Efficacy and safety of denosumab de-escalation in giant cell tumor of bone

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Abstract. Giant cell tumor of bone (GCTB) is a locally aggressive intermediate bone tumor. Denosumab has shown effectiveness in GCTB treatment; however, the benefits of denosumab de-escalation for unresectable GCTB have not been well discussed. The present study investigated the efficacy and safety of denosumab de-escalation for GCTB. The medical records of 9 patients with unresectable GCTB or resectable GCTB not eligible for resection, who received de-escalated denosumab treatment at Okayama University Hospital (Okayama, Japan) between April 2014 and December 2021, were retrospectively reviewed. The denosumab treatment interval was gradually extended to every 8, 12 and 24 weeks. The radiographic changes and clinical symptoms during standard and de-escalated denosumab therapy were assessed. The denosumab interval was de-escalated after a median of 12 months of a standard 4-weekly treatment. Imaging showed that the re-ossification of osteolytic lesions obtained with the 4-weekly treatment were sustained with 8- and 12-weekly treatments. The extraskeletal masses reduced significantly with standard treatment, while tumor reduction was sustained during de-escalated treatment. During the 24-weekly treatment, 2 patients remained stable, while 2 patients developed local recurrence. The clinical symptoms improved significantly with standard treatment and remained improved during de-escalated treatment. There were severe adverse events including osteonecrosis of the jaw (2 patients), atypical femoral fracture (1 patient) and malignant transformation of GCTB (1 patient). In conclusion, 12-weekly de-escalated denosumab treatment showed clinical benefits as a maintenance treatment in patients with unresectable GCTB, in addition to sustained stable tumor control and improved clinical symptoms with standard treatment. A 24-weekly treatment can also be administered, with careful attention paid to detecting local recurrence.

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Introduction

Giant cell tumor of bone (GCTB) is a locally aggressive intermediate bone tumor occurring in long bones such as the femur, tibia, radius, humerus, and spine. GCTB predominantly arises in the second to fourth decades of life and is slightly more common in women (1,2). The treatment mainstays are surgical treatment including curettage or en bloc resection (1,2). Complete surgical excision is preferred for optimal oncological outcomes. However, surgical treatment is often challenging, with severe impairment in cases of GCTB in the spine and pelvis due to the proximity of critical structures, including major nerves and vessels, and the high incidence of postoperative complications (3,4). Furthermore, GCTB recurs postoperatively in 10-50% of patients (1,2). While radiotherapy is used to treat unresectable or advanced GCTB, the risk of malignant transformation after radiotherapy is relatively high (5,6). Although selective serial embolization may be useful for treating GCTB in the spine and pelvis, the recurrence rate is 22-75% (7,8).

GCTB comprises reactive non-neoplastic multinucleated giant cells (osteoclasts) expressing the receptor activator of nuclear factor-κB (RANK) and neoplastic mononuclear stromal cells expressing RANK ligand (RANKL) (9). RANK-RANKL interactions promote osteoclast proliferation and survival, thus facilitating bone resorption. Denosumab, a monoclonal antibody inhibitor of RANKL, recently showed effectiveness in GCTB treatment (10,11). Denosumab suppresses the osteoclast activity promoted by mononuclear tumor cells, induces new bone formation in the destroyed bone, and improves bone stability. The marked and extensive re-ossification of osteolytic lesions indicates the tumor-suppressive effect of denosumab (12). Multicenter phase 2 studies demonstrated that denosumab was an effective and promising treatment option for advanced or unresectable GCTB (13-16). However, the severe adverse events (AEs) of denosumab treatment include hypocalcemia, osteonecrosis of the jaw (ONJ), atypical femoral fracture (AFF), and malignant transformation of GCTB (9-11,17), likely because 4-weekly denosumab treatment is required for difficult-to-treat GCTB. Furthermore, denosumab is not generally used in women who want to become

pregnant, although GCTB is likely to occur at childbearing age. Denosumab cessation to address these issues resulted in high rates of local recurrence (15,18,19). Chawla *et al* reported disease or recurrence progression after denosumab cessation in 26% of patients with surgically unsalvageable GCTB within a median of 39 months (15). Palmerini *et al* observed that 40% of patients with unresectable GCTB developed tumor progression at a median of 8 months after denosumab cessation (18).

Denosumab was widely used in managing bone metastases before GCTB treatment. Recent studies demonstrated the efficacy and safety of extended-interval denosumab treatment (de-escalation) for bone metastases (20,21). Clemons *et al* showed similar clinical results, including symptomatic skeletal events related to bone metastases, for a 12-weekly treatment of bone-modifying agents, including denosumab, compared to a 4-weekly treatment (20). However, the benefits of denosumab de-escalation for unresectable GCTB have not been well discussed, with only two related case reports regarding denosumab de-escalation for GCTB (22,23). The denosumab dosing interval was extended after achieving good therapeutic effects with standard 4-weekly treatment, mainly to avoid AEs. The present study investigated the efficacy and safety of denosumab de-escalation in a series of cases with unresectable GCTB to address i) how long the denosumab dosing interval can be extended, ii) whether denosumab de-escalation can sustain the therapeutic change in GCTB on imaging, and iii) if denosumab de-escalation can prevent AEs.

Patients and methods

Study population. The medical records of nine patients (2 men and 7 women) with GCTB that were either unresectable or resectable but not candidates for resection, who received de-escalated denosumab treatment at Okayama University Hospital (Okayama, Japan) between April 2014 and December 2023 were retrospectively reviewed. Patients who had undergone radiotherapy or surgery with neoadjuvant denosumab treatment were excluded (Table I). The median age at initial denosumab treatment was 44 (range, 25-77) years. The tumors were located in the sacrum (5 patients), femur (2 patients), thoracic spine (1 patient), and lumbar spine (1 patient). Four patients were newly diagnosed with primary tumors, while five had locally recurrent tumors, two of whom were previously treated with repeated embolization for sacral GCTB, one with intralesional resection (curettage) followed by repeated embolization for sacral GCTB, and two with intralesional resection and bone grafting for femoral GCTB. Two patients with resectable recurrent femoral GCTB received definitive denosumab treatment as both refused prosthetic replacement. One patient (case 7) who originally participated in a multicenter phase 2 clinical trial on denosumab and received denosumab therapy in another hospital was treated in our hospital after the therapy for GCTB was covered by the National Health Insurance in Japan.

Treatment. All patients received 120 mg of denosumab on days 1, 8, 15, and 29 and every 4 weeks thereafter. The treatment interval was gradually extended to every 8, 12, and 24 weeks after careful discussion with the patient based on the clinical symptoms and radiological findings. The patients were administered calcium and vitamin D supplements daily. The denosumab treatment was defined based on the treatment interval: standard treatment (every 4 weeks) and de-escalated treatment (every 8, 12, and 24 weeks). We investigated the duration and dose of denosumab treatment in each period, as well as the AEs related to denosumab treatment.

Imaging assessment. Computed tomography (CT) (Discovery CT750 HD, GE) images, obtained at 120 kV and a 5-mm slice thickness, were viewed in a routine bone window setting (window level 200 HU, window width 2,000 HU) in the axial, sagittal, and coronal planes. The magnetic resonance imaging (MRI) (MEGNETOM Prisma, Siemens) findings included T1- and T2-weighted images obtained in the axial, sagittal, and coronal planes. All patients underwent plain radiography, CT, and MRI before denosumab treatment, every 1-5 months in patients administered standard denosumab treatment, and every 4-12 months in patients administered de-escalated treatment. The radiological responses of the tumor to denosumab treatment were assessed using the MD Anderson (MDA) criteria (24-26) (Table II). Re-ossification of osteolytic lesions on CT images indicated successful repair with denosumab treatment (10). The time to response (TTR) was defined as the duration from the first denosumab treatment to the identification of sclerotic changes inside the tumor based on the MDA criteria. Five tumors were associated with extraskeletal masses, which were evaluated as grade 3 according to the Campanacci classification, while four tumors were classified as grade 2 (27). The sizes of the extraskeletal masses were measured after completing the course of denosumab treatment. The spinal instability neoplastic score (SINS) was evaluated in seven patients with spinal GCTB (Table III). The total score was divided into three categories: stable (0-6 points), potentially unstable (7-12 points), and unstable (13-18 points).

Clinical and physical examinations. Local pain was assessed using the numerical rating scale (NRS), with scores ranging from 0 (no pain) to 10 (worst pain). Patients with GCTB of the spine were also examined. Functional impairment was assessed using the American Spinal Injury Association (ASIA) impairment scale for patients with spinal GCTB (28).

Statistical analysis. The median sizes of the extraskeletal masses before and after standard treatment, the median SINS for spinal GCTB before and after standard treatment, and at the latest follow-up, and median NRS before and after standard treatment were analyzed using Wilcoxon signed-rank tests. All analyses were conducted using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Tokyo, Japan). For all analyses, $P<0.05$ was considered significant.

Results

Denosumab de-escalation and clinical course. The median overall duration of denosumab treatment was 84 (range, 28-137) months (Fig. 1). The interval of denosumab treatment was extended after a median of 12 (range, 12-34) months, with a median treatment time for de-escalation of 46 (range, 11-96) months (Table IV). The median number of denosumab injections was 40 (range, 20-110), with medians of 17 (range,

Table I. Patient characteristics.

Case	Sex	Age, years	Location	Campanacci grading	Prior treatment
1	Female	77	L5	2	
2	Female	44	T10	2	
3	Female	25	S1	3	
4	Female	64	S3	3	Embolization
5	Female	30	S2	3	Embolization and surgery
6	Male	27	S1	3	Embolization
7	Female	44	S2	3	Embolization
8	Male	59	Femur	2	Surgery
9	Female	26	Femur	2	Surgery

L, lumber spine; S, sacrum spine, T, thoracic spine.

Table II. MD Anderson criteria.

Response category	Plain X-ray or computed tomography	Magnetic resonance imaging
Complete response	Complete sclerotic fill-in of lytic lesions Normalization of bone density	Disappearance of tumor signal
Partial response	Development of a sclerotic rim or partial sclerotic change or sclerosis of lytic lesions Regression of measurable lesion	Regression of measurable lesion
Stable disease	No change in measurable lesion	No change in measurable lesion
Progressive disease	Increase in the size of measurable lesions	Increase in the size of measurable lesions

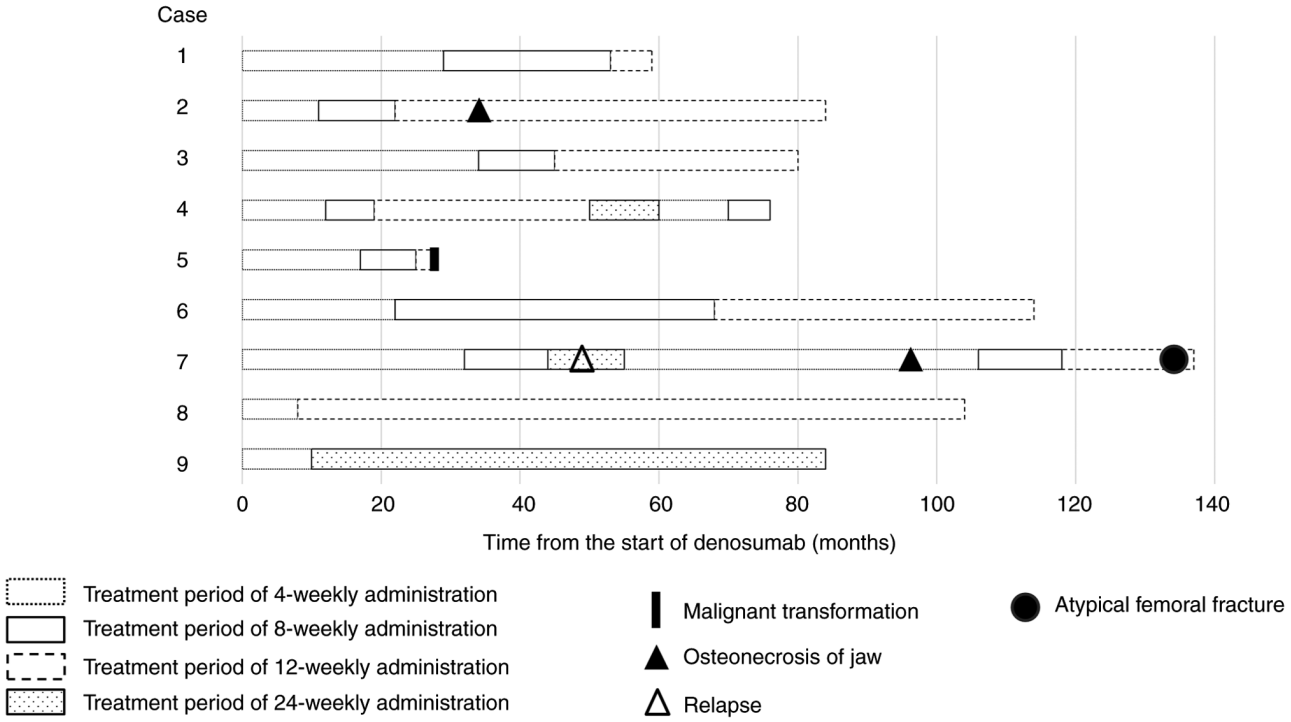

Figure 1. Swimmer plot. The median overall duration of denosumab treatment was 58 months (range, 33-118 months). The interval of denosumab treatment was extended after a median of 12 months (range, 8-36 months), with a median treatment time of de-escalation of 46 months (range, 9-75 months). Eight of the nine patients received de-escalated treatment at the last follow-up.

Table III. Spinal instability neoplastic scores.

Component	Score
Location	
Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	3
Mobile spine (C3-C6, L2-L4)	2
Semirigid (T3-T10)	1
Rigid (S2-S5)	0
Pain[a]	
Yes	3
Occasional pain but not mechanical	1
Pain-free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
>50% collapse	3
<50% collapse	2
No collapse with >50% body involved	1
None of the above	0
Posterolateral involvement of spinal elements[b]	
Bilateral	3
Unilateral	1
None of the above	0

[a]Pain improvement with recumbency and/or pain with movement/loading of the spine. [b]Facet, pedicle or costovertebral joint fracture, or replacement with tumor. C, cervical spine; L, lumber spine; S, sacrum spine; T, thoracic spine.

8-37) injections for standard treatment and 15 (range, 5-41) injections for de-escalated treatment. Eight of the nine patients had received de-escalated treatment at the latest follow-up.

All seven patients with spinal GCTB had stable disease following 8-weekly treatment for a median of 11 (range, 7-46) months. Six patients proceeded to 12-weekly treatment, with five showed stable disease following 12-weekly treatment for a median of 35 (range, 6-62) months. One patient (case 4) proceeded to 24-weekly treatment and experienced tumor regrowth 10 months after de-escalation to 24-weekly treatment. The patient was re-treated with standard denosumab therapy. Imaging showed tumor reduction with sclerotic changes; hence, the patient received 8-weekly treatment of denosumab and demonstrated stable disease. One patient (case 5) developed malignant transformation 2.3 years after the first denosumab treatment and 3 months after the first 12-weekly treatment. One patient (case 7) treated with de-escalated therapy from 8-weekly to 24-weekly treatment experienced tumor regrowth 6 months after de-escalation to 24-weekly treatment. The patient was re-treated with standard denosumab therapy. Imaging showed tumor reduction with sclerotic changes; hence, the patient received 8-weekly treatment, then 12-weekly treatment of denosumab and demonstrated stable disease. One (case 8) of the two patients with femoral GCTB proceeded to 12-weekly treatment of denosumab; the other patient (case 9) proceeded to 24-weekly treatment of denosumab and both patients had stable disease at the latest follow-up. All patients were alive at the latest follow-up visit. None of the patients, except for one with malignant transformation, developed pulmonary metastasis.

Imaging assessments. Plain radiography and computed tomography (CT) revealed sclerotic changes inside and around the tumor in eight patients after receiving standard denosumab treatment. The median TTR was 3.5 (range, 1.1-5.3) months (Table V), and the median time to identify the maximum sclerotic change was 11 (range, 6-17) months after the first denosumab treatment. Sclerotic changes were continuously identified on CT without progressive osteolytic change after 8-weekly and 12-weekly treatment in all nine patients. One patient achieved a complete response (CR), while eight achieved partial response (PR) following a standard denosumab treatment according to the MDA criteria and remained unchanged during de-escalated treatment (Table V). One patient (case 9) showed stable radiographic changes after 24-weekly treatment of denosumab, while two patients (case 4 and 7) developed a recurrent tumor with progressive osteolytic change after 24-weekly treatment of denosumab, which demonstrated sclerotic changes after resuming standard treatment.

Extraskeletal masses were identified in five patients, with a median size of 8.3 (range, 2.6-15) cm before denosumab treatment (Table V). The sizes of the masses decreased significantly to a median of 7.0 (range, 0.2-11.8) cm after standard treatment in all five patients compared to the sizes before treatment (P=0.043), corresponding to a mean of 79% (range, 8-98%) of the original sizes. The median time to identify initial tumor reduction was 4.6 (range, 1.1-5.3) months after the first denosumab treatment (Fig. 2), while the median time to identify maximum tumor reduction was 14 (range, 3-17) months. Three patients showed stable disease following de-escalated treatment, while two patients (case 4 and 7) experienced tumor regrowth.

Imaging of spinal GCTB before denosumab treatment demonstrated <50% collapse in two patients, no collapse with >50% body involvement in three patients, and no collapse with ≤50% body involvement in two patients according to SINS. At the latest follow-up, six patients did not experience further spinal collapse, while one patient with T10 disease (case 2) progressed from <50 to >50% collapse. The median SINS for spinal GCTB before denosumab treatment was 8 (range, 5-10) points; two patients had stable disease, while five patients had potentially unstable disease based on their SINS. The SINS improved to a median of 4 (range, 1-10) points after standard treatment (P=0.024): six patients had stable disease, while one patient had potentially unstable disease based on their SINS. One patient showed further improvement in SINS after de-escalated treatment. The SINS further improved to a median of 3 (range, 1-10) points at the latest follow-up (P=0.026), which was not significantly different from that

Table IV. Denosumab treatment.

		Number of denosumab doses				Duration of denosumab treatment (months)			
Case	Denosumab treatment	4-weekly	8-weekly	12-weekly	24-weekly	4-weekly	8-weekly	12-weekly	24-weekly
1	8-weekly → 12-weekly	17	12	2		29	24	6	
2	8-weekly → 12-weekly	14	7	18		11	11	62	
3	8-weekly → 12-weekly	37	4	11		34	11	35	
4	8-weekly → 12-weekly → 24-weekly (progression) → 4-weekly → 8-weekly	16 10	4 2	10	2	12 10	7 6	31	10
5	8-weekly → 12-weekly (malignant transformation)	20	4	1		17	8	3	
6	8-weekly → 12-weekly	27	24	17		22	46	46	
7	8-weekly → 24-weekly (progression) → 4-weekly → 8-weekly → 12-weekly	37 52	5 8	6	2	32 51	12 12	19	11
8	12-weekly	8		32		8		96	
9	24-weekly	8			12	10			74

after the standard treatment (P=0.317). The tumors in six patients were classified as stable, while that in one patient was classified as potentially unstable after receiving de-escalated treatment.

Clinical symptoms. Eight of the nine patients experienced local pain before denosumab treatment, with a median NRS score of 4 (range, 0-10) (Table VI). Seven patients became pain-free (NRS=0) after standard denosumab treatment, with a median NRS score of 0 (range, 0-2) (P=0.001). Pain disappeared at a median of 97 (range, 7-181) days after the first denosumab treatment and after a median of five (range, 2-8) injections of standard treatment. One patient (case 1) experienced pain (NRS=2) at the latest follow-up. Tumor recurrence (case 4 and 7) was identified after treatment de-escalation to 24-weekly treatment due to progressive severe pain (NRS=10), which subsequently disappeared (NRS=0) after resuming standard treatment.

All seven patients with spinal GCTB experienced numbness or hypoesthesia in the lower legs, and two patients had bladder and bowel dysfunction. Two patients were classified as having grade D, while five were classified as having grade E impairments before denosumab treatment, based on the ASIA scale. Sensory disturbance improved in all seven patients after receiving standard treatment, although three had slight numbness during standard and de-escalated treatment. One of the two patients with bladder and bowel dysfunction before treatment completely recovered; the other experienced persistent mild constitution symptoms after denosumab treatment. All seven patients were classified as having grade E impairments based on the ASIA scale after receiving de-escalated treatment.

AEs. Two patients experienced ONJ after the treatment was de-escalated to every 12 weeks. Both patients received ONJ treatment without denosumab discontinuation. One patient (case 2) developed pain, mucosal swelling, and bone exposure of the jaw 3.3 years after the first denosumab treatment and 2.3 years after the initial de-escalation. A dental panoramic radiograph showed an osteolytic lesion of the jaw, which the dentist diagnosed as ONJ. The symptoms improved with oral antibacterial medication. However, the patient underwent sequestrectomy after experiencing purulent discharge from the exposed bone for 1 year. Although the pain subsequently improved, the patient still had a small amount of purulent discharge. The other patient (case 7) also showed pain,

Table V. Radiological responses.

	Extraskeletal mass, cm (% of the original site)			MDA criteria			SINS		
Case	Before denosumab	Standard period	De-escalation period	Standard period	De-escalation period	TTR, months	Primary	Standard period	De-escalation period
1				PR	PR	4	10	9	9
2				PR	PR	2	7	4	4
3	8.3	7 (84%)	7 (84%)	PR	PR	3	8	3	3
4	5.6	5.5 (98%)	5.5 (98%)	PR	PR	3	6	2	2
5	2.6	0.2 (8%)	0.2 (8%)	PR	PR	4.6	5	1	1
6	14.2	8.9 (62%)	8.9 (62%)	PR	PR	1.1	10	6	6
7	15	11.8 (79%)	11.8 (79%)	PR	PR	5.3	9	5	2
8				PR	PR	4			
9				CR	CR	4.3			

TTR, time to response; MDA, MD Anderson; SINS, spinal instability neoplastic score; PR, partial response; CR, complete response.

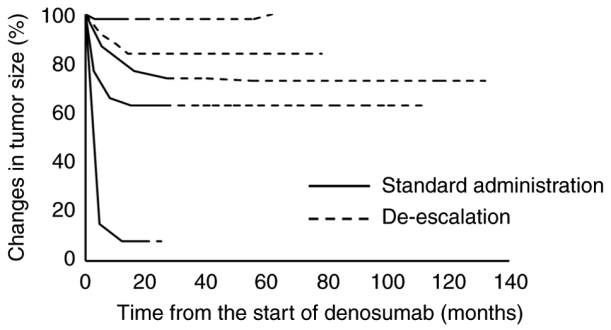

Figure 2. Changes in tumor size after denosumab treatment initiation during the standard treatment and de-escalation periods. Extraskeletal masses were identified in five patients, with a median size of 8.3 cm before denosumab treatment. The extraskeletal masses were reduced to a median size of 7.0 cm after standard treatment in all five patients. Four patients showed stable disease after de-escalated treatment, while one patient experienced tumor regrowth.

mucosal swelling, and bone exposure in the jaw at 7.8 years after the first denosumab treatment and 5.2 years after the initial de-escalation. CT showed an osteolytic lesion of the jaw, which the dentist diagnosed as ONJ. The symptoms improved with periodic cleaning of the affected area and oral antibacterial medication. However, mucosal pain and swelling recurred 1 year and 3 months later. CT showed progression of the osteolytic lesion. The patient underwent sequestrectomy, after which the symptoms improved. AFF occurred in one patient (case 7) during 12-weekly treatment of denosumab. At that time, the patient had received denosumab treatment for 11 years. Internal fixation with intramedullary nail was performed and bone union could obtain without delay. Four patients had asymptomatic hypocalcemia (median: 8.6; range, 8.2-8.7 mg/dl) that did not require additional treatment. Hypocalcemia was identified transiently at a median of 1 (range, 1-2) weeks after the initial denosumab treatment and was not detected thereafter. One patient (case 5) with grade 3 sacral GCTB according to the Campanacci classification developed malignant transformation after 12-weekly treatment of denosumab. The patient had undergone primary surgical resection elsewhere and developed local recurrence 4 months postoperatively. After referring to this hospital, multiple courses of selective embolization were performed for treatment of the recurrent tumor, which remained stable for >6 years. MRI showed enlargement of a soft tissue mass adjacent to the sacrum 6.5 years after the initial embolization. The pathological diagnosis by CT-guided biopsy was recurrent GCTB without malignant change. The recurrent tumor reduced in size following denosumab treatment and remained stable for 2 years, after which regular MRI revealed tumor regrowth. Denosumab therapy was discontinued, and the recurrent tumor was finally resected. The surgical specimen was pathologically diagnosed as a malignant transformation of GCTB.

Case 3.A 25-year-old woman with sacral GCTB presented with severe pain (NRS=9) and numbness in her left buttocks and lower limbs. CT imaging revealed a huge mass in the sacrum with cortical destruction and extensive soft tissue involvement (Fig. 3A). MRI revealed a large tumor in the sacrum with high intensity on T2-weighted images (Fig. 3B). The patient underwent standard denosumab therapy. Her pain decreased (NRS=2) after 1 week and disappeared after 2 weeks. Five months later, MRI revealed remarkable tumor shrinkage (Fig. 3C). The patient showed stable disease over the next 2 years, with remarkable sclerosis of the lytic lesions (Fig. 3D). After 8-weekly treatment of denosumab for 6 months, the patient achieved stable disease (Fig. 3E). She then received 12-weekly denosumab therapy. At the last follow-up, she continued to show stable disease (Fig. 3F, G).

Case 9. A 26-year-old woman had GCTB of the femoral head. CT images (Fig. 4A) showed a lytic lesion. She underwent two rounds of curettage and bone grafting with internal fixation. CT revealed a lytic lesion in the femoral neck (Fig. 4B). Hence, denosumab was initiated. After 4 months, a change in sclerosis was observed (Fig. 4C). After 10 months, the lytic lesion was completely filled with newly formed bone (Fig. 4D).

Table VI. Pain assessment.

	NRS		
Case	Before denosumab treatment	Standard administration period	De-escalation period
1	7	2	2
2	1	0	0
3	9	0	0
4	10	0	0
5	4	0	0
6	4	0	0
7	10	0	0
8	0	0	0
9	2	0	0

NRS, numerical rating scale.

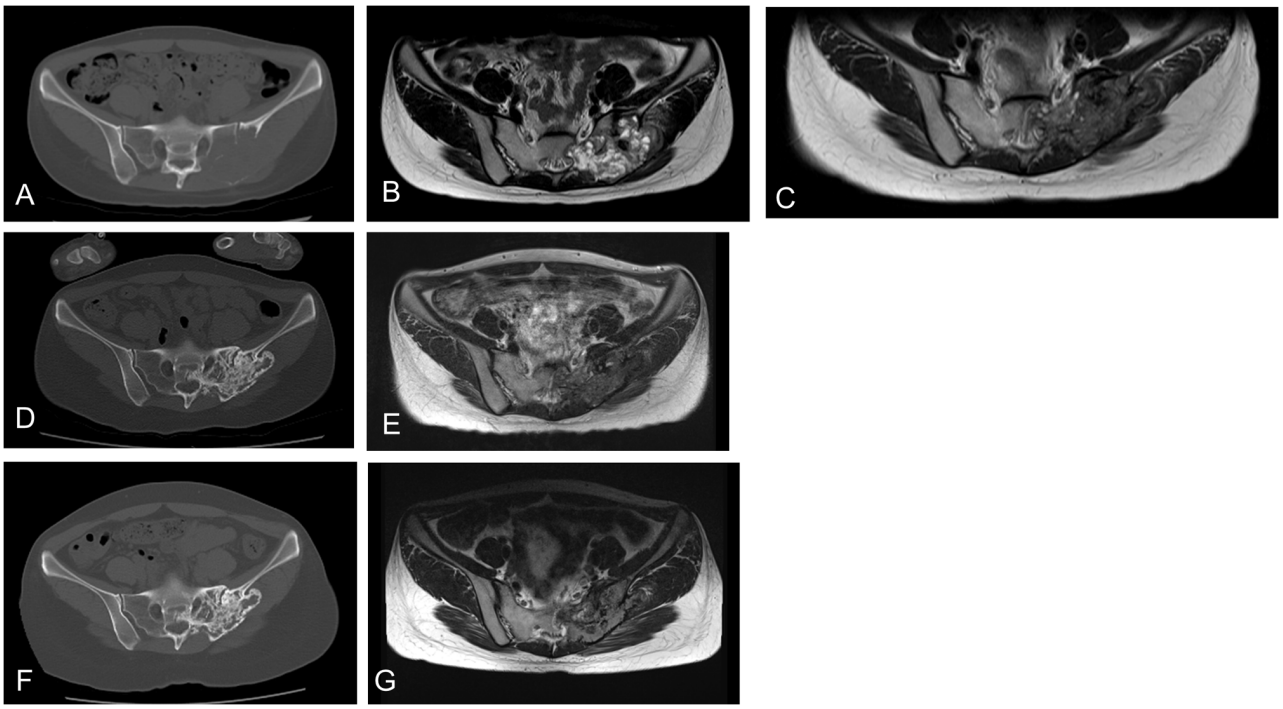

Figure 3. A 25-year-old woman with sacral GCTB. (A) A huge mass in the sacrum with cortical destruction and extensive soft tissue involvement was observed on CT. (B) MR imaging revealed a large tumor in the sacrum with high intensity in T2-weighted images. (C) Five months after the start of denosumab treatment, MR imaging showed remarkable shrinkage of the tumor. (D) Stable disease was observed over the next 2 years, with remarkable sclerosis of the lytic lesions. (E) The following 8-weekly treatment of denosumab for 6 months resulted in stable disease; hence, a 12-weekly denosumab treatment was provided. (F) At the last follow-up, the patient showed stable disease as shown in CT. (G) At the last follow-up, the patient showed stable disease as shown in MRI. GCTB, giant cell tumor of bone; CT, computed tomography; MR, magnetic resonance.

Denosumab was administered every 24 weeks. At the last follow-up, the patient showed stable disease (Fig. 4E).

Discussion

The interval of denosumab treatment to unresectable GCTB was extended to minimize the risk of AEs associated with long-term denosumab treatment. A phase 2 clinical study was planned in Europe to evaluate the risks and benefits of a reduced dose density of denosumab for unresectable GCTB (29). However, this study was discontinued before its completion owing to poor accrual. Only two related case reports have described denosumab de-escalation for GCTB (22,23). Tanikawa *et al* demonstrated that extending the dosing interval to 6 months was useful and appropriate measure (22). Hence, whether denosumab de-escalation is beneficial for unresectable GCTB remains unclear. The present study confirmed that gradual de-escalation to 8- and 12-weekly treatment achieved stable disease with therapeutic changes inside the tumor, including sclerotic changes and

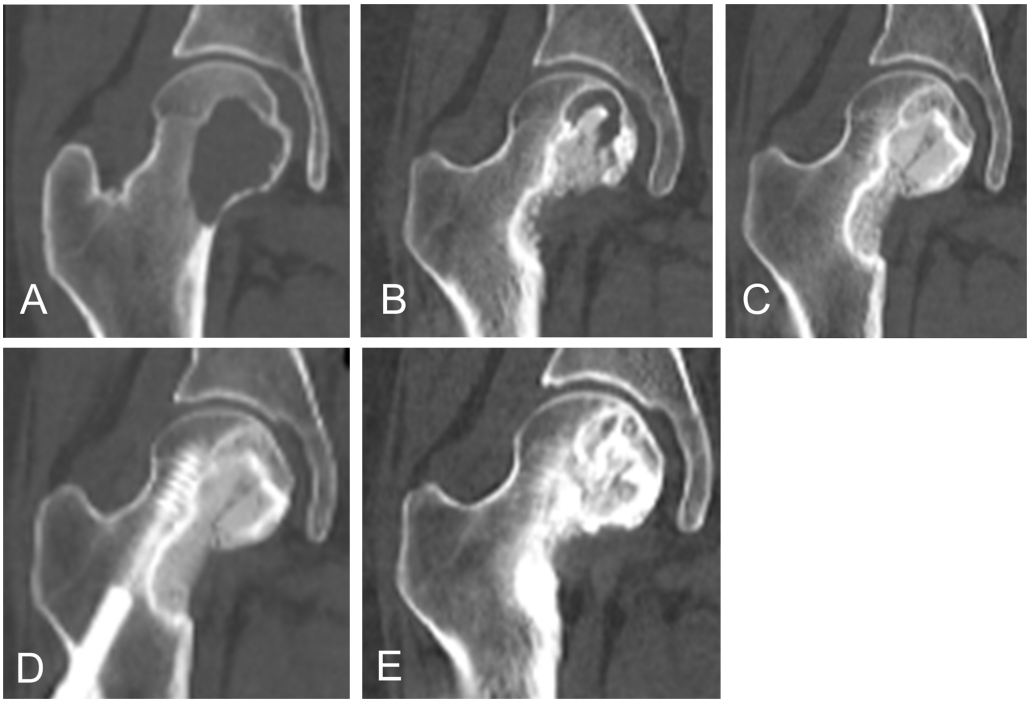

Figure 4. A 26-year-old woman with GCTB in the femoral head. (A) CT images showed a lytic lesion. She underwent two rounds of curettage and bone grafting with internal fixation. (B) CT image showed a lytic lesion in the femoral neck. (C) Denosumab treatment was initiated. After 4 months, sclerosis change was confirmed. (D) After 10 months, the lytic lesion was filled with newly formed bone. Then, 24-weekly denosumab treatment was administered. (E) At the last follow-up, the patient showed stable disease. GCTB, giant cell tumor of bone; CT, computed tomography.

extraskeletal mass reduction, which were obtained via standard 4-weekly treatment. However, two of the three patients who received 24-weekly treatments developed tumor recurrence during 24-weekly treatment. Thus, 24-weekly treatment should be performed carefully for local recurrence.

In the present study, all patients demonstrated sclerotic change within a median of 3.5 months after the first denosumab treatment, which was consistent with previous reports. Many studies have reported re-ossification inside and around the tumor after denosumab treatment on plain radiographs and CT images (10-12). Sclerotic changes with newly formed bone identified on CT images suggest successful therapeutic effects due to the reparative process of denosumab treatment (9,10). New bone formation is important, especially in patients with spinal structural instability caused by tumor invasion since most spinal GCTBs are considered unresectable (9,10). Nakazawa *et al* reported dramatic tumor regression and sclerosis 6 months after 4-weekly denosumab treatment in a patient with GCTB arising from the C5 vertebral body, which led to complete regression on CT 24 months after denosumab treatment (30). In the present study, the good therapeutic changes in imaging with standard treatment remained unchanged after de-escalated 8-weekly and 12-weekly treatments. After 24-weekly treatment, one lesion showed stable disease and two patients developed local recurrence. However, re-de-escalation was effective for these recurrent lesions, and long-term control had been obtained by 8-weekly and 12-weekly treatment. These results suggest that de-escalated 12-weekly treatment, but not 24-weekly treatment can maintain good therapeutic responses, as shown on imaging.

All five patients with an extraskeletal mass showed tumor reduction at a median of 17 months after the first denosumab treatment. Chawla *et al* reported that 72% of patients achieved partial or complete responses, as assessed based on RECIST version 1.1, within a median of 95 weeks after 4-weekly denosumab treatments for surgically unresectable GCTB including 63 patients with spinal GCTB (14). In the present study, one and eight patients achieved CR and PR, respectively, according to the MDA criteria, during standard treatment. The MDA criteria are used to assess for sclerotic changes in the tumor and changes in tumor size following denosumab treatment. RECIST1.1 might not be suitable for assessing the therapeutic effect on GCTB without extraskeletal masses, as it only measures tumor size, which often remains unchanged within the bone after denosumab treatment (14,15,31). The MDA criteria are more useful for the assessment of GCTB on imaging after denosumab treatment (32), although these criteria were initially developed to evaluate bone metastases. The median duration to identify maximum sclerotic change was 11 months after denosumab treatment, with a median duration of this maximum change of 14 months, suggesting that the maximum effect of denosumab on GCTB can be achieved approximately 1 year after the first treatment.

Denosumab can improve the clinical symptoms such as pain due to GCTB in patients with unsalvageable GCTB (8-14). Chawla *et al* reported the clinical benefit of denosumab treatment in 67 of 169 (40%) patients with unresectable GCTB, with pain reduction the most frequent benefit (28%) (15). Bukata *et al* assessed only patients with GCTB of the spine and observed the clinical benefit of denosumab treatment in 87 of 103 (85%) patients with unresectable GCTB of the spine; with pain reduction reported in 77 of 103 patients (75%) (33). In the present study, all eight patients who experienced local pain at diagnosis reported pain reduction after denosumab treatment, which was sustained after 8-weekly and 12-weekly treatments.

The reported AEs related to denosumab treatment in patients with GCTB include ONJ (9-13%), hypocalcemia (5%), AFF (1-4%), and malignant transformation (1-4%) (15,18,34). ONJ was reported in two patients who received a 12-weekly denosumab treatment: one patient developed ONJ 3.3 years after the first denosumab treatment and 2.3 years after the first de-escalated treatment; the other patient developed ONJ 7.8 years after the first denosumab treatment and 5.2 years after the initial de-escalated treatment. Previous studies demonstrated that ONJ occurs in a dose-dependent manner. Raimondi *et al* reported that 4 of 29 (13.8%) patients experienced ONJ during denosumab treatment at 125, 119, 85, and 41 months after denosumab administration, respectively (35). Bukata *et al* reported a median time to ONJ onset of 41 months after standard denosumab treatment (33). No previous paper reported the occurrence of ONJ after de-escalated denosumab treatment. Palmerini *et al* reported a 5-year ONJ-free survival rate of 92% after standard denosumab treatment (18). However, whether denosumab de-escalation can prevent ONJ remains unclear. Hence, careful attention should be paid to the occurrence of ONJ in patients receiving denosumab treatment for >3 years, even if treatment is de-escalated. Further clinical trials are needed to determine whether denosumab de-escalation prevents ONJ. Chawla *et al* reported four cases (1%) of AFF in a phase II study showing the clinical benefits of denosumab treatment in 532 patients with GCTB (15). They all occurred after 48 months of denosumab treatment. In the present study, one patient developed AFF after the start of denosumab treatment for 11 years. Then, careful observation is required and X-rays should be undertaken to investigate AFFs when clinical signs such as thigh pain arise in patients with long-term denosumab treatment.

This study has several limitations. First, the sample size was small, as only nine patients were analyzed. GCTB is relatively rare, accounting for approximately 3-5% of all primary bone tumors; moreover, unresectable GCTB such as spinal and pelvic GCTB occurs in only 2-15% of all GCTB. As mentioned above, the international clinical study on reduced dose density of denosumab for unresectable GCTB was discontinued before its completion owing to poor accrual. Thus, it was relatively difficult to study enough patients with unresectable GCTB. Second, this study had no comparison group and did not perform randomization. The patients treated with denosumab de-escalation were only described and the result of de-escalation could not be compared to that of standard treatment because all patients in this hospital with unresectable GCTB received de-escalated denosumab treatment. Owing to the small number of patients with unresectable GCTB, it is difficult to provide a control group for comparison. Third, the patients in this study were not managed according to a set protocol. Most patients underwent gradual denosumab de-escalation (4-, 8-, 12-, and 24-weekly treatments). However, some patients skipped the 8- or 12-weekly treatments and directly received a 24-weekly de-escalated treatment after standard treatment. In addition, there remains no single clinical indication to determine the duration of de-escalated treatment. De-escalation was initiated after discussion among doctors, patients, and/or their families based on the patient's clinical symptoms and imaging findings. Multicenter trials are needed to compare groups of patients and confirm the appropriate dosing interval for denosumab treatment, although one multicenter study was discontinued before its completion due to poor accrual. Lastly, structured chart review methodology was not used in this study, which can influence the outcome.

In conclusion, 12-weekly de-escalated denosumab treatment showed clinical benefits as a maintenance treatment in patients with unresectable GCTB, in addition to sustained stable tumor control and improved clinical symptoms with standard treatment. A 24-weekly treatment can also be administered, with careful attention to detecting local recurrence. Meanwhile, whether denosumab de-escalation prevented ONJ, AFF, and malignant transformation remained unknown. Patients receiving long-term denosumab treatment should be carefully examined for ONJ and AFF, even during the period of de-escalated treatment. Further investigation and more case studies are warranted to identify the clinical significance of denosumab de-escalation in severe AEs.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

EN and TK wrote the main manuscript text. EN, TF, TK and TO designed the study. EN, HK and TI treated the patients and collected the data. EN, HK, and TI collected and analyzed data. EN and TI confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This retrospective chart review study involving human participants was performed in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of Okayama University Hospital approved this study (approval no. K 2103-040). The opt-out strategy was used for patient consent.

Patient consent for publication

As this study is a retrospective study, patient consent was obtained using an opt-out consent method.

Competing interests

The authors declare that they have no competing interests.

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