Long-term outcomes of denosumab therapy and treatment discontinuation in patients with bone metastases

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Significance & Hypothesis/Techniques:

Bone-modifying agents are effective in reducing skeletal-related events (SREs) in patients with metastatic bone disease. As survival has improved in patients with advanced cancer, the long-term management of bone metastases has become increasingly important. In particular, the clinical balance between sustained prevention of SREs and cumulative toxicities such as medication-related osteonecrosis of the jaw (MRONJ) remains uncertain. The purpose of this study is to evaluate the efficacy and risks of long-term denosumab therapy and denosumab discontinuation.

Innovation:

To identify the results of denosumab treatment in real-world clinical practice.

Approach:

We retrospectively reviewed 335 consecutive Japanese patients with bone metastases who received denosumab at a single institution between 2012 and 2024. Risk factors for SREs during denosumab therapy were analyzed, together with the incidence of long-term adverse events including MRONJ and atypical femoral fracture (AFF). Patients were divided into discontinuation and continuation groups to identify factors associated with treatment discontinuation. In patients who discontinued denosumab, the incidence and timing of post-discontinuation SREs and fragility vertebral fractures were evaluated. Finally, patients with and without post-discontinuation SREs were compared to identify factors associated with safer discontinuation.

Results:

SREs during denosumab treatment were significantly associated with a history of SREs before treatment initiation and the presence of lung metastases at the start of therapy (figure). MRONJ developed in 12.5% of patients with a mean treatment duration of 34.2 months. No cases occurred within the first year. AFF occurred in 1.2%, with the earliest case observed at 27 months.

Denosumab was discontinued in 86 of 335 patients (25.7%). Compared with the continuation group (n=249), the discontinuation group had significantly longer treatment duration and a significantly higher frequency of MRONJ. In contrast, visceral metastases and SREs during denosumab treatment were more

common in the continuation group, suggesting that patients with greater systemic disease burden or ongoing skeletal complications were more likely to remain on treatment (table 1).

Among the 86 patients who discontinued denosumab, 24 (27.9%) developed SREs after discontinuation. The mean time from the final denosumab administration to SRE occurrence was 14.8 months. No post-discontinuation SREs occurred within the first 3 months. Fragility vertebral fractures occurred in 3.5% of patients, with the earliest event observed 7 months after final administration.

Comparison of patients with post-discontinuation SREs (n=24) and those without SREs (n=62) showed no significant differences in age, sex, duration of denosumab treatment, primary tumor type, or prior SRE history. However, both the Spinal Instability Neoplastic Score (SINS) and Mirels score at the time of discontinuation were significantly higher in the post-discontinuation SRE group (table 2).

Discussions:

Long-term denosumab treatment was associated with a substantial incidence of MRONJ in this Japanese cohort, particularly after prolonged administration. After discontinuation, SREs and fragility vertebral fractures were not immediate events, but they developed in a clinically meaningful proportion of patients over time. Higher SINS and Mirels scores at discontinuation were associated with subsequent SREs, indicating that skeletal instability and fracture risk should be carefully assessed when considering denosumab discontinuation.

Figure

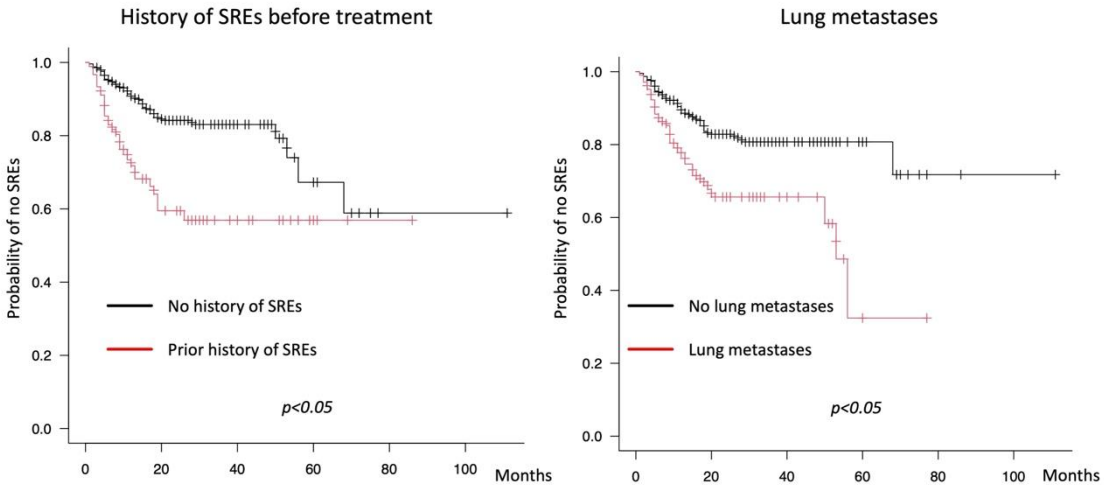

Table 1

	Total (n=385)	Continuation group (n=249)	Discontinuation group (n=86)	P-value
Age	66.8	66.9	67.9	n.s.
Gender; male	192 (57.5%)	139 (55.8%)	53 (61.6%)	n.s.
Follow-up (months)	28	20.6	50.4	<0.001
No. of doses	19	17.62	23.70	0.001
Dosing period (months)	22.6	20.3	29.2	<0.001
Primary cancer				
Prostate	81 (24.2%)	58 (23.3%)	23 (26.7%)	n.s.
MMK	70 (20.9%)	49 (19.7%)	21 (24.4%)	n.s.
LK	79 (18.6%)	63 (25.3%)	16 (18.6%)	n.s.
Others	105 (31.3%)	73 (29.7%)	26 (30.2%)	n.s.
Bone metastases; axis	327 (97.6%)	245 (98.4%)	82 (95.3%)	n.s.
Bone metastases; extremity	73 (21.8%)	57 (22.9%)	16 (18.6%)	n.s.
Visceral metastases	183 (54.6%)	147 (59.0%)	36 (41.9%)	0.008
Adverse events				
ONJ	42 (12.5%)	7 (2.8%)	35 (40.7%)	< 0.001
AFF	4 (1.2%)	1 (0.4%)	3 (3.5%)	0.054
Hypocalcemia	51 (15.2%)	41 (16.5%)	10 (11.6%)	n.s.
SREs prior to denosumab	90 (26.9%)	71 (28.5%)	19 (22.1%)	n.s.
SREs during denosumab	65 (19.4%)	54 (21.7%)	11 (12.8%)	0.082

Table 2

	All discontinuation cases (n=86)	Post-discontinuation SREs		P-value
		No (n=62)	Yes (n=24)	
Age	68.0	67.7	68.5	n.s.
Gender; male	53 (61.6%)	36 (58.1%)	17 (70.8%)	n.s.
Follow up (months)	50.4	51.7	47.1	n.s.
Post discontinuation follow up	22.8	22.8	22.9	n.s.
Primary cancer				n.s.
Prostate	23 (26.7%)	15 (24.2%)	8 (33.3%)	n.s.
MMK	21 (24.4%)	16 (25.8)	5 (20.8%)	n.s.
LK	16 (18.6%)	10 (16.1%)	6 (25.0%)	n.s.
Others	26 (30.2%)	21 (33.9%)	5 (20.8%)	n.s.
Visceral metastases	36 (41.9%)	28 (45.2%)	8 (33.3%)	n.s.
No. of doses	24.0	24.9	20.5	n.s.
Dosing period	28.7	30.0	25.4	n.s.
SREs prior to denosumab treatment	19 (22.1%)	14 (22.6%)	5 (20.8%)	n.s.
SREs during denosumab treatment	10 (11.6%)	6 (9.7%)	5 (20.8%)	n.s.
SINS (n=35 VS 16)	4.0 (0-8)	3.20 (0-6)	5.75 (2-8)	<0.001
Mirels' score (n=10 VS 6)	4.9 (3-8)	4.40 (3-6)	5.83 (4-8)	0.0328