A nonrandomized controlled study of sacral giant cell tumors with preoperative treatment of denosumab

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Abstract

The aim of this nonrandomized controlled study (level 3) was to evaluate whether preoperative denosumab treatment can reduce intraoperative blood loss, facilitate surgical treatment, and improve local control of sacral giant-cell tumor (GCT).

Surgical treatment of sacral GCT is very difficult due to extensive bone destruction and complex anatomical structures. The huge intraoperative blood loss may interrupt surgical management and judgment of tumor range. Denosumab can inhibit the differentiation of osteoclast-like giant cells and bone destruction by blocking RANKL-RANK pathway.

Study group (preoperative denosumab treatment) and control group (no denosumab treatment) were matched for age, gender, tumor site, staging, and tumor size. In study group, enhanced computed tomography (CT) was performed before and after denosumab treatment. The comparison parameters between 2 groups: CT enhancement rate, intraoperative blood loss, and oncologic outcome.

The mean preoperative time of denosumab treatment was 5.2 months in study group. The mean CT enhancement rate of study group was 2.60 before treatment and 1.37 after treatment (P = .012). The posttreatment CT enhancement rate of study group was significantly lower than that of control group (P = .007). The mean intraoperative bleeding of study group and control group was 2166.7 and 5240 mL, respectively (P = .040). The mean operative time of study group and control group was 268.3 and 268.5 minutes, respectively (P = .997). The recurrence rate of study group (66.7%) was significantly higher than that of control group (0%) (P = .046).

Preoperative denosumab treatment has the tendency to reduce blood supply and intraoperative bleeding of sacral GCT. But the sclerosis and bony separation can increase the difficulty of tumor curettage and lead to high recurrence rate after denosumab treatment. It is necessary to study the best surgical opportunity after denosumab treatment and precise method to judge tumor range.

Abbreviations: CT = computed tomography, GCT = giant-cell tumor, RANK = receptor activator of nuclear factor-κB, RANKL = receptor activator of nuclear factor-κB ligand, VAS = visual analog scale.

Keywords: blood loss, denosumab, giant cell tumor, sacrum, surgery

1. Introduction

Giant-cell tumor (GCT) of bone is a primary intramedullary bone tumor with local aggressiveness. It accounts for about 5% of primary bone tumors. Most of tumors occur in the epiphysis of long bone.[1,2] The sacral tumor accounts for 2% to 8% of primary bone tumors. Many reports. In 1982, Sung et al[4] reported 208 cases of GCT. Because of low incidence of sacral GCT, there were not many reports. In 1982, Sung et al[4] reported 208 cases of GCT and only 4 cases were sacral tumors. Turcotte et al[3] reported a big sample study with 26 cases of sacral GCT in 1993. The early clinical symptoms of sacral GCT are occult and maybe confused with other nonspecific diseases, so it is difficult to detect tumor. When tumor grows bigger with extensive bone destruction and sacral nerve is involved, obvious symptoms can appear. Therefore, most of sacral GCT was Campanacci stage 3 which was different from limb GCT.[3,5–7]

Surgical treatment of sacral GCT is difficult due to extensive bone destruction and complex anatomical structures. Moreover, the huge intraoperative blood loss may interrupt surgical management and the judgment of tumor range. The treatment of sacral GCT is still challenging and controversial.[8] Wide or marginal resection may improve local control, but resection can lead to unsatisfactory postoperative function and high complications. Intralesional curettage may avoid nerve roots injury and preserve the integrity of pelvic ring, but high local recurrence is induced.[1,3,9] Therefore, it is important that how to improve safety and reduce blood loss in the premise of removing tumor completely.

The formation and regulation mechanisms of osteoclast-like multinucleated giant cells in GCT have become clear with related study on receptor activator of nuclear factor-κB (RANK) and receptor activator of nuclear factor-κB ligand (RANKL).[10–12] Denosumab is a new type of humanized RANKL monoclonal
antibody which can combine with RANKL specifically and block RANKL-RANK pathway. So denosumab can inhibit the differentiation and activation of osteoclast-like giant cells by blocking RANKL-RANK pathway. A phase 2 clinical trial[13] with 35 cases of recurrent or unresectable GCT showed 86% of the patients had effective response and clinical benefit. Pain relief and functional improvement was presented. In our clinical practices, we found an interesting tendency that enhanced computed tomography (CT) value of sacral GCT seemed to decrease after denosumab treatment. Therefore, we performed this study to evaluate whether denosumab can reduce blood loss, facilitate surgical treatment and improve local control of on sacral GCT.

2. Materials and methods

2.1. Patients’ enrollment

All cases were from the musculoskeletal tumor database of our department. Inclusion criteria were as follows: pathologic diagnosis confirmed as GCT of bone; sacral tumor; stage 3 tumor; extensive bone destruction; tumor curettage was performed in our department. Six patients who received denosumab treatment before surgery were eligible for study group and 10 patients who did not receive denosumab treatment were matched as control group. Study and control groups were matched for the following factors: age, gender, tumor site, staging, and tumor size (measured by CT). The treatment period of study group was from December 2015 to September 2016. As all similar cases at the same time received denosumab treatment, the control group was selected from earlier period when denosumab was not applied in our department. The treatment period of control group was from January 2014 to September 2015. There was no significant difference between these 2 groups (Tables 1 and 2).

2.2. Denosumab treatment and CT evaluation procedures

All patients in study group complied with following conditions: patients were informed and consented for denosumab treatment; patients were adults or mature adolescents with GCT that was unresectable or surgical resection may result in severe morbidity; calcium and Vitamin D levels were normal; no contraindication of denosumab existed. Patients received subcutaneous denosumab 120mg every 4 weeks, with additional doses administered on days 8 and 15 during the 1st month. Enhanced CT examination was performed before denosumab treatment and 12 weeks after treatment. If tumor was resectable or important structure can be retained, denosumab was stopped and the patient received surgery. If the above standard was not achieved, the patient continued treatment. All patients received CT examinations in the same CT machine. The injection volume, speed of contrast and CT scan times were same before and after treatment. About 4 to 8 levels of tumor were selected for evaluation. The CT value of the same tumor substance areas (liquid, cystic formation, and bone formation areas were excluded) were measured before and after treatment (Fig. 1). The CT enhancement rate was calculated as the ratio of enhanced CT value and unenhanced CT value of the same tumor area. It represents a percentage increase in tumor density on post- to precontrast CT images.

2.3. Surgical treatment

All patients received high selective tumor blood supply embolization preoperatively. A posterior approach was applied in operation. A median longitudinal incision was performed and the flap with fascia was opened. The gluteus maximus, erector spinae, and sacroiliac joint were exposed. Curettage of tumor was performed and high-speed burr was used until tumor was removed and normal bone was left. Tumor above S3 level received curettage. If tumor destructed sacrum below S3, distal part of tumor would be resected with clear margin.

2.4. Data record and follow-up

The following parameters were recorded and compared between 2 groups: CT enhancement rate; intraoperative blood loss; operative time; surgical treatment; and local recurrence. All

| Table 1 | Matching of 2 groups of patients. |
|---------|----------------------------------|
| Study group | Control group | P-value |
| Cases | 6 | 10 | |
| Gender | 2 males, 4 females | 4 males, 6 females | .317 |
| Age | Mean 36.2 (21-63) | Mean 30.5 (16-50) | .406 |
| Tumor site | All above S3 | All above S3 | |
| Tumor staging | All 3 | All 3 | |
| Tumor size, cm² | Mean 197.5 (100.4-336.0) | Mean 158.1 (100.8-261.8) | .264 |
| Enhancement rate of CT (before treatment) | Mean 2.6 (2.1-4.05) | Mean 2.38 (1.6-3.4) | .602 |

CT = computed tomography.

| Table 2 | Clinical results of 2 groups of patients. |
|---------|----------------------------------|
| Study group | Control group | P-value |
| Enhancement rate of CT (after treatment) | Mean 1.37 (1.11-1.65) | Mean 2.38 (1.6-3.4) | .007 |
| Blood loss, mL | Mean 2166.7 (1300-3000) | Mean 5240 (2500-14,000) | .04 |
| Operation time, min | Mean 268.3 (210-360) | Mean 268.5 (180-450) | .997 |
| Local recurrence | 66.7% (4/6) | 0 (0/10) | .046 |
| MSTS scores | Mean 25.9 (18-30) | Mean 22 (17-27) | .142 |

MSTS = Musculoskeletal Tumor Society.
patients were followed every 3 months postoperative. Physical examination, plain radiography, and sacral CT were performed every 3 months. The bone scanning and chest CT were performed every 6 months. Postoperative recurrence was recorded.

2.5. Statistical analysis

The data were analyzed by SPSS software (version 19.0; SPSS, Chicago, IL). The mean-value \( t \) test was performed to compare CT value, intraoperative blood loss, and operative time in different groups. The recurrence rates in different groups were compared by Chi-squared test or Fisher exact probability method. All statistical values were considered significant at \( P < .05 \).

3. Results

3.1. Denosumab treatment brought clinical benefits and had no significant side effects

The mean preoperative time of denosumab treatment was 5.2 (median 4.5, range 3–10) months in study group. The mean pre- and posttreatment visual analog scale (VAS) was 3.8 (2–6) and 0.7 (0–2), respectively (\( P = .001, F = 21.235 \)). All 6 patients presented clinical benefits such as pain relief and increased function after treatment. All 6 patients tolerated well and no serious side effect was found.

3.2. Decreasing of CT enhancement rate and increasing of unenhanced CT value after denosumab treatment

The CT in study group showed mixed new bone formation with low-density areas in the lesion after denosumab treatment. Multiple uncommunicated bony sclerosis divisions were formatted in tumor. The sclerotic bony shell was found on the edge of tumor or soft-tissue mass (Fig. 1). The mean pre- and posttreatment unenhanced CT value was 42.0 (37–54) and 56.4 (41–70), respectively (\( P = .045, F = 5.431 \)). The increasing of unenhanced CT value suggested the raising of osteogenesis and sclerosis. The mean CT enhancement rate of study group was 2.60 (2.11–4.05) before treatment and 1.37 (1.11–1.65) after treatment (\( P = .012, F = 10.636 \)) (Fig. 2). The decreasing of CT enhancement rate suggested the decreasing of tumor blood supply. The mean CT enhancement rate of control group was 2.38 (1.6–3.4). The pretreatment CT enhancement rate of study group was similar with control group (\( P = .602, F = 0.289 \)); the posttreatment CT enhancement rate of study group was significantly lower than that of control group (\( P = .007, F = 10.829 \)) (Fig. 3).

3.3. Denosumab treatment reduced intraoperative blood loss but increase the difficulty of tumor curettage

The mean intraoperative blood loss of study group and control group was 2166.7 (1300–3000) mL and 5240 (2500–14,000) mL, respectively (\( P = .040, F = 5.016 \)). The mean operative time of study
The computed tomography enhancement rate of the 6 cases in the study group (before and after denosumab treatment, \(P=0.012\)).

**Figure 2.**

The mean value of computed tomography (CT) enhancement rate of the study group (before and after denosumab treatment) and control group. The posttreatment CT enhancement rate of study group was significantly lower than that of control group \((P=0.007)\). **Figure 3.**

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3.4. **Study group had higher recurrence rate**

The study group was followed an average 12 (7–18) months and 4 patients had recurrence (66.7%). The control group was followed an average 35.3 (13–61) months and there was no recurrence. The recurrence rate of study group was significantly higher than that of control group \((P=0.046, \chi^2=4.000)\). The mean Musculoskeletal Tumor Society (MSTS) score of study group and control group was 25.9 (18–30) and 22 (17–27), respectively \((P=0.142, F=2.505)\).

4. **Discussion**

The incidence rate of sacral GCT is low and surgical treatment is difficult.\([1–4]\) Complex local structures and huge intraoperative
blood loss make it very challenging. The local recurrence rate of sacral GCT is high.\textsuperscript{6–9} Denosumab is a new type of humanized RANKL monoclonal antibody. It combines with RANKL specifically and block RANKL-RANK pathway. Thus it can interfere with the survival and differentiation of osteoclasts and inhibit osteoclast mediated bone destruction.\textsuperscript{14} In our clinical practices, we found an interesting tendency that enhanced CT value of tumor seemed to decrease after denosumab treatment. Therefore, we performed this study to evaluate whether denosumab can reduce intraoperative blood loss, facilitate surgical treatment and improve local control of sacral GCT.

Our study showed significantly decreasing of VAS after denosumab treatment. All patients presented pain relief and clinical benefit. Thomas et al\textsuperscript{[13]} reported a phase 2 study which showed 84% of patients had clinical benefit such as reduced pain or improvement in functional status. Martinbroto et al\textsuperscript{[14]} reported another phase 2 study and most patients showed clinically relevant decreases in pain within 2 months of treatment. These previous reports had similar results with our study.

Our results showed mean intraoperative blood loss of study group and control group was 2166.7 and 5240 mL, respectively. The bleeding was significantly reduced after denosumab treatment. The significantly decreasing of CT enhancement rate (mean 2.60 vs 1.37) after denosumab treatment also supported the decreasing of tumor blood supply. As far as we know, there has been no quantifying enhanced CT analysis on the effect of denosumab treatment. The tumors in our study were aggressive and huge, while the blood loss in study group was relative small compared with that in previous reports. Ozaik et al\textsuperscript{[9]} reported the mean intraoperative blood loss of sacral GCT was 6900 mL. In 2016, Guo et al\textsuperscript{[16]} reported a big case series of sacral GCT and mean intraoperative blood loss was 3223.3 mL. In 2015, Domovitch et al\textsuperscript{[17]} reported 24 sacral GCT who underwent conservative surgery (intralesional resection/curettage) and preoperative embolization may decrease the bleeding. The rich blood supply of tumor can lead to high risk of huge intraoperative bleeding. Less intraoperative bleeding can obtain clear visible surgical field and bring benefit for removing tumor thoroughly.

In the present study, the operative time of study group (mean 268.3 minutes) and control group (mean 268.5 minutes) was almost same. All tumors were located above sacral level 3 with extensive bone destruction, so the surgical treatment was difficult and challenging. The results showed preoperative denosumab treatment did not make surgery faster or easier from the perspective of time expenditure. In fact, although the relative less bleeding made surgeons unhurried, but new problems appeared and need to be resolved in operation. The mean pretreatment unenhanced CT value (mean 42.0) was significantly lower than posttreatment (mean 56.4). The increasing of CT value suggested the raising of osteogenesis and sclerosis. Müller et al\textsuperscript{[18]} suggested denosumab can build a new-formed peripheral bone rim around tumor in their case series. Nishimura et al\textsuperscript{[19]} reported the sacral GCT refractory to combination therapy with arterial embolization and zoledronic acid. CT also showed gradual appearance of bone sclerosis around sacrum after denosumab treatment. But our study showed tumor became hardening and bony septa increased after denosumab treatment, so it was difficult to judge tumor boundary and perform curettage. Focal sclerosis led to adhesion between tumor and sacral nerve. It is difficult to separate nerve from tumor.

After near 3 years follow-up, no local recurrence was found in control group. However, 4 of 6 cases (66.7%) in study group showed local recurrence after only 1 year follow-up. The main reason was that intralesional sclerosis and bony septa increased difficulty of tumor curettage. Another reason of high recurrence rate was that extensive curettage could not be performed in sacrum as that in limbs. Guo et al\textsuperscript{[14]} reported the recurrence rate was 18.3% after marginal resection and curettage. In 2010, Pietro et al\textsuperscript{[20]} reported 31 sacral GCT and the recurrence rate was 10%. The authors suggested that preoperative embolization and postoperative radiotherapy did not decrease the recurrence rate. Adjuvant treatment with phenol and liquid nitrogen was not associated with recurrence. Combined with previous reports before 2010, the recurrence rate of sacral GCT after intralesional curettage was about 20% to 40%.\textsuperscript{[3,21–25]}

In 2015, Memorial Sloan Kettering Cancer Center\textsuperscript{[17]} reported 24 cases received intralesional curettage and local recurrences rate was 30%. Radiation and preoperative embolization were associated with prolonged disease-free survival. There were no local recurrences among the 11 patients who were treated with both modalities. Another report\textsuperscript{[26]} analyzed risk factor of recurrence and compared intracompartmental (T1) tumors and extracompartmental (T2) tumors in 2013. It showed that T1/T2 was the only risk factor of recurrence while age, gender, tumor site, tumor volume, and radiation were not. However, some reports\textsuperscript{[27–31]} show that local recurrence rate after wide resection (20.3–38.9%) was not significantly decreased. Due to the low incidence and small sample report of sacral GCT, surgical treatment is still challenging and controversial.

There have been some clinical studies which reported oncologic results of GCT after denosumab treatment, but they did not focus on sacral tumor. Traub et al\textsuperscript{[32]} reported a prospective nonrandomized study of 18 patients who received preoperative denosumab and intralesional surgery. The local recurrence rate was 17%. Müller et al\textsuperscript{[18]} reported a local recurrence rate of 8.3% in 12 patients treated by curettage after denosumab treatment. The authors thought that tumor cells can remain in the newly formed bone induced by denosumab and newly formed bone makes curettage difficult. The new osseous matrix and thickened cortical bone raises a new surgical challenge by not allowing surgeons to delineate the true extent of tumor. The authors also considered that tumor cells can hide within the thickened bone matrix, which led to local recurrence when denosumab therapy discontinued. The high recurrence rate of study group in our study also supported this opinion. But up to now, there is no relevant report that recommends continuing denosumab therapy after surgery. Therefore, we suggest that it is important to curettage tumor thoroughly according to initial tumor boundary, but not the boundary after denosumab treatment.

The present study had some limitations. First, it was a retrospective small case series study. It was due to low incidence of sacral GCT. Second, all cases had aggressive huge tumor and selection bias may existed. The potential bias may be caused high recurrence rate in study group. More cases were required for observing and evaluating the results of denosumab treatment on sacral GCT.

In conclusion, our study showed denosumab treatment had tendency to reduce blood supply and intraoperative blood loss of sacral GCT. However, because of the increasing of sclerosis and bony separation, it is difficult to judge and completely remove tumor. The high recurrence rate was shown. Therefore, caution should be taken when selecting sacral tumors for denosumab treatment. The positive and negative effect may be balanced by controlling preoperative medication time. It is necessary to study the best preoperative medication duration and proper surgical
opportunity, and also how to accurately judge tumor range during operation.

**Author contributions**

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