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The Results of treatment of giant cell tumor of long bones with denosumab

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Surgical intervention remains a gold standard for the treatment of giant cell tumors (GCT) of long bones. The significant risk of recurrence after the curettage and a high complication rate after radical resections is still an unsolved problem. Targeted therapy with denosumab could solve this problem in favor of curettage, but recent studies have shown negative results with denosumab in such situation. Objective. To analyze the results of the denosumab application in patients with long bone GCP with indications for joint salvage surgery. Methods. We compared the treatment results in two groups of patients: 1st retrospective (control) group — 57 patients, who underwent curettage with surgical treatment and the 2nd prospective (main) group — 42 patients with combination of surgery with neoadjuvant and adjuvant denosumab tretment. In the 2nd group of patients received 5 neoadjuvant and 5 adjuvant cycles of denosumab. The median follow-up period was 189 months in the control group, and 45 months in the main group. Results. Disease progression which identified as a local recurrence was revealed in the control group in 15 patients (25.4 %) and in 7 patients (16.7 %) in the main group (p = 0.19). In the main group, the median time to relapse was 19.8 months (8–34 months) from the date of surgery, in the control group — 15.1 months (9–28 months), respectively. The statistically significant difference in relapse-free survival (RFS) between patients in the main group and in the control group (p = 0.18) was not revealed. But the 5-year RFS in the main group was higher and reached to 85 % (95 % CI 74–96 %) versus 75 % (95 % CI 64–86 %) in control group, respectively. There was no evidence of malignant transformation in the main group and one case in retrospective group. Conclusions. The application of denosumab in the regimen before and after curettage is associated with lees number of relapses — 16.7 % vs. 25.4 % without denosumab, respectively. The lack of statistically significant difference between groups does not provide the sufficient reasons for denosumab prescription in neoadjuvant regimen. But adjuvant administration of denosumab can be considered as preventing factor of recurrence after primary tumor curettage, which may be perspective for further study and optimization of indications for its application in patients with GCT. Key words. Giant cell tumor, denosumab, relaps, complications.

Хірургічне втручання дотепер є золотим стандартом лікування гігантоклітинної пухлини (ГКП) довгих кісток. Проте існує значний ризик розвитку рецидивів після екскохлеації та велика кількість ускладнень після радикальних резекцій. Таргетна терапія деносумабом змогла б вирішити проблему на користь екскохлеації, але останні дослідження показали негативні результати використання препарату. Мета. Дослідити результати застосування деносумабу у хворих на ГКП довгих кісток із показаннями до збережних хірургічних втручань. Методи. Проведено порівняльний аналіз результатів лікування двох груп хворих: ретроспективної (контрольної) групи — 57 пацієнтів після хірургічного лікування у вигляді екскохлеації (кюретажу), проспективної (основної) — 42 особи після комбінації екскохлеації з неоад'ювантним і ад'ювантним введенням деносумабу (5 курсів перед операцією, 5 — після неї). Медіана часу спостереження за хворими склала в контрольній групі 189 міс., в основній — 45 міс. Результати. Прогресування захворювання у вигляді локального рецидиву відзначено в контрольній групі у 15 пацієнтів (25,4 %), в основній — у 7 (16,7 %) (p = 0,190). В основній групі час розвитку рецидиву склав у середньому 19,8 (8–34) міс. після втручання, у контрольній — 15,1 (9–28) міс. Суттєвої відмінності показника безрецидивної виживаності між групами пацієнтів не виявлено (p = 0,180). Утім, п'ятирічна безрецидивна виживаність в основній групі була вищою і склала 85 % (95 % ДІ 74–96 %), а в контрольній — 75 % (95 % ДІ 64–86 %). Висновки. Використання деносумабу в режимі до та після екскохлеації зменшує частоту рецидивів — 16,7 % проти 25,4 % без нього. Відсутність суттєвої різниці показника між групами не надає переконливих обґрунтованих аргументів до застосування деносумабу в неоад'ювантному режимі. Разом із тим, післяопераційне введення препарату можна розглядати як чинник профілактики виникнення рецидиву після первинної екскохлеації пухлини, що може бути перспективним для подальшого дослідження й оптимізації показань до його застосування у хворих на ГКП.

Key words. Giant cell tumor, denosumab, relaps, complications

Introduction

Giant cell tumor (GCT) is a primary bone tumor with local aggressive behavior. In almost 80 % of cases, GCT occurs between the ages of 20 and 50 years. Despite the fact that this tumor is classified as benign, the frequency of local recurrences after curettage is 20–40 %, up to 5 % of tumors undergo malignant transformation in case of recurrence, and in 2–4 % of cases determine lung metastases [1]. Morphologically, GCT is characterized by the presence of numerous multinucleated giant cells of the osteoclastic type, which are responsible for the aggressive osteolytic nature of the tumor. In general, GCT tissue consists of three types of cells, namely neoplastic stromal, which have a proliferative fraction, mononuclear histiocytic and multinucleated giant. *In vivo* and *in vitro* studies have confirmed that GCT stroma cells (immature osteoblasts according to phenotype) originate from mesenchymal stem cells and are a true neoplastic part of the tumor [2, 3]. These cellular components are affected by factors that play a role in regulating osteoclast function in normal bone tissue (e. g., RANK and RANKL). During the development of GCT, osteoclasts are stimulated by tumor-secreting factors, and the expression of RANKL, which binds osteoprotegerin, is increased, leading to bone resorption.

The main method of GCT treatment is surgery — resection with a single block or curettage with additional methods of impact on the walls of the cavity. Ideally, curettage combined with high-speed wall treatment and topical applications with liquid nitrogen or phenol should be the method of choice to save the adjacent joint, but if this method is used, the recurrence rate is much higher. Single block resection is recommended in the case of tumors with extensive bone destruction. This minimizes the risk of local recurrence, but correlates with a higher frequency of surgical complications and functional disorders. The frequency of local recurrence of GCT ranges from 27 to 50 % for excochleation in combination with adjuvants, from 0 to 12 % in the case of extensive resection [4, 5]. This prompted the search for ways to reduce recurrence while maintaining the optimal rate of complications and functional outcome of the affected joint. The emergence of the monoclonal target drug denosumab, which is an inhibitor of RANKL activity and prevents the formation and function of osteoclasts, allows, according to many researchers, to reduce the number of local recurrences after GCT curettage. Clinical trials have shown that denosumab provides long-term disease control in patients with GCT [5, 6]. However, a higher frequency of recurrences and malignancies of GCT after denosumab therapy was later established [7, 8]. Therefore, whether denosumab in combination with excochleation can reduce the number of local recurrences and in what mode of use remains unresolved.

The purpose of the study: to investigate the results of the use of denosumab in patients with giant cell tumors of long bones with indications for conservative surgery.

Material and methods

The cohort study included 99 patients with GCT who were treated at the National Cancer Institute in the period from 1987 to 2019, with localization of the tumor in the long bones of the extremities. Two groups were formed for comparative analysis: control (retrospective) group with 57 patients who underwent surgical treatment in the form of excochleation with filling of the defect with biodegradable bone grafts or materials; and main (prospective) group with 42 patients who underwent targeted denosumab therapy in neoadjuvant and adjuvant regimens, excochleation with bone cement defect plastics. All patients were diagnosed morphologically (GCT without signs of malignancy). The staging of GCT was performed according to Campanacci radiological criteria [9].

The study was performed in compliance with modern ethical norms and standards and approved at a meeting of the Ethics Commission of the National Cancer Institute (Protocol No. 185 of 25 May 2021). All patients gave written informed consent to participate in the study.

The criterion for exclusion from the study were patients with localization of the tumor in the distal radial bone, as a negative prognostic factor for conservative surgery, which has been proven in several studies [10]. The distribution of patients in both groups by sex and age is given in Table 1.

In the main group, patients received a neoadjuvant course of denosumab therapy — 120 mg subcutaneously according to scheme 1; 8; 28th days with evaluation of the therapeutic effect according to clinical and radiological criteria, and then on the 56th and 84th days. After that, surgical treatment was performed in the amount of excochleation of the tumor to visually unaffected bone structures with additional treatment of the bone cavity with liquid nitrogen and plasticity of the defect with polymethyl methacrylate. Postoperatively, patients received denosumab 120 mg subcutaneously 5 times with an interval of 28 days.

In the control group, patients underwent only surgery with allogeneic bone graft, hydroxylapatite, or

a combination of these materials. Additional methods of exposure were not used.

The median time of observation of patients was 189 months in the control group (interquartile range 60.5–278.5 months); 45 months in the main one (interquartile range 23.7–82.2 months).

The main purpose of the study was to investigate the effect of the use of denosumab under conditions of tumor excochleation and preservation of the adjacent joint. Evaluation criteria: 1) recurrence; 2) complications; 3) recurrence-free survival.

The findings were assessed using the EZR v. 1.54 package. The distribution law for quantitative variables differed from the normal one, so the median (Me) and interquartile range (QI – QIII) were calculated to provide results, and comparisons between groups were performed according to the Mann-Whitney test. For qualitative traits, the frequency at each trait level (%) was calculated, and comparisons were performed according to Fisher's exact criterion in the case of an alternative distribution or the χ-square criterion in the case of more than two qualitative trait gradations.

The difference in the recurrence-free survival rate was calculated by the Kaplan-Meier method, using the Lograng criterion for comparison. To study the risk factors for local tumor recurrence, an analysis using the Cox proportional intensity model was used, the degree of influence of the factor trait was assessed by hazard ratio (HR) with an estimate of 95 % confidence interval (95 % CI) [11]. The critical level of significance (p) was 0.05.

Table 1

Distribution of patients in groups by sex, age, localization of tumors and spread by Campanacci

Indicator		Group			
		main, n = 42		control, n = 57	
		n	%	n	%
Sex	Male	19	45.2	28	49.1
	Female	23	54.8	29	51.9
Age, years	Up to 25	14	33.3	14	24.6
	26–50	19	45.3	31	54.4
	51 and over	9	21.4	12	21.1
Localization	Femur	20	47.6	24	42.1
	Tibia	17	40.5	27	47.4
	Proximal humerus	5	11.9	6	10.5
Campanacci criteria	Grade I	10	23.8	25	43.9
	Grade II–III	32	76.2	32	56.1

Results and their discussion

Progression of the disease in the form of local recurrence was determined in the control group in 15 (25.4 %) patients and in 7 (16.7 %) in the main one (p = 0.190). In the main group, the time to recurrence averaged 19.8 months (8–34) from the moment of intervention, in the control one it was 15.1 months. (9–28).

Table 2 shows the distribution of patients with local recurrence of GCT, taking into account gender, age, tumor location and extent. All persons of the control group with recurrences underwent extensive resections with different methods of reconstruction (endoprosthesis, resection arthrodesis). In the main group, two patients underwent extensive resections with joint arthroplasty, the rest were administered repeated combination treatment with excochleation and continuous administration of denosumab. There were no amputations.

In the main group, complications associated with the use of liquid nitrogen (in the form of skin necrosis) occurred in 4 (9.5 %) patients. In the control group, postoperative complications (superficial and deep infections) were found in 2 (3.5 %) subjects. There was no statistically significant difference between the groups according to this criterion.

Table 2

Distribution of relapses in groups depending on sex, age, tumor localization and spread by Campanacci

Indicator		Group			
		main, n = 42		control, n = 57	
		n	%	n	%
Sex	Male	4/19	21.05	12/28	42.50
	Female	3/23	13.40	13/29	41.93
Вік, роки	Up to 25	5/15	33.33	9/14	64.28
	26–50	2/29	6.89	6/31	19.35
	51 and over	0/3	0.00	0/12	0.00
Localization	Distal femur	3/18	16.66	6/23	26.08
	Proximal femur	0/2	0.00	0/1	0.00
	Distal tibia	1/3	33.30	2/3	66.70
	Proximal tibia	2/14	14.28	5/24	20.80
	Proximal humerus	1/5	20.00	2/6	33.33
Campanacci criteria	Grade I	0/19	0.00	5/25	20.00
	Grade II–III	7/28	25.00	10/32	31.25

Among the 42 patients included in the assessment for complications of denosumab treatment, 3 (7.1 %) had hypocalcemia without significant clinical manifestations, and 2 (4.8 %) had a prolonged flu-like condition after the first administration (up to 8 and 10 days) with a weak reaction to the use of paracetamol. Osteonecrosis of the jaw in this cohort of patients was not observed in any case.

Malignant transformation of recurrence after excochleation of the primary tumor of the distal femur was detected in only one patient in the control group.

To assess long-term treatment outcomes, the recurrence-free survival of patients in both groups was analyzed by the Kaplan-Meier method (Figure). There were no statistically significant differences in the relapse-free survival curves for patients in the main and control groups (p = 0.180 according to the Lograng criterion). At the same time, it should be noted that the five-year recurrence-free survival in the main group was 85 % (95 % CI 74–96), and 75 % in the control group (95 % CI 64–86).

Pulmonary metastases were detected in 2 patients of the main group at the time of diagnosis, their frequency was 1.4 %. Table 3 illustrates the relationship between factor traits and the risk of recurrence in single-factor Cox models. One-factor analysis revealed that the risk of recurrence did not depend on the use of denosumab. Only a statistically significant dependence on the age of patients (p = 0.015) was found — the risk is reduced only for elderly patients, HR = 0.33 (95 % CI 0.14–0.81) compared with the category under 25 years.

To identify the set of signs associated with the risk of recurrence, a multifactor analysis was performed with the selection of significant signs by AIC. In the process of selection, four factors were identified:

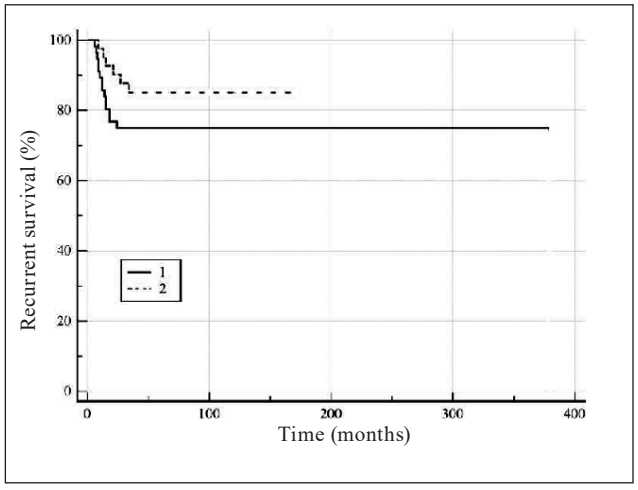

Figure Long-term results of Kaplan-Meier treatment

group, age, localization of GCT in the bones (femur or other) and bone (distal or proximal part). Cox model, based on the selected features, is adequate, C-index — 0.71 (95 % CI 0.62–0.80), which indicates the severity of the relationship of medium degree. Table 4 presents an analysis of the relationship between factor traits and the risk of recurrence in a multifactorial Cox model.

It should be noted that during standardization by other factors, the relationship between the risk of recurrence changes, but the lack of dependence on the group is unchanged (Tables 3, 4).

Discussion

The study showed that GCT usually triggers thinning of the cortical bone, which can be perforated with minimal pressure during excochleation. GCT responds to preoperative denosumab in 100 % of cases and in 2–3 months while taking the drug there is a reduction in tumor size and a new mineralized matrix, which creates favorable conditions for curettage. However, the hope for a sharp improvement in cancer results has not yet materialized. Recurrence with denosumab was lower by 16.4 % than in the control group by 25.4 %, but without statistical significance. Similar results were published by F. Traub et al. [6]. Cox regression analysis did not reveal a significant difference in the groups of our patients. Most researchers indicate a recurrence of GCT in the range of 17–30 % without denosumab [4]. Recurrence-free survival analysis showed better results in denosumab-treated patients: five-year recurrence-free survival in the main group was 10 % higher than in the control group. This fact speaks against the conclusions of many skeptics, who generally yielded worse results when using neoadjuvant denosumab than without it [12, 13]. In these studies, denosumab was used only in the neoadjuvant mode (6 courses), whereas we performed 5 courses before surgery, and 5 after. Whether there would be an increase in recurrences if we did not use the postoperative regimen of denosumab remains unresolved.

Of course, the recruited cohorts of patients differ greatly in the time of observation, but based on the fact that the development of relapse occurs in the period of 12–24 months. [8, 12], we can hope that in the main group of recurrences in the future can be only episodic. In addition, it should be noted that additional measures to treat the tumor bed (liquid nitrogen) in the control group were mostly not used. This could lead to an increase in the number of relapses.

The frequency of lung metastases in 2 patients of the main group at the time of diagnosis was 1.4 %,

Table 3

Coefficients of one-factor models of proportional Cox intensities predicting the risk of recurrence

Factor attribute		Value of the model coefficient, b ± m	Level of significance of the difference of the model coefficient from 0, p	HR indicator (95 % CI)
Group	control	reference		
	main	–0.64 ± 0.49	0.190	0.53 (0.20–1.37)
Sex	Female	reference		
	Male	0.34 ± 0.45	0.451	—
Age, years	Up to 25	reference		
	Over 25	–1.10 ± 0.45	0.015	0.33 (0.14–0.81)
Localization in the bone	Distal	reference		
	Proximal	–0.08 ± 0.45	0.861	—
Localization in the skeleton	Femur	reference		
	Humerus чи Tibia	0.40 ± 0.47	0.389	—
Campanacci criteria	Grade I	reference		
	Grade II–III	–0.62 ± 0.45	0.169	0.54 (0.22–1.30)

Table 4

Coefficients of the four-factor model of proportional Cox intensities for predicting the risk of recurrence

Factor attribute		Value of the model coefficient, b ± m	Level of significance of the difference of the model coefficient from 0, p	HR indicator (95 % CI)
Group	control	reference		
	main	–0.83 ± 0.50	0.099	0.53 (0.16–1.17)
Age, years	25–50	reference		
	Up to 25	–1.43 ± 0.56	0.010	4.2 (1.4–12.5)
	51 and over	0.68 ± 0.70	0.329	—
Localization in the bone	Distal	reference		
	Proximal	–1.48 ± 0.70	0.033	0.23 (0.06–0.89)
Localization in the skeleton	Femur	reference		
	Humerus чи Tibia	1.44 ± 0.70	0.040	4.2 (1.1–16.7)

which is similar to the previous study — from 0.5 to 4 %.

Another important fact of our study is that no case of malignant transformation of GCT in the main group has been recorded.

Conclusions

The use of denosumab before and after excochleation gives a lower recurrence rate, 16.7 %, compared to 25.4 % without it. The absence of a significant difference in the indicator between the groups does not provide convincing substantiated arguments for its application, especially in the neoadjuvant mode. Postoperative administration of denosumab can be considered as a factor in the prevention of recurrence after primary excochleation of the tumor, which may be promising for further study and optimization of indications for its use in patients with GCT.

Conflict of interest. The authors declare the absence of conflict of interest.

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