJ) representing the most severe complication. The evaluation of MRONJ was based on both imaging findings and documented dental-related complaints during follow-up. When dental issues were reported or suspected, further imaging examinations, including panoramic dental X-rays or CT scans, were performed to confirm or exclude MRONJ. Acute phase reactions (APRs) were defined as flu-like symptoms (fever, chills, fatigue, and musculoskeletal pain) occurring within the first week of treatment. Renal impairment was defined as an increase in serum creatinine by ≥0.5 mg/dL or 1.0 mg/dL for patients with baseline serum creatinine levels of <1.4 mg/dL or >1.4 mg/dL, respectively, or serum creatinine that increased to at least twice that of the baseline value. Hypocalcemia was defined as a serum calcium level below 2.1 mmol/L after treatment, with baseline serum calcium in the normal range.

Ethics

The study was approved by the Independent Ethics Committee of the National Cancer Center/Cancer Hospital Chinese Academy of Medical Sciences and Peking Union Medical College (25/020-4966). Given the retrospective nature of the study and the use of anonymized data, the requirement for written informed consent was formally waived by the ethics committee. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Statistical Analysis

For continuous data with a normal distribution, statistical descriptions were presented as mean ± standard deviation, while for continuous data with a non-normal distribution, they were presented as median and interquartile range. The continuous data between the two groups were compared using the independent samples *t*-test, provided the data met the assumptions of normality and homogeneity of variance. If these assumptions were not satisfied, the independent samples nonparametric test was applied instead. Categorical data were presented as percentages (%), and comparisons between groups were conducted using the chi-square test or Fisher's exact test. Binary univariate and multivariate logistic regression analyses were performed to explore the risk factors associated with the occurrence of dental-related issues and acute phase reactions. The odds ratio (OR) and its 95% confidence interval (95% CI) were used to quantify the impact of different factors on the endpoint events. A p-value <0.05 was considered statistically significant. Variables with p <0.05 in the univariate analysis were included in the multivariate analysis. To assess potential multicollinearity among independent variables in the multivariate logistic regression, variance inflation factors (VIFs) were calculated. All variables included had VIF values <2, indicating no significant multicollinearity. SPSS 27.0 and R Studio were used for statistical analyses.

Results

Patient Characteristics

A total of 84 breast cancer patients with bone metastases who met the inclusion criteria were included in our study. The detailed characteristics of patients are shown in Table 1. The mean age of the patients was 55.3 (range 33–82) years, and the average BMI was 24.67 kg/m² with obesity status assessed based on BMI values. In terms of comorbidities, 15 patients had

Table 1 Patients' Baseline Characteristics

Patient Characteristic	
Age (years)	55.30±11.33
BMI (kg/m2)	24.67±3.58
Diabetes mellitus [n, (%)]	15(17.86)
Antiangiogenic therapy [n, (%)]	8(9.52)
Total duration of medication (months)	7.54±5.83
Duration of medication [n, (%)]	
< 1 year	67(79.76)
≧ 1 year	17(20.24)

(*Continued*)

Table 1 (Continued).

Patient Characteristic	
Per dose (mg) [n, (%)]	
5	24(28.57)
10	60(71.43)
Dosing interval [n, (%)]	
< 1 month	72(85.71)
> 1 month	12(14.29)
Tumor IHC [n, (%)]	
Hormone receptor-positive	68(80.95)
HER2-positive	26(30.95)
Triple-negative	10(11.90)
Site of metastases [n, (%)]	
Bone	34(40.48)
Bone and others	50(59.52)
Bone metastases [n, (%)]	
Primary metastases	28(33.33)
Secondary metastases	56(66.67)
EOD grade at induction [n, (%)]	
< 2	20(23.81)
≧ 2	64(76.19)

Abbreviations: BMI, body mass index; IHC, immunohistochemistry; HER2, human epidermal growth factor receptor 2.

diabetes mellitus. Eight patients received anti-angiogenic therapy simultaneously: seven received bevacizumab, and one received anlotinib. The mean duration of treatment was 7.5 (range 2–32) months, with 17 patients receiving treatment for more than one year. A total of 60 patients received the standard dose of 10 mg per infusion, and 72 patients had an infusion interval of less than one month. Regarding the tumor immunohistochemistry (IHC), 80.95% of the patients were hormone receptor-positive, 30.95% were HER-2 positive, and 11.9% were triple-negative. Thirty-four patients had bone metastases alone, while the remaining patients had metastases in locations other than bone, such as the liver, lungs, or other regions. Twenty-eight patients had bone metastases at the time of their breast cancer diagnosis, while in the others, bone metastases occurred secondarily. According to the EOD grade for evaluating the number of bone metastatic lesions, 64 patients had a stage of ≥2. Bone metastases were observed in 59 patients with axial skeletal involvement and in 25 patients with appendicular skeletal involvement. In terms of adverse events, our study found that dental-related issues were the most frequent complications, occurring in 28 patients (33.3%), followed by acute phase reactions (APRs) in 22 patients (26.2%). Other reported AEs included hypocalcemia in 4 patients (4.8%) and renal dysfunction in 1 patient (1.2%) (Figure 2).

Incidence and Risk Factors of Dental-Related Issues

In our follow-up, a total of 28 patients developed dental-related issues, with an incidence rate of 33.3%. The most common symptoms included gingival recession or swelling, tooth sensitivity, fractures, and jaw pain. Notably, only one patient (1.2%) was definitively diagnosed with osteonecrosis, and the medication was discontinued in this case. A comparison of baseline characteristics between patients with and without dental-related issues is presented in Table 2. The total duration of treatment, the time of bone metastasis onset, concurrent use of anti-angiogenesis therapy, and hemoglobin levels were found to be associated with the occurrence of dental-related issues ($p < 0.05$). Table 3 presents the results of the analysis of factors associated with dental-related issues. In the univariate analysis, a treatment duration exceeding one year was identified as a significant risk factor for the occurrence of dental-related issues (OR = 3.89, 95% CI:1.30–12.24, $p = 0.016$). Compared to primary bone metastases, secondary bone metastases were more likely to cause dental-related issues (OR = 4.5, 95% CI:1.50–16.84, $p = 0.013$). Patients using anti-angiogenic drugs (OR = 7.36, 95% CI:1.56–52.98, $p = 0.02$) and those with lower hemoglobin levels (OR = 3.33, 95% CI:1.31–8.79, $p = 0.013$)

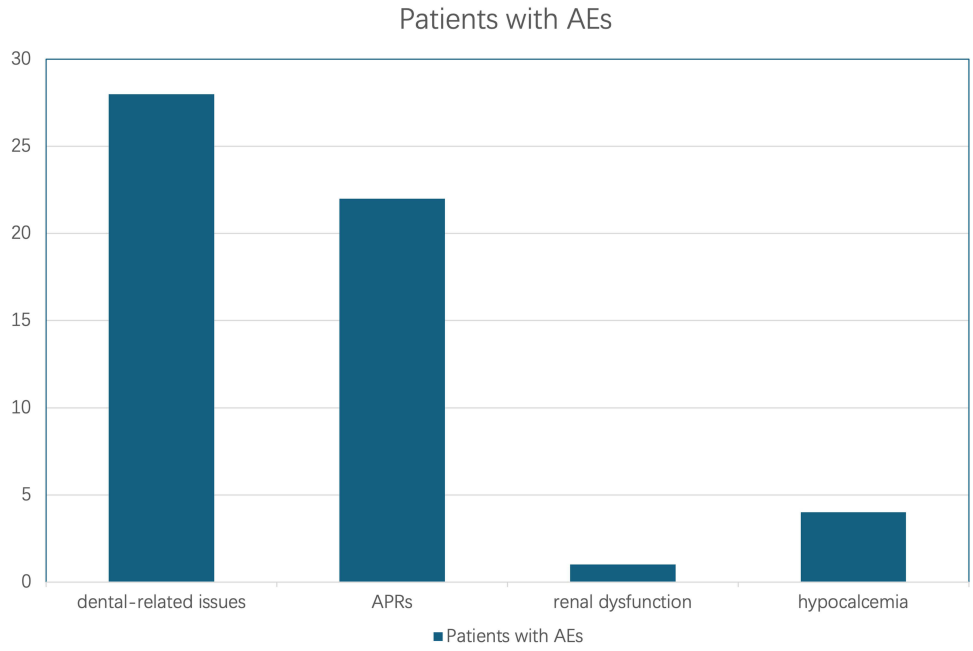

Figure 2 Distribution of adverse events (AEs) among patients treated with Incadronate Disodium. The most common AEs were dental-related issues and acute phase reactions (APRs), followed by hypocalcemia and renal dysfunction.

were also more likely to have dental problems. In multivariate analysis, secondary bone metastases were a significant predictor of dental issues (OR = 6.3, 95% CI:1.58–25.00, $p = 0.009$). A total treatment duration of more than 1 year (OR = 4.33, 95% CI:1.21–15.50, $p = 0.024$) and hemoglobin levels below 120 g/L (OR = 4.16, 95% CI:1.31–13.2, p=0.016) also increased the likelihood of dental issues.

Table 2 Characteristics of Patients with and Without Dental-Related Issues at Induction

Patient Characteristic	No Dental-Related Issues (n=56)	Dental-Related Issues (n=28)	*p* value
Age (years)	55.36±10.77	55.18±12.59	0.946
BMI (kg/m2)	24.94±3.52	24.15±3.72	0.354
Diabetes mellitus [n, (%)]	8 (14.3)	7 (25.0)	0.365
Total duration of medication (months)	6.12±4.58	10.36±7.02	**0.001**
Duration of medication [n, (%)]			**0.027**
< 1 year	49 (87.5)	18 (64.3)	
≧ 1 year	7 (12.5)	10 (35.7)	
Per dose [n, (%)]			0.442
5mg	18 (32.1)	6 (21.4)	
10mg	38 (67.9)	22 (78.6)	
Dosing interval [n, (%)]			0.741
< 1 month	49 (87.5)	23 (82.1)	
> 1 month	7 (12.5)	5 (17.9)	
Tumor IHC [n, (%)]			
Hormone receptor-positive	47 (83.9)	21 (75.0)	0.492
HER2-positive	19 (33.9)	7 (25.0)	0.559
Triple-negative	4 (7.1)	6 (21.4)	0.121

(*Continued*)

Table 2 (Continued).

Patient Characteristic	No Dental-Related Issues (n=56)	Dental-Related Issues (n=28)	*p* value
Site of metastases [n, (%)]			0.387
Bone	25 (44.6)	9 (32.1)	
Bone and others	31 (55.4)	19 (67.9)	
Bone metastases [n, (%)]			**0.018**
Primary metastases	24 (42.9)	4 (14.3)	
Secondary metastases	32 (57.1)	24 (85.7)	
EOD grade at induction [n, (%)]			0.651
< 2	12 (21.4)	8 (28.6)	
≧ 2	44 (78.6)	20 (71.4)	
Antiangiogenic therapy [n, (%)]	2 (3.6)	6 (21.4)	**0.025**
Blood test results at induction			
Hb (g/L)	124.71±13.11	117.89±13.10	**0.027**
Alb (g/L)	40.82±6.13	41.54±3.68	0.572
ALP (U/L)	126.19±188.76	93.48±33.84	0.367
TC (mmol/L)	5.00±1.20	5.27±1.28	0.373
Ca (mmol/L)	2.33±0.11	2.31±0.10	0.495
CEA (ng/mL)	19.65±43.11	7.44±10.29	0.145
CA125 (U/mL)	42.11±92.11	26.66±24.59	0.387
CA15-3 (U/mL)	54.97±77.98	122.83±341.83	0.166

Note:Bold values indicate $p < 0.05$.

Abbreviations: BMI, body mass index; IHC, immunohistochemistry; HER2, human epidermal growth factor receptor 2; EOD, extent of disease; Hb, hemoglobin; Alb, serum albumin; ALP, serum alkaline phosphatase; TC, serum total cholesterol; Ca, serum calcium; CEA, carcinoembryonic antigen; CA125, cancer antigen 125; CA15-3, cancer antigen 15–3.

Table 3 Risk Factors for Dental-Related Issues (Univariate and Multivariate Analyses)

	Univariate Analysis			Multivariate Analysis		
	OR	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Duration of medication (years)						
≧ 1 vs.< 1	3.89	1.30–12.24	**0.016**	4.33	1.21–15.50	**0.024**
Per dose (mg)						
10 vs.5	1.12	0.91–1.40	0.309			
Dosing interval (month)						
> 1 vs.< 1	1.52	0.41–5.29	0.510			
Bone metastases						
Secondary vs Primary	4.50	1.50–16.84	**0.013**	6.30	1.58–25.0	**0.009**
EOD grade at induction						
≧ 2 vs.< 2	0.68	0.24–1.98	0.470			
Antiangiogenic (AA) therapy						
Yes vs No	7.36	1.56–52.98	**0.020**	2.20	0.33–14.74	0.415
Hb at induction (g/L)						
<120 vs ≧120	3.33	1.31–8.79	**0.013**	4.16	1.31–13.2	**0.016**

Note:Bold values indicate $p < 0.05$.

Abbreviations: EOD, extent of disease; Hb, hemoglobin.

Incidence and Risk Factors of Acute Phase Reactions

Acute phase reactions were observed in 22 patients (26.2%), characterized by flu-like symptoms such as mild fever, fatigue, and joint and muscle pain, which occurred 2–3 days after infusion. Most patients recovered spontaneously within a week. Table 4 describes the baseline data of patients with or without acute phase reactions. The dose of each infusion, the site of metastases, and hemoglobin levels were all associated with the occurrence of acute phase reactions ($p < 0.05$). Table 5 outlines the results of analyzing the factors associated with acute phase reactions. In univariate analysis, 10mg per dose increased the risk of acute phase reactions compared to 5mg (OR = 1.41, 95% CI:1.07–2.05, $p = 0.030$).

Table 4 Characteristics of Patients with and Without Acute Phase Reactions at Induction

Patient Characteristic	Non-APRs (n=62)	APRs (n=22)	*p* value
Age (years)	55.87 (11.39)	53.68 (11.27)	0.440
BMI (kg/m2)	24.52 (3.75)	25.08 (3.13)	0.535
Diabetes mellitus [n, (%)]	12 (19.4)	3 (13.6)	0.781
Total duration of medication (months)	7.77 (5.60)	6.86 (6.54)	0.532
Duration of medication [n, (%)]			0.556
< 1 year	48 (77.4)	19 (86.4)	
≧ 1 year	14 (22.6)	3 (13.6)	
Per dose [n, (%)]			**0.038**
5mg	22 (35.5)	2 (9.1)	
10mg	40 (64.5)	20 (90.9)	
Dosing interval [n, (%)]			0.999
< 1 month	53 (85.5)	19 (86.4)	
> 1 month	9 (14.5)	3 (13.6)	
Tumor IHC [n, (%)]			
Hormone receptor-positive	50 (80.6)	18 (81.8)	0.999
HER2-positive	20 (32.3)	6 (27.3)	0.868
Triple-negative	8 (12.9)	2 (9.1)	0.927
Site of metastases [n, (%)]			**0.026**
Bone	30 (48.4)	4 (18.2)	
Bone and others	32 (51.6)	18 (81.8)	
Bone metastases [n, (%)]			0.661
Primary metastases	22 (35.5)	6 (27.3)	
Secondary metastases	40 (64.5)	16 (72.7)	
EOD grade at induction [n, (%)]			0.879
< 2	14 (22.6)	6 (27.3)	
≧ 2	48 (77.4)	16 (72.7)	
Antiangiogenic therapy [n, (%)]	7 (11.3)	1 (4.5)	0.615
Blood test results at induction			
Hb (g/L)	124.74 (13.28)	115.95 (11.83)	**0.008**
WBC (*10^9/L)	5.35 (2.06)	5.40 (1.86)	0.924
Alb (g/L)	40.81 (6.03)	41.77 (3.19)	0.478
ALP (U/L)	123.84 (179.62)	91.08 (32.05)	0.399
TC (mmol/L)	5.14 (1.21)	4.99 (1.29)	0.642
Ca (mmol/L)	2.32 (0.09)	2.33 (0.14)	0.776
CEA (ng/mL)	15.47 (31.55)	15.51 (46.50)	0.996
CA125 (U/mL)	40.94 (85.74)	25.64 (39.55)	0.424
CA15-3 (U/mL)	78.77 (234.40)	76.42 (123.49)	0.964

Note:Bold values indicate $p < 0.05$.

Abbreviations: APRs, acute phase reactions; BMI, body mass index; IHC, immunohistochemistry; HER2, human epidermal growth factor receptor 2; EOD, extent of disease; Hb, hemoglobin; WBC, white blood cell; Alb, serum albumin; ALP, serum alkaline phosphatase; TC, serum total cholesterol; Ca, serum calcium; CEA, carcinoembryonic antigen; CA125, cancer antigen 125; CA15-3, cancer antigen 15–3.

Table 5 Risk Factors for Acute Phase Reactions (Univariate and Multivariate Analyses)

	Univariate Analysis			Multivariate Analysis		
	OR	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Duration of medication (years)						
≧ 1 vs.< 1	0.54	0.12–1.89	0.375			
Per dose (mg)						
10 vs.5	1.41	1.07–2.05	**0.030**	1.35	0.99–1.86	0.062
Dosing interval (month)						
> 1 vs.< 1	0.93	0.19–3.50	0.919			
Bone metastases						
Secondary vs Primary	1.47	0.52–4.58	0.484			
EOD grade at induction						
≧ 2 vs.< 2	0.78	0.26–2.50	0.658			
Site of metastases						
Bone and others vs Bone	4.22	1.39–15.89	**0.018**	3.45	1.00–11.96	0.051
Hb at induction (g/L)						
<120 vs ≧120	3.27	1.21–9.22	**0.021**	2.65	0.91–7.76	0.076

Note: Bold values indicate $p < 0.05$.
Abbreviations: EOD, extent of disease; Hb, hemoglobin.

Multiple metastatic sites (OR = 4.22, 95% CI:1.39–15.89, $p = 0.018$) and lower hemoglobin levels (OR = 3.27, 95% CI:1.21–9.22, p=0.021) were also significant risk factors for acute phase reactions. Variables with p<0.05 in the univariate analysis were included in the multivariate analysis. No significant variables were found to be associated with acute phase reactions, but patients with bone and other site of metastases were considered at higher risk due to the p-value being close to 0.05.

Other Adverse Effect

One patient (1.2%) developed renal dysfunction after treatment, with a baseline creatinine level of 0.63mg/dL, which increased to 1.17mg/dL after treatment. Four patients (4.76%) had a decrease in serum calcium to below 2.1mmol/L after treatment and experienced symptoms such as numbness in the hands and feet, and muscle cramps. Other adverse reactions associated with bisphosphonate use, such as atrial fibrillation and conjunctivitis, were not observed in this study.

Discussion

Bone is the most common site of metastasis in breast cancer, and therefore, the clinical management of bone metastasis is an important aspect of treatment for advanced tumors.[18] Bisphosphonates are widely used in clinical practice for their ability to inhibit osteoclast activation and thereby reduce bone destruction, and their efficacy has been significantly recognized. However, the occurrence of side effects remains an unavoidable part of clinical applications, especially those that may be associated with long-term use. Bisphosphonates have now progressed to the third generation. The first-generation non-nitrogen-containing bisphosphonates are represented by clodronate; the second-generation nitrogen-containing bisphosphonates are exemplified by pamidronate; the third-generation bisphosphonates feature extended side chains, leading to further enhanced pharmacological activity, such as incadronate disodium, which is derived from cycloheptylamine.[19] Incadronate disodium, as a new drug, there is limited knowledge about its safety. Previous

retrospective studies have suggested that incadronate disodium provides effective protection against bone metastases with a favorable safety profile. Reported adverse events include fever (9.4%) and fatigue (25%), indicating acceptable tolerability in clinical practice. Although some studies have compared incadronate disodium with other bisphosphonates such as zoledronic acid, robust head-to-head evidence remains limited, and our study primarily focused on the safety assessment of incadronate disodium itself in breast cancer patients with bone metastases and revealed some risk factors. Our findings showed that dental-related issues and acute phase reactions were common adverse effects. Among the patients, 28 (33.3%) experienced dental-related issues, but only 1 (1.2%) developed osteonecrosis of the jaw. This rate is within the lower range of incidence reported in prior studies on bisphosphonates. Literature data on MRONJ incidence are variable. A single-center retrospective study involving 179 prostate cancer patients with bone metastasis reported that 13% of those treated with zoledronic acid developed MRONJ.[20] Other studies on real-world data have reported incidences as high as 24% and 6.7%.[21,22] A 20-year multicenter retrospective study also reported that 2.8% of breast cancer patients treated exclusively with zoledronic acid developed MRONJ, while the incidence increased to 16.3% in patients who were sequentially treated with denosumab after bisphosphonates.[23] The above studies have reported the incidence of MRONJ, but none have focused on dental-related issues prior to the occurrence of necrosis. Prior to the appearance of clinically detectable bone necrosis, potential signs and symptoms may include chronic dull jaw pain, toothache, looseness of teeth, and gum swelling.[24] Our study mainly followed up on the early dental symptoms in patients, which allows for early recognition when such symptoms occur, enabling preventive measures to avoid progression to MRONJ, and provides some guidance for future treatments.

In the univariate analysis, our study showed that total medication duration (p=0.016), time of bone metastasis occurrence (p=0.013), concurrent anti-angiogenesis treatment (p=0.02), and hemoglobin levels (p=0.013) were associated with the occurrence of dental-related issues. Like previous studies on zoledronic acid, our further multivariate analysis found that a total medication duration of over 1 year with incadronate disodium was significantly associated with the occurrence of dental-related issues (p=0.024). A prospective observational cohort study, the SWOG S0702 trial, which included 3491 patients treated with zoledronic acid for bone metastases, found that those treated for longer duration were at a higher risk, with cumulative MRONJ incidence rates of 0.8%, 1.2%, and 2.8% at 1, 2, and 3 years, respectively.[25] Therefore, it might be considered to extend the dosing interval in long-term medication patients to reduce adverse events. A systematic review of three randomized trials showed that compared with dosing every 4 weeks, administering zoledronic acid every 12 weeks reduced the incidence of MRONJ.[26] In breast cancer, both dosing intervals of every 3 to 4 weeks and every 12 weeks for zoledronic acid are recommended as the preferred options.[27] There were also 12 patients in our study with dosing intervals longer than 1 month, but no clear correlation was found between dental-related issues and the dosing interval, possibly due to the small sample size. Thus, in the future use of incadronate disodium, the total medication duration and dosing interval should be carefully monitored.

In the multivariate analysis of our study, lower hemoglobin levels (p=0.016) and secondary bone metastases (p=0.009) were also identified as significant factors related to dental issues. The pathophysiological mechanisms of osteonecrosis of the jaws are not yet fully understood, and the main hypotheses include excessive suppression of bone conversion or bone remodeling, inhibition of blood supply, persistent microtrauma, and infection or inflammation.[28] Our study found that patients with hemoglobin levels below 120 g/L are more likely to have dental-related issues. The association between low hemoglobin levels and dental-related adverse events may be partially explained by tissue hypoxia. Anemia can impair oxygen delivery to oral and maxillofacial tissues, compromising mucosal integrity and impairing wound healing. Additionally, hypoxic conditions may alter immune responses, increasing susceptibility to chronic inflammation and infection, which are known contributors to the development of MRONJ. These mechanisms, although plausible, require further validation in experimental and clinical studies. Currently, no other studies have observed a correlation between the timing of bone metastasis occurrence and dental-related issues. However, factors such as immunosuppression and inflammation can promote tumor cell colonization and metastasis,[29] and we speculate that patients with secondary metastases are more immunosuppressed, and that immunosuppressed patients will be more susceptible to infections and inflammation, which are important risk factors for bisphosphonate-related dental and jaw complications. Therefore, further large sample studies are necessary to confirm our hypothesis.

Although no significant association was found between the use of anti-angiogenic drugs and dental issues in our multivariate analysis, the number of patients with dental adverse reactions was three times higher in those treated with anti-angiogenic drugs than in those without. Previous evidence suggests that anti-angiogenic drugs play a role in the development of osteonecrosis, especially when combined with osteoclast inhibitors.[30,31] These drugs inhibit the development of new blood vessels, which can lead to osteonecrosis of the jaw through ischemia. In summary, these findings indicate the potential role of anti-angiogenic drugs in the risk of MRONJ, which deserves further study.

The other major adverse reaction found in our study was acute phase reaction with an incidence of 26.2%, which mainly manifested as mild fever, fatigue, joint and muscle pain, occurring in most patients within 3 days after the first dose and resolving spontaneously within a week. A previous multicenter, randomized, double-blind study on breast cancer patients with bone metastasis found that 27.3% of patients receiving zoledronic acid infusion experienced acute phase reactions after treatment.[32] In cancers other than breast and prostate cancer, a study by David H. Henry also reported that acute phase reaction occurred in 14.5% of patients treated with zoledronic acid.[33] Furthermore, these studies all indicate that the use of denosumab reduces the risk of acute phase reactions. Our data are generally consistent with previous reports. It is speculated that the cause of acute phase reactions may be a transient increase in cytokine production.[34] According to univariate analysis, higher medication doses (10mg vs 5mg), multiple metastatic sites, and lower hemoglobin levels were all related to acute phase reactions ($p<0.05$). While no significant statistical relationship was found in the multivariate analysis, patients with multiple metastatic sites were at higher risk for acute phase reactions. This may be because multiple sites of metastases imply a higher degree of disease progression and the involvement of bones and other organs may lead to excessive immune response activation, resulting in acute phase symptoms. These findings should be interpreted cautiously due to limited statistical power and may serve as the basis for hypothesis generation in future studies. Future studies could further explore personalized dosing regimens for patients at high risk to improve drug tolerance.

Our study also recorded one case of renal dysfunction (1.2%) and four cases of hypocalcemia (4.76%). Although these adverse reactions have a low incidence, they still require special attention. A report that included 120 patients who received a total of 546 infusions of zoledronic acid for multiple myeloma or another malignancy showed that 42 (35%) patients developed hypocalcemia after 55 infusions (10% of the total).[35] In terms of renal dysfunction, a study on bone metastases in breast cancer patients showed that 4% of patients developed an increase in serum creatinine after zoledronic acid infusion.[32] The probability of all the above adverse events in our study due to incadronate disodium was lower than zoledronic acid. Also, other side effects of bisphosphonates such as atrial fibrillation, diarrhea, atypical fractures, and ocular toxicity have been reported,[9,10,36] but none of these adverse events were observed in our research.

Although our study provided important data for the safety evaluation of incadronate disodium, there were still several limitations. First, the sample size was limited, and all patients were from a single center and were breast cancer patients, which may introduce selection bias. The inclusion of patients with both bone and non-bone metastases introduces potential heterogeneity; however, the primary focus remained on bone-targeted toxicity. Stratified analysis in larger cohorts is warranted. Second, the relatively short follow-up period in this study did not allow assessment of the safety of long-term medication and its impact on patients' quality of life. Third, due to the limitations of a retrospective study, it was impossible to determine whether participants had new medical conditions or were using other drugs during the follow-up period that might have caused serious adverse reactions, which could have affected the outcomes. Fourth, there was a lack of data on outcomes in patients with dental-related issues, so it remained unclear whether these early lesions improve, remain stable, or progress to osteonecrosis of the jaw. To address these limitations, prospective multicenter cohort studies with standardized dental assessments, longer surveillance, and biomarker profiling should be conducted to further investigate the safety profile of incadronate disodium and validate the risk factors identified in this study.

Conclusion

In conclusion, this retrospective study demonstrated that incadronate disodium was generally well-tolerated in breast cancer patients with bone metastases, with a relatively low incidence of severe adverse events, including osteonecrosis of the jaw. Our findings indicate that patients receiving prolonged treatment or presenting with lower hemoglobin levels may be at increased risk for dental-related complications and require closer monitoring. Routine assessment of

hemoglobin levels and regular dental evaluations are recommended, particularly for patients undergoing long-term therapy, to help mitigate the risk of osteonecrosis of the jaw. Further prospective studies are warranted to validate these findings and to better characterize the long-term safety profile of incadronate disodium in this population.

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Disclosure

The authors report no conflicts of interest in this work.

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