THE ROLE OF DENOSUMAB IN THE COMPLEX TREATMENT OF GIANT CELL TUMOR OF THE SPINE: REDUCING OF LOCAL RECURRENCE RATE, SURGERY TIME AND BLOOD LOSS

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Objective. To assess the effect of the combined treatment method including preoperative denosumab therapy on the results of treatment of patients with giant cell tumors of the spine.

Material and Methods. A single-center retrospective-prospective study of a series of clinical cases included 15 patients with giant cell tumors of vertebrae. The average follow-up period was 56 months. A total of 11 patients received denosumab therapy according to the following scheme: 120 mg subcutaneously on the 1st, 8th, 15th and 28th days of the first month and then once every 28 days. Surgical options included marginal resection, segmental resection, or en-bloc resection with or without spinal reconstruction/stabilization. In the case of locally advanced and inoperable disease, long-term therapy with denosumab was carried out until the disease progressed or serious adverse events appeared.

Results. Thoracic vertebrae were involved in 7 (46.6 %) of 15 cases, lumbar in 4 (26.7 %) and cervical in 4 (26.7 %). Local recurrence rate after surgery alone was 40 % (2/5), average time to recurrence onset was 4.5 months. No relapses were observed after combined treatment performed in four patients. Disease progression during long-term denosumab therapy for inoperable disease recurrence was not recorded (0/7). The average number of denosumab injections before surgery and during long-term therapy was 15 and 24 injections, respectively. Denosumab therapy allows reducing the duration of surgery and the volume of blood loss.

Conclusion. Combined therapy of giant cell vertebral tumor allows to reduce the risk of recurrence of the disease, as well as to reduce surgery duration and blood loss. Long-term continuous therapy for inoperable cases allows achieving long-term stabilization of the effect. Due to the rarity of giant cell tumors of the spine, a further prospective recruitment of patients is required to study the efficacy and safety of combined therapies.

Key Words: giant cell tumor, denosumab, bone tumor, RANKL, local recurrence, spine, surgery duration, blood loss.

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Giant cell tumor (GCT) of bone is a relatively rare locally aggressive osteolytic neoplasm of skeletal bones. According to World Health Organization classification (2020), giant cell tumor refers to neoplasms of an uncertain behavior. Nevertheless, due to the clinical features of disease, treatment strategy is used as in a benign neoplasm. It does not require, for example, the use of high-dose chemotherapy, as in osteosarcomas [1]. Rare localization of GCT include vertebrae (3–6 %), pelvis (4–9 %), sacrum (4–9 %), skull and bones of the facial skeleton (2–4 %), as well as small bones of hands and feet (1–5 %) [2, 3]. The most frequent clinical manifestation of GCT is pain syndrome, which requires pain killers: from non-opioid analgesics and NSAIDs to weak and strong opioids [4]. GCT of the spine is often inoperable. It causes serious and disabling complications (for example, pelvic organ dysfunction, severe pain syndrome requiring opioids. Also, GCT may be a reason for sensory decrement, paraplegia, or quadraparesis).

The treatment of patients with GCT of the spine is a great challenge. This group has a significantly worse prognosis and a higher (up to 80 %) frequency of local recurrences than in patients with GCT lesions of the long bones [5]. An appropriate surgical treatment option has not yet been determined. Tumor curettage is associated with a high frequency of local recurrences with even greater limitations of surgical treatment after each subsequent recurrence [6]. A wide volume of surgical treatment, such as en-block resection, is associated with a lower frequency of local recurrences [5–7]. However, it is technically difficult and not always possible due to considerable or unacceptable risks of postoperative complications or deterioration of the life quality.

The advent of denosumab and its neoadjuvant and/or adjuvant administration significantly expands the surgical treatment possibilities of patients with GCT of spine. However, most often it allows avoiding traumatic intervention and becomes an alternative to any other treatment techniques [8–15]. We have considered the treatment outcomes of GCT of the spine in the era of denosumab.

The objective is to assess the effect of the combined treatment method including preoperative denosumab therapy on the results of treatment of patients with giant cell tumors of the spine.

Material and Methods

In 2005–2020, a total of 295 patients with GCT were treated; 15 (5.1 %) of them had GCT of vertebrae. The average follow-up time in the study was 56 months (from 2 to 312). It is worth noting that the highest incidence of GCT was observed in patients aged 20–29 (36.3 %) with a slight predominance of females (1.0 : 1.2); a similar situation was also among patients with vertebral lesions. All cases of GCT of vertebrae were divided into 3 groups:

Group 1 (retrospective): 5 patients who underwent only surgical treatment (the group was recruited in 2005–2020);

Group 2: 4 patients who received combined treatment: neoadjuvant therapy with denosumab at the 1st stage, surgical treatment at the 2nd stage (the group was prospectively recruited in 2016–2020);

Group 3: 7 patients with inoperable GCT of vertebrae and/or with metastases. Due to tumor extension, long-term therapy with denosumab was administered (the group was prospectively recruited in 2013–2020).

The number of patients in groups is explained by the fact that the patients could move from one group to another, where they were administered appropriate treatment. For example, after an inoperable recurrence, a patient from Group 1 with GCT of C6 vertebra was transferred to Group 3. There he was prescribed long-term denosumab treatment.

The first treatment stage in Group 2 included denosumab administration in neoadjuvant mode according to the following scheme: 120 mg subcutaneously on the 1st, 8th, 15th and 28th days of the first month, then once every 28 days. The administration of drugs was performed in a medical institution at the place of residence. The neoadjuvant treatment duration was defined as follows: the minimum number of injections – 6 injections that is equal to 3 months of treatment and the first control examination (CT/MRI). In all cases, with a continuing positive clinical and radiological picture, the treatment was continued up to two control studies confirming the disease stabilization. The volume of planned surgical treatment was considered. It was assessed at the initial admission to the hospital under radiological (CT and MRI) data on the localization, classification and relation of tumor to the neurovascular structures. If the disease was anatomically complex, patients were administered at least 15 injections of the drug, i.e., a year of neoadjuvant treatment.

In Group 3, patients were prescribed long-term denosumab treatment due to the extension and localization of the disease according to the following scheme: 120 mg subcutaneously on the 1st, 8th, 15th and 28th days of the first month, then – once every 28 days. Due to the expected risks associated with long-term treatment and complications, patients were administered supporting therapy (120 mg subcutaneously once every three months). This was done after more than two years of treatment and with a picture of disease stabilization, according to clinical and imaging findings. All patients were administered daily preventive medication of calcium (1000 mg) and vitamin D (400 IU).

In this study, the effectiveness of denosumab was assessed according to RECIST and Choi criteria. For patients from Group 2, the percentage of giant multinucleated cells was assessed in the postoperative sample.

Considering the rarity of tumor localization in the vertebrae, this study is presented as an analysis of clinical series from a general group of patients. All the data chosen for the study were formalized, processed and entered to an Excel database (Microsoft Office 2016).

Results

The incidence of GCT in vertebrae was 5.1 % (15/295). Distribution of patients depending on the spine department: thoracic – 46.6 % (7/15), lumbar – 26.7 % (4/15), and cervical – 26.7 % (4/15). Group 1 included 5 cases of GCT of the spine; Group 2 – 4; Group 3 – 7. One patient from Group 1 moved to Group 3.

Surgical results (Group 1). Out of five patients, three underwent surgical treatment in a hospital of place of residence. In our hospital, four patients underwent a nonradical spinal surgery with stabilization and one radical surgery with a combined stabilization. The patients' profile is given in Table 1.

The local recurrence rate of GCT of the spine in Group 1 was 40 % (2/5) with an average time before its development – 4.5 months (from 1 to 8 months); the average operation duration – 174.74 ± 79.3 minutes; the average blood loss volume – 756.41 ± 1051.01 ml. Both recurrences were registered after marginal excision,. In two cases, the previous intervention performed in a hospital at the place of residence was not radical. After GCT recurrence, the patient was administered beam therapy (a total focal dose of 40 GR), and during 60 months of follow-up the disease progression was not revealed. The treatment was performed in the pre-denosumab era. In the second case, due to an inoperable recurrence, denosumab was administered. The outcomes of this observation were assessed in Group 3.

Combination therapy outcomes (Group 2). Out of four cases, two had previous surgical intervention performed at the place of residence. At the 1st stage, patients were administered denosumab treatment; the average number of denosumab injections was 15 (from 9 to 20). The stabilization effect according to radiological and clinical data occurred on average after 12 injections (from 9 to 15). There were no complications or complaints associated with the treat-

ment. Two operations were conducted in a nonradical volume with fixation and two in a radical volume with combined stabilization. The patients' profile is given in Table 2.

There were no recurrences in Group 2 with an average follow-up for 27 months (from 5 to 44). In all cases of GCT of vertebrae, the elimination of giant cells of at least 95 % was observed in the postoperative sample, in contrast to Group 1 where there was no elimination of giant cells (Fig.1).

In Group 2, the average operation duration was 148.3 ± 115.1 minutes; the average blood loss volume – 420.8 ± 895.8 ml. The maximum blood loss at vertebral localization of tumor was 5000 ml, whereas in Group 1 its value reached 7500 ml at the same localization. Generally, there is a reduction in both surgery duration and blood loss volume.

Long-term treatment outcomes (Group 3). In all 7 cases, patients had previous surgical treatment performed at the place of residence. Due to this treatment, inoperable local recurrence developed. In one patient metastases in the lungs were found 14 months after surgical treatment, in addition to local recurrence.

The average number of denosumab injections was 24 (from 9 to 39). Disease stabilization according to X-ray and clinical data occurred on average after 9 injections (from 6 to 23); the full effect according to RECIST and Choi criteria was not observed.

In three cases denosumab treatment was interrupted due to prolonged disease stabilization. Nevertheless, within 6 months the disease progressed both in the form of negative clinical dynamics (pain syndrome) and according to the X-ray findings. Therefore, denosumab treatment was resumed. There were no complications or complaints in the course of treatment. The patients' profile is given in Table 3.

In ongoing denosumab treatment, there were no signs of disease progression in the form of continued growth or onset of new focuses in lungs (Fig. 2).

Table 1
Patients' profile with giant cell tumor of the spine in the surgical treatment group

Sex	Age, y.o.	Region	Case history	Surgery extent performed at National Medical Research Center	Control, month	Recurrence
M	30	Thoracic spine	Surgery	Non-radical	8	Yes
F	22	Cervical spine	Surgery	Non-radical	1	Yes
F	27	Thoracic spine	Surgery	Radical	168	–
M	18	Lumbar spine	–	Non-radical	3	–
F	21	Cervical spine	–	Non-radical	156	–

Discussion

Surgical treatment of patients with GCT of the spine is a difficult clinical challenge due to tumor localization. An appropriate surgical treatment has not yet been established. V.D. Usikov et al. [19] noted the impossibility of performing radical surgery in 3 out of 13 patients with GCT of vertebrae, since wide excision was associated with a high risk of complications. The average blood loss was 1900 ± 625.4 ml. A recurrence was revealed after 1–1.5 years in 3 out of 10 operated patients. The authors managed to perform reoperations in only two cases. In the first case, reoperation did not result in success, as well as radiation in case of recurrence. Due to the small number of patients, it was impossible to draw any conclusions regarding the combination therapy effectiveness. Meanwhile, the authors observed a decrease in blood loss volume after preoperative therapy. However, it should be noted that the use of beam therapy is associated with a risk of malignant transformation of the tumor into sarcoma [20, 21]. In NCCN guidelines beam therapy is treated as an option in the absence or exhaustion of other treatment options. In this study, the combination therapy, including preoperative denosumab administration, considerably affected the reduction of blood loss and of surgery duration. Considering the possibility of surgery, it can be assumed that after preoperative denosumab treatment, surgery in a radical volume becomes safer and technically uncomplicated. The influence and effectiveness of using one preoperative method before another remain unclear. Nevertheless, it is certain that in comparison with beam therapy, preference should be given to denosumab as a safer technique. However, it is not worth excluding the influence of other possible methods, for example, vessel embolization feeding the tumor.

Tumor curettage is associated with a high frequency of local recurrences and even greater limitations of surgical treatment of each subsequent recurrence [6]. En-block resection is associated with a lower incidence of local recurrence [5–7], but it is technically difficult to perform and not always possible. Additionally, there may be considerable or unacceptable risks of postoperative complications or deterioration in life quality. More and more published papers claim the success of total spondylectomy using various fixation options. Nevertheless, such experience has been collected only in large multidisciplinary centers, which shows the rarity of nosology and an individual approach in the treatment of these patients [22–24]. I.V. Basankin et al. [25] submitted a clinical case of surgical treatment of a giant cell tumor in the thoracic spine. The patient underwent total spondylectomy of three vertebrae. The surgery duration was 420 minutes, blood loss – 800 ml. There was no recurrence during follow-up for four years from the moment of surgery. This case is an example of performing the most possible radical surgery and a high level of surgical team. Nevertheless, if combination therapy is used, a gentler option of sur-

Table 2
Patients' profile with giant cell tumor of spine in a combination therapy group

Sex	Age, y.o.	Region	Case history	Stabilization	In total	Surgery extent performed at National Medical Research Center	Control, month	Recurrence
M	24	Thoracic spine	Surgery	9	9	Non-radical	24	–
M	26	Thoracic spine	–	10	13	Radical	5	–
F	34	Thoracic spine	Surgery	12	20	Radical	27	–
F	28	Lumbar spine	–	15	19	Non-radical	44	–

Stabilization – the number of denosumab injections at which effect was achieved, in total – the total number of denosumab injections.

gical treatment with the same outcome would be possible.

The appearance of denosumab and its neoadjuvant and/or adjuvant administration considerably expands the surgical treatment possibilities of patients with GCT of spine. More often, this technique avoids traumatic intervention and becomes an alternative to any other treatment [8–15]. The identification of RANKL (Receptor activator of nuclear factor kappa B ligand) as a key mediator of osteoclast biology has generated great interest as a potential therapeutic target in case of bone diseases. Amgen company, which actively participated in the first discoveries of RANKL biology, has developed a fully human monoclonal antibody to RANKL (denosumab), which is structurally identical to osteoprotegerin [26].

The use of denosumab in the neoadjuvant mode is based on several phase II clinical trials and other observational studies. They showed a decrease in tumor mass in course of treatment, which has allowed performing more high-precision and less traumatic surgical interventions [27–30]. The results of the largest open phase II study involving 532 adult patients and adolescents over 12 with GCT were published in 2013 and 2018 [30, 31]. In the study in cohort 2 (253/532), in which functionally safe surgical treatment was planned, neoadjuvant therapy with denosumab was conducted on the 1st stage. Then a total tumor resection was performed followed by subsequent adjuvant (postoperative) administration of six denosumab doses. In this group, with an average follow-up period of about 53 months, it became possible to perform surgery in 157 (63 %) patients, and in 40 % (106) less extensive operations were performed, including curettage. The median time before surgery was 9.2 months (95 % CI 8.5–10.5), the frequency of postoperative recurrence was 27 % (42/157). Prior to disease progression or recurrence, the median time was not reached. The probability of disease progression or recurrence according to Kaplan–Meier method was 5.6 % (95 % CI 1.8–9.4) in the first year, 28.1 % (19.8–36.5) – in the second year and 40.8 % (30.2–51.3) – in the third year. Out of 90 patients who underwent tumor curettage, a recurrence was recorded in 31 (34 %) cases. In the case of marginal tumor resection, a recurrence was recorded in 6 out of 51 cases (12 %); the median time before the recurrence was not reached in any of these subgroups. The study results are based on a large sample of patients with various tumor localizations. Nevertheless, cohort 2 is represented by tumor localization in long tubular bones (tibial, femoral and radial); the tumor is found in sacrum and spine only in cohort 1 and it was inoperable cases.

A large multicenter study for the effectiveness of denosumab in patients with GCT and lesions of the axial skeleton was the 2021 study. It analyzed 113 cases of GCT of vertebrae and sacrum [32]. There was a significant reduction in pain syndrome during treatment; in 57 % of cases,

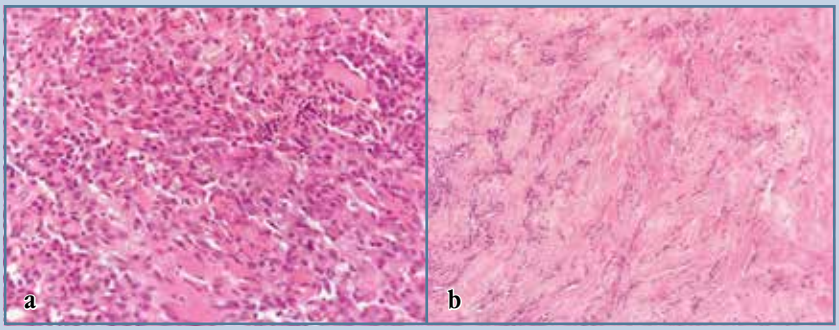

Fig 1
Microscopic appearance of a giant cell tumor in postoperative sample: **a** – a complete elimination of giant multinucleate cells is observed against the background of combination therapy; the sample is presented by a mononuclear tumor component; mag. 200; **b** – a complete elimination of giant multinucleate cells is observed against the background of combination therapy; the sample is presented with fibrotic changes on the background of treatment and insignificant mononuclear tumor component; mag. 200

Table 3

Patients' profile with giant cell tumor of spine in the group of long-term treatment for inoperable recurrence and/or metastases

Sex	Age, y.o.	Region	Case history	Recurrence	Metastases	Stabilization	In total	Control, month	DP
M	23	Thoracic spine	Surgery	Yes	–	17	39	58	–
M	29	Cervical spine	Surgery	Yes	–	18	18	21	–
F	23	Thoracic spine	Surgery	Yes	Yes	9	9	12	–
F	22	Cervical spine	Surgery	Yes	–	9	25	44	–
F	30	Lumbar spine	Surgery	Yes	–	6	15	12	–
F	25	Lumbar spine	Surgery	Yes	–	6	24	21	–
F	29	Cervical spine	Surgery	Yes	–	23	38	35	–

Recurrence – inoperable recurrence; stabilization – the number of denosumab injections at which effect was achieved; in total – the total number of denosumab injections; DP – disease progression.

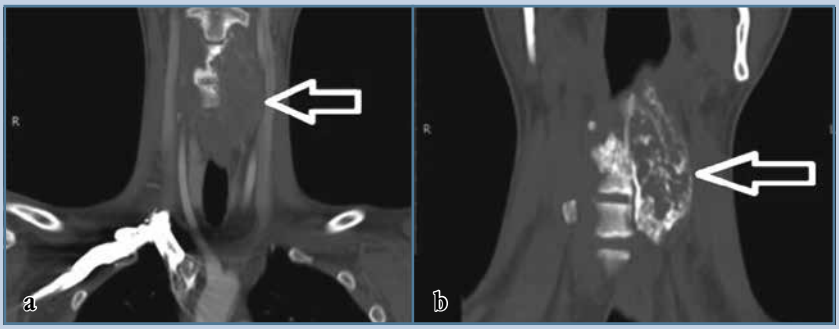

Fig 2

Giant cell tumor of C5 vertebra: **a** – August 2016, condition against the background of 24 denosumab injections; positive clinical picture in the form of pain reduction; X-ray studies: a sclerotic rim appearance on the background of the treatment; **b** – October 2019, condition against the background of 44 denosumab injections; X-ray studies during the last year: stabilization; in comparison with 2016: pronounced sclerotic changes on the background of treatment, as well as a tumor reduction in size

the planned operation was postponed. Nevertheless, one of the first prospective studies demonstrating the effectiveness of preoperative denosumab treatment for vertebral GCT was presented by Goldschlager et al. [11]. It includes combination therapy outcomes for five patients. On average 9 denosumab injections were performed preoperatively; in the course of preoperative treatment, a tumor reduction of up to 10 % and therapeutic response of more than 90 % were observed. There were no signs of recurrence during average follow-up of four cases within 12 months after surgery. One patient continued to receive medical treatment by the time the study was published.

According to Urakawa et al. [33], it is recommended to perform long-term preoperative denosumab treatment in anatomically complex localizations of GCT. Meanwhile, the recurrence rate after neoadjuvant, adjuvant and neoadjuvant, plus adjuvant administration of the drug was 28.6 % (6/21 patients), 22.2 % (2/9), and 0.0 % (0/10), respectively. In the control group where individuals did not take denosumab, the recurrence rate was 21.5 % (34/158 patients). Despite the high recurrence rate in the neoadjuvant denosumab group, joint preservation was reached in 26 (86.7 %) cases out of 30 among patients with peripheral skeletal lesions. On average, 6 (from 2 to 41) and 6 (from 1 to 14) denosumab injections were performed in neoadjuvant and adjuvant mode, respectively. The authors report a substantial decrease by more than 5 times in the recurrence rate after tumor curettage ($p < 0.001$) against the background of neoadjuvant administration of denosumab.

The results obtained in this study correspond to ones of international studies which associate GCT of axial skeleton bones, forearm bones or distal tibia bones with high risks of recurrence. Moreover, high recurrence risks are associated with performing marginal resection or curettage of the tumor i.e., non-radical operation volume. Despite the small number of observations, the findings show the effectiveness of combination therapy, including neoadjuvant denosumab in terms of reducing the recurrence risk. Nevertheless, a further set of clinical cases with a comparable follow-up period and, possibly, the level of lesion is required.

If surgery duration depends on experience and level of the surgical team, then the reduction in blood loss during spinal surgery in this study is an effectiveness result of a combined approach. Such outcomes are associated with denosumab, which reduces the blood supply

to the tumor, causes the development of fibrotic and sclerotic changes and, accordingly, reduces blood loss. In all cases of GCT of vertebrae, at least 95 % elimination of giant cells was observed in the postoperative sample; no elimination of giant cells was found in Group 1. Consequently, a decrease in blood loss may indirectly be a factor affecting the surgery duration.

It is worth noting that with the combined treatment, the volume of surgical intervention in Group 2 expands, whereas in Group 1, non-radical volume prevailed, where the worst oncological outcomes were observed. Due to the small sample of patients with GCT of vertebrae, it is inappropriate to calculate the statistical significance of recurrence in surgical and combined treatment.

Currently, there are reports of long-term complete and radiologically confirmed regression of both primary GCT and recurrence of spinal tumor during denosumab treatment [34, 35]. However, the frequency of this happening and its predictors are unclear. In our series, long-term control of tumor growth under stabilization is noted. If therapy was interrupted after an average of 6 months, the progression of tumor growth was observed, whereas when switching to supporting therapy, control over tumor growth was preserved. The question of the long-term safety of denosumab in long-term (lifelong) therapy remains open.

Further prospective selection of patients with this localization is obvious. However, it was important for the authors to separate and analyze a cohort of patients with GCT of vertebrae from the general study group. This is due to the fact that the treatment of patients with vertebral lesions, especially in the case of an inoperable process, is a complex clinical challenge. An increase in the number of observations is possible due to the creation of a unified information base and data unification from large oncological, orthopedic and neurosurgical hospitals. Due to the benign nature of the disease, patients with GCT of the spine are not firstly examined by oncologists. They are referred to orthopedists, traumatologists, neurosurgeons, and spine specialists.

Meanwhile, the modern achievements of medicine are not static. For example, proton beam therapy is one of the alternative treatment methods for inoperable GCT of vertebra (in case when denosumab is ineffective or serious complications develop). This technique is being mainstreamed into clinical practice. Proton beam therapy, however, needs to be studied in detail. This is especially true for the long-term safety results of this technique.

Conclusions

Giant cell tumor (GCT) of bone is a relatively rare, locally aggressive tumor. The disease is characterized by a high recurrence rate and potential disability due to tumor localization, bone destruction and compression of nearby neurovascular structures. Consequently, the life quality of patients dramatically worsens with each recurrence. Denosumab appearing in the range of GCT treatment increases the possibilities of patient management, especially in cases of inoperable vertebral lesions or in the presence of distant (metastatic) disease manifestations. A preoperative combination therapy including denosumab promotes the reduction in recurrence risk, surgery duration and blood loss volume. With consideration to the disease rarity and even rarer lesions of axial skeleton bones, a further accumulation of patients is required. It is essential to evaluate the effectiveness of surgical treatment in combination with and without denosumab. It is also crucial for long-term follow-up in cases of long-term or lifelong use of denosumab when it is impossible to perform surgery.

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