Relationship between the Incidence of Osteonecrosis of the Jaw due to Bone-Modifying Drugs Administered for Bone Metastases of Breast Cancer, Risk Factors, and Overall Survival

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Background

Bone-modifying agents (BMAs), including zoledronic acid and denosumab, are essential for preventing skeletal-related events in patients with breast cancer and bone metastases. However, medication-related osteonecrosis of the jaw (MRONJ) has become a significant late adverse event. Long-term real-world data on its incidence, risk factors, and clinical outcomes remain limited, particularly in Asian populations. This study aimed to evaluate the incidence, risk factors, and clinical outcomes of MRONJ in breast cancer patients receiving BMAs.

Methods

We retrospectively reviewed breast cancer patients with bone metastases who received BMAs between January 2015 and December 2024 at our hospital.

- MRONJ was diagnosed according to the 2023 Japanese Position Paper.
- Exclusion: Patients who received radiotherapy to the oral cavity or jaw.
- Statistical analysis: EZR v1.68[1)]

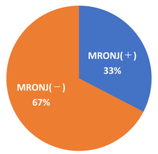
Results

A total of 46 patients were included (median age, 58 years; range, 35–90). Pre-treatment dental examinations were performed in 78.3% of patients, and 58.7% underwent tooth extraction before initiating BMAs(Table 1). The median duration of BMA administration was 33 months (range, 6–85).MRONJ occurred in 15 patients (32.6%)(Figure 1), with a median time to onset of 24 months. The incidence continued to increase steadily after 2 years of treatment(Figure 2). Tooth extraction was statistically identified as a significant risk factor(Table 2). Among the 15 cases, 12 were treated conservatively and three surgically, resulting in complete healing in one patient(Figure 3). Overall survival was significantly longer in the MRONJ group than that in the non-MRONJ group (median, 2048 vs. 1092 days; $p = 0.0332$)(Figure 4).

Table 1. Patient characteristics

Age (years)	median [range]	58 [35–90]
Sex		
	Female	46 (100%)
	Male	0 (0%)
Diagnosis		
	de novo	26 (56.5%)
	recurrence	20 (43.5%)
ER Status		
	Positive	41 (89.1%)
	Negative	5 (10.9%)
HER2 Status		
	Positive	9 (19.6%)
	Negative	37 (80.4%)
BMA duration	median [range]	33 [6–85]
BMA		
	Zoledronic acid	4 (8.7%)
	Denosumab	37 (80.4%)
Dental Exam Before BMA		
	Yes	36 (78.3%)
	No	10 (21.7%)
Tooth Extraction		
	Yes	27 (58.7%)
	No	19 (41.3%)

Figure 1. Incidence of MRONJ



MRONJ occurred in 15 of 46 patients (32.6%).

Figure 2. Duration of BMA until MRONJ

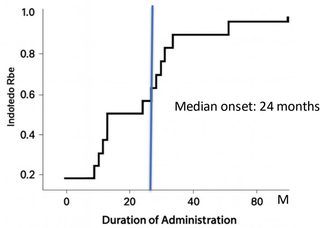


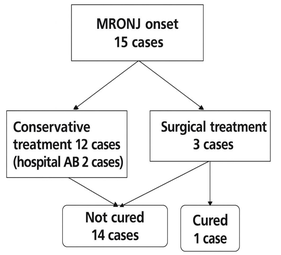
Table 2. Univariate Analysis of Risk Factors for MRONJ

	MRONJ Group	Non-MRONJ Group	*p*-value
	(n=15)	(n=31)	
Age, median (range)	59 [36-84]	58 [35−79]	0.839
Diagnosis			0.53
de novo StageⅣ	7 (46.6%)	19 (61.3%)	
recurrence	8 (53.3%)	12 (38.7%)	
Treatment duration, median (months)			0.067
	29.6	42	
Medication			
Zoledronic acid	1 (6.7%)	3 (9.7%)	0.75
Denosumab	13 (86.7%)	24 (77.4%)	
Both	1 (6.7%)	4 (12.9%)	
Pre-treatment dental consultation			0.46
Yes	13 (86.7%)	23 (74.2%)	
No	2 (13.3%)	8 (25.8%)	
Tooth extraction			＜0.001
Yes	13 (86.7%)	13 (41.9%)	
No	2 (13.3%)	18 (58.1%)	

p-values were calculated using the Chi-square test.

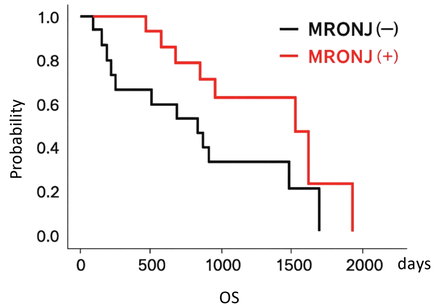
Extraction during therapy : higher MRONJ risk ($p < 0.001$)

Figure 3. Treatment Course and Outcomes of MRONJ



- 12 received conservative treatment
- 3 underwent surgery
  → 1 achieved complete healing.

Figure 4. Overall Survival by MRONJ Status



Median OS was significantly longer in the MRONJ group (2048 vs. 1092 days; $p = 0.0332$).

Discussion

MRONJ is a recognized adverse event associated with bisphosphonate and denosumab therapy. Major risk factors include tooth extraction, periodontal disease, prolonged treatment duration, and steroid use[2)]. In clinical trials, the incidence ranged from 1.9–6.9% [3)], whereas real-world Japanese data show rates up to 32%[2)], our observed incidence (32.6%) was consistent with long-term, high-exposure cohorts.

Tooth extraction during treatment was a major risk factor, highlighting the need for dental evaluation before and during therapy. Although the mechanism remains unclear, longer survival in MRONJ patients may reflect prolonged disease control or closer monitoring. These findings emphasize the importance of multidisciplinary management, including proactive dental evaluation and patient education, to prevent MRONJ without compromising oncologic outcomes. Future multicenter studies are warranted to validate these results and to develop preventive strategies tailored to Asian populations.

Conclusion

MRONJ occurred in one-third of patients receiving long-term BMAs. Tooth extraction during therapy was the major risk factor. Longer survival among patients with MRONJ should be interpreted with caution.

Close collaboration between oncology and dental teams remains essential.

Contact

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