Clinical efficacy and safety of long-term treatment, discontinuation, and extended dosing intervals of denosumab treatment for solid cancer bone metastasis: a single center retrospective study

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INTRODUCTION: Metastatic bone tumors in solid cancer often induce excessive local bone resorption leading to skeletal related events (SRE) which may impact patients' quality of life and survival of the primary cancer. Denosumab, a bone resorption inhibitor, is commonly used to prevent SRE in patients with solid cancer bone metastasis. With the prolonged life prognosis of cancer patients, the number of cases of long-term denosumab administration has increased. Consequently, we have seen more cases discontinuing denosumab or cases with extended dosing intervals in real-world clinical practice and questions arise regarding the efficacy and safety of such cases.

METHODS: A total of 298 patients who received denosumab treatment for bone metastasis of solid cancer from 2012 to 2022 at our institute were included for evaluation. We retrospectively reviewed the incidence of SRE (pathological fracture, spinal cord compression, surgical intervention, hypercalcemia, radiotherapy intervention) and incidence of adverse events (osteonecrosis of the jaw, atypical femoral fracture) after denosumab administration began. Risk factors of SRE during denosumab treatment, adverse events in patients with long-term treatment, safety and efficacy upon discontinuing denosumab treatment were evaluated. Denosumab discontinuation was defined as no administration for more than 24 consecutive weeks. To evaluate the cases with extended dosing intervals, the patients were divided according to whether the average dosing interval was shorter or longer than once every 6 weeks, and the risks of SRE and adverse events were compared between the two groups.

RESULTS:

Lung cancer and other solid cancers showed a significant lower SRE-free survival (SFS) than breast and prostate cancer cases (Figure 1). Cases with prior SRE (SRE before denosumab administration) and cases with lung metastasis also had significant lower SFS during denosumab treatment.

Osteonecrosis of the jaw (ONJ) was seen in 33 cases (11.1%). The mean duration of exposure to denosumab in cases of ONJ was 149.7 weeks. The incidence rate of ONJ adjusted for patient-years of follow-up was 6.2% in total and showed the highest in the third year of treatment (16.8%). There were no cases of ONJ during the 1st year of treatment. Atypical femoral fracture was seen in one case in this series with a dosing period of 217 weeks.

Denosumab discontinuation was seen in 84 cases (28%). SRE after the discontinuation was seen in 20.2% of the discontinued cases. The median time after final administration to SRE was 48 (26-169) weeks. There were no SRE cases during the first 24 weeks, and SRE increased after 25 weeks or more has passed after final administration. There were no cases of multiple vertebral fracture after denosumab discontinuation in this case series.

For the safety and efficacy of extended dosing intervals, 247 cases and 51 cases were included in the short interval group and long interval group respectively. For the background of the two groups, the mean dosing interval of the short and long group was once every 4.62 weeks and once every 8.05 weeks, respectively. The number of doses were similar between the groups; therefore, the dosing period was significantly longer in the long interval group. There was no difference in age, gender, ratio of primary cancer, visceral metastasis, location of bone metastasis and prior SRE between the two groups (Table 1). There was no difference in the incidence rate of SRE and 2-year SFS between the two groups (Table 2, Figure 2). For the adverse events, there was no difference in the incidence rate of hypocalcemia, ONJ, and AFF between the two groups (Table 2).

DISCUSSION AND CONCLUSION:

Higher degree of malignancy, prior SRE, lung metastasis are risk factors for SRE during denosumab administration. Particular attention should be paid to adverse events when the duration of treatment is prolonged. The incidence rate of ONJ was higher than that of international reports, though similar to reports from Japan, suggesting higher risk of ONJ in the Japanese population.

The risk of SRE increases when denosumab is withdrawn for more than 25 weeks, which matches the timing of the increase of bone resorption after discontinuing denosumab, recommending resumption of denosumab within 24 weeks.

Extending dosing intervals to up to three months did not increase the risk of SRE nor decrease the risk of adverse events. However, since the risks of ONJ and AFF tend to be higher in the long interval group which had a longer dosing period as a background, dosing period may be a risk factor of severe adverse events, even with dosing intervals extended and the amount of total dose is reduced.

Figure 1

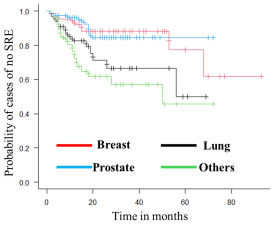

Figure 2

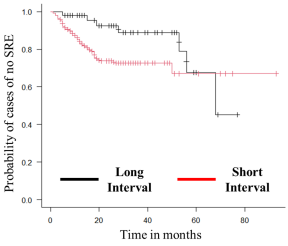

Table 1. Backgrounds of all cases and the short and long interval groups.
SRE: Skeletal related events. Ca: Calcium. Vit. D: Vitamin D.

	All cases	Short interval group	Long interval group	p value
Number of cases	298	247	51	
Gender				n.s.
Male	173 (58.1%)	146 (59.1%)	27 (52.9%)	
Female	125 (41.9%)	101 (40.9%)	24 (47.1%)	
Age	67.1	66.9	67.7	n.s.
Follow up (weeks)	113.3	103.9	158.9	<0.001
Primary cancer				n.s.
Breast	66 (22.1%)	49 (19.8%)	17 (33.3%)	
Prostate	77 (25.8%)	65 (26.3%)	12 (23.5%)	
Lung	67 (22.4%)	57 (23.1%)	10 (19.6%)	
Others	88 (29.5%)	76 (30.8%)	12 (23.5%)	
Visceral metastasis	159 (53.4%)	132 (53.4%)	27 (52.9%)	n.s.
Lung	91 (30.5%)	72 (29.1%)	19 (37.3%)	n.s.
Liver	57 (19.1%)	46 (18.6%)	11 (21.6%)	n.s.
Brain	22 (7.4%)	20 (8.1%)	2 (3.9%)	n.s.
Other	28 (9.4%)	27 (10.9%)	1 (2.0%)	n.s.
Lymph node metastasis	144 (48.3%)	120 (48.6%)	24 (47.1%)	n.s.
Bone metastasis only	67 (22.4%)	54 (21.9%)	13 (25.5%)	n.s.
Location of bone metastasis				n.s.
Trunk only	231 (77.5%)	191 (77.3%)	40 (78.4%)	
Trunk and extremity	59 (19.7%)	50 (20.2%)	9 (17.6%)	
Extremity only	8 (2.7%)	6 (2.4%)	2 (3.9%)	
Prior SRE	82 (27.5%)	68 (27.5%)	14 (27.5%)	n.s.
Use of Ca/Vit. D tablets	275 (92.3%)	231 (93.5%)	44 (86.3%)	n.s.
Dosing period (weeks)	94.8	85.7	138.6	<0.001
Number of doses	18.4	18.6	17.8	n.s.
Average dosing interval (weeks / number of dose)	5.2	4.6	8.1	<0.001

Table 2. Results of the difference between short and long interval groups.

	Short interval group	Long interval group	p value
No. of cases	247	51	
SRE	50 (20.2%)	8 (15.7%)	n.s.
Adverse events			
Hypocalcemia	42 (17.0%)	11 (21.6%)	n.s.
ONJ	24 (9.7%)	9 (17.6%)	n.s.
AFF	0 (0%)	1 (2.0%)	n.s.