

Original Article

Effects of bevacizumab combined with oxaliplatin intrathoracic injection on tumor markers and survival rate in patients with malignant pleural effusion of lung cancer

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Abstract: Objective: This study aims to explore the therapeutic effects of bevacizumab combined with oxaliplatin on patients with malignant pleural effusion of lung cancer. Methods: A total of 109 patients with malignant pleural effusion of lung cancer admitted to our hospital from March 2015 to April 2017 were selected as research objects. Among them, 59 patients treated with bevacizumab combined with oxaliplatin intrathoracic injection were enrolled in the observation group, and another 50 patients treated with oxaliplatin intrathoracic injection were enrolled in the regular group. Clinical efficacy and safety of the two groups were compared, as well as the expression of vascular endothelial growth factor (VEGF), vascular endothelial growth factor receptor (VEGFR) and tumor markers before and after treatment. The two groups of patients were followed up for 3 years to compare their prognosis, survival and quality of life. Results: The cure rate of the observation group was higher than that of the regular group ($P < 0.05$), but there was no difference in the incidence of adverse reactions ($P > 0.05$). After treatment, VEGF, VEGFR and tumor markers in the observation group were significantly lower than those in the regular group ($P < 0.05$), while the survival rate and quality of life of the observation group were significantly higher than those in the regular group ($P < 0.05$). Conclusion: Bevacizumab combined with oxaliplatin intrathoracic injection is effective in treating malignant pleural effusion of lung cancer.

Keywords: Bevacizumab combined with oxaliplatin, lung cancer, malignant pleural effusion, prognosis

Introduction

Lung cancer is one of the malignant tumors with a high incidence all over the world [1], and the incidence among smokers is significantly increased [2]. At present, the pathogenesis of lung cancer is not clear, and it is believed to have a great relationship with human inhalation in clinical practice [3]. Early stage lung cancer shows no special clinical symptoms, but often manifests cough, chest tightness, etc., which are easily overlooked or mismanaged by patients, and is usually in the middle and late stage once diagnosed [4]. At this stage, the treatment difficulty of lung cancer is greatly increased, and the prognosis is extremely poor [5]. According to statistics, the 5-

year survival rate of patients with advanced lung cancer is the lowest among all tumors, only 5%-10% [6]. Advanced lung cancer usually presents with a large amount of malignant pleural effusion due to metastasis and infiltration of the disease into pleural tissue [7]. Pleural effusion can not only cause dyspnea and cyanosis, but also make lung cancer surgery or radiotherapy and chemotherapy more difficult [8]. Therefore, the management of malignant pleural effusion is fundamental in the treatment of patients with advanced lung cancer.

At present, thoracocentesis, pleurodesis, perfusion and other methods are commonly used to treat pleural effusion in clinical practice, of

which intrathoracic drainage combined with intrathoracic drug injection is the most effective and most commonly utilized method [9]. Therefore, the key to the treatment of pleural effusion is to choose an appropriate injection drugs. Oxaliplatin, as an extensively used anti-tumor chemotherapy drug in clinics, plays a therapeutic role by inducing immune response to reduce cytotoxicity and apoptosis of tumor cells. It is also one of the common drugs for malignant pleural effusion of lung cancer [11]. In recent years, it has been found that bevacizumab combined with oxaliplatin is extremely effective in the treatment of cancers [12, 13]. Moreover, the team of Mir [14] pointed out that bevacizumab in combination with oxaliplatin is superior to oxaliplatin monotherapy for lung cancer. However, there is no research to confirm the effects of the combination of the two on pleural effusion. Bevacizumab, as a monoclonal antibody of vascular endothelial growth factor, has the effect of inhibiting tissue formation [15]. We speculate that the combination of the two can greatly enhance the inhibition of pleural effusion, and verified our conjecture through experiments, so as to provide reliable theoretical guidance for future clinical treatment of patients with pleural effusion of lung cancer.

Materials and methods

Patient data

With the approval of the Ethics Committee of our hospital, the patients with lung cancer admitted to Affiliated Tumor Hospital of Guangxi Medical University from March 2015 to April 2017 were selected as the research objects for prospective analysis. Based on the inclusion criteria (patients diagnosed with lung cancer by biopsy in our hospital's pathology department and determined to have malignant pleural effusion by X-ray, ultrasound, and pleural effusion pathology tests, patients aged 30-60 years old), 162 patients who received oxaliplatin or bevacizumab in our hospital after admission were included in the study. Based on the exclusion criteria (patients with multiple tumors, other cardiovascular and cerebrovascular diseases, autoimmune defects, organ dysfunction or mental disorders, patients with estimated survival time \leq 1 month, patients who received bevacizumab or oxaliplatin within 3 months before admission, patients in pregnancy or lac-

tation period, patients transferred to other hospitals), 109 cases of research objects were finally determined. This experiment was conducted with the informed consent of all subjects.

Patient grouping

Among 109 patients, 59 patients treated with bevacizumab combined with oxaliplatin intrathoracic injection were enrolled in the observation group, and another 50 patients treated with oxaliplatin intrathoracic injection were enrolled in the regular group. There was no significant difference in age, gender, BMI and pathological stage between the two groups ($P > 0.05$).

Treatment methods

After admission, all patients underwent central venous catheter puncture by ultrasonic localization, and the central venous catheter was guided by guide wire and connected with drainage bag. The initial drainage was less than 1000 mL, and the drainage was less than 2000 mL within 24 hours. When pleural effusion was drained in 3 days, 20 mL 100 mg/m² oxaliplatin and 5% glucose solution were injected into pleural cavity. On this basis, patients in the observation group were intrapleural injected with 20 mL normal saline containing 300 mg bevacizumab. After drug injection, the catheter was clipped, and the patient was assisted to turn over once every 20 minutes to promote the drug release in the chest cavity. After 48 hours, the drainage tube was opened, and the medicine was given once every 2 weeks, and the treatment was considered as complete after 3 times of administration.

Detection methods

The fasting venous blood was taken from patients in the two groups before and after treatment and centrifuged for 10 min (1505×g, 4°C) to obtain the serum. The serum was divided into two parts. The concentration of vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor (VEGFR) of one part of serum was determined by ELISA. The kit was purchased from Chuzhou Shinoda Biotechnology Co., Ltd., and the operation process was carried out strictly in accordance with the kit instructions. Immunochemiluminometric

Table 1. Comparison of clinical efficacy between the two groups

	CR	PR	SD	PD	Cure rate (%)
Observation group (n=59)	25 (42.37)	24 (40.68)	8 (13.56)	2 (3.39)	83.05
Regular group (n=50)	15 (30.00)	17 (34.00)	12 (24.00)	6 (12.00)	64.00
χ^2	1.784	0.514	1.969	2.950	5.146
<i>p</i>	0.182	0.473	0.161	0.086	0.023

assay was used to detect carcinoembryonic antigen (CEA), carbohydrate antigen (CA199, CA72-4) and tumor associated material (TAM) in the other part of serum.

Determination of efficacy

Complete response (CR): the patient's pleural effusion disappeared completely and remained for more than 4 weeks; partial response (PR): the pleural effusion decreased by $\geq 50\%$ and maintained for more than 4 weeks; stable disease (SD): the pleural effusion decreased by $< 50\%$ or increased by $\leq 25\%$ and maintained for more than 4 weeks; progressive disease (PD): the pleural effusion increased by $> 25\%$. Cure rate = (CR+PR)/total number $\times 100\%$.

Follow-up of prognosis

Patients in both groups were followed up for 3 years in the form of hospital reexamination. Their 3-year survival was recorded, and the survival curve was drawn. A questionnaire was used to investigate the patients' quality of life, including sleep quality, physical function, social activities and mental state. The full score was 100, and the higher the score, the better the state.

Outcome measures

Clinical efficacy (cure rate), safety (adverse reactions such as nausea, vomiting, bleeding, myelosuppression, etc., and the incidence of adverse reactions were calculated), the expression changes of VEGF, VEGFR and tumor markers in two groups, prognosis, survival and quality of life.

Statistical methods

SPSS23.0 statistical software was utilized to analyze and process the data, and Graph Pad 7 software to plot all the pictures. Chi-square test was applied to compare the counting data, and independent sample t test to com-

pare the measurement data. Paired t test was used for comparison before and after treatment. Kaplan-Meier method was used for the calculation of the survival rate, and Log-rank test for its comparison. The difference was statistically significant when $P < 0.05$.

Results

Comparison of clinical efficacy

In the observation group, there were 25 cases of CR, 24 cases of PR, 8 cases of SD, and 2 cases of PD, with the total cure rate of 83.05%. In the regular group, there were 15 cases of CR, 17 cases of PR, 12 cases of SD, and 6 cases of PD, with the total cure rate of 64.00%. The total cure rate of the observation group was higher than that of the regular group ($P=0.023$), but there was no statistically significant difference in CR, PR, SD, PD between the two groups ($P > 0.05$) (Table 1).

Comparison of safety

In the observation group, there were 2 cases with nausea and vomiting, 1 case with bleeding, 2 cases of blood pressure changes, and 1 case with abnormal blood routine, with the incidence of total adverse reactions of 10.17%. In the regular group, there were 3 cases with nausea and vomiting, 2 cases with bleeding, 1 case with blood pressure change, 1 case with myelosuppression, 1 case with peripheral neurotoxicity, and 1 case with abnormal blood routine, with the incidence of total adverse reactions of 18.00%. There was no statistical difference in the incidence of adverse reactions between the two groups ($P > 0.05$) (Table 2).

Comparison of VEGF and VEGFR

There was no significant difference in VEGF and VEGFR between the two groups before treatment ($P > 0.05$), and VEGF and VEGFR in the observation group were lower than those in the regular group after treatment ($P < 0.05$).

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Table 2. Comparison of the incidence of adverse reactions between the two groups

	Nausea and vomiting	Bleeding	Blood pressure changes	Myelosuppression	Peripheral neurotoxicity	Abnormal blood routine	Incidence rate (%)
Observation group (n=59)	2 (3.39)	1 (1.69)	2 (3.39)	0 (0.00)	0 (0.00)	1 (1.69)	10.17
Regular group (n=50)	3 (6.00)	2 (4.00)	1 (2.00)	1 (2.00)	1 (2.00)	2 (4.00)	20.00
χ^2							2.088
p							0.148

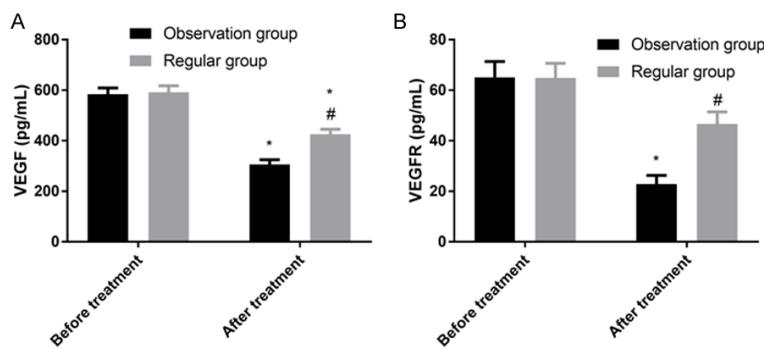


Figure 1. Comparison of VEGF and VEGFR between the two groups. A. Comparison of VEGF between the two groups before and after treatment. B. Comparison of VEGFR between the two groups before and after treatment. * vs the same group, $P < 0.05$, # vs the observation group after treatment, $P < 0.05$.

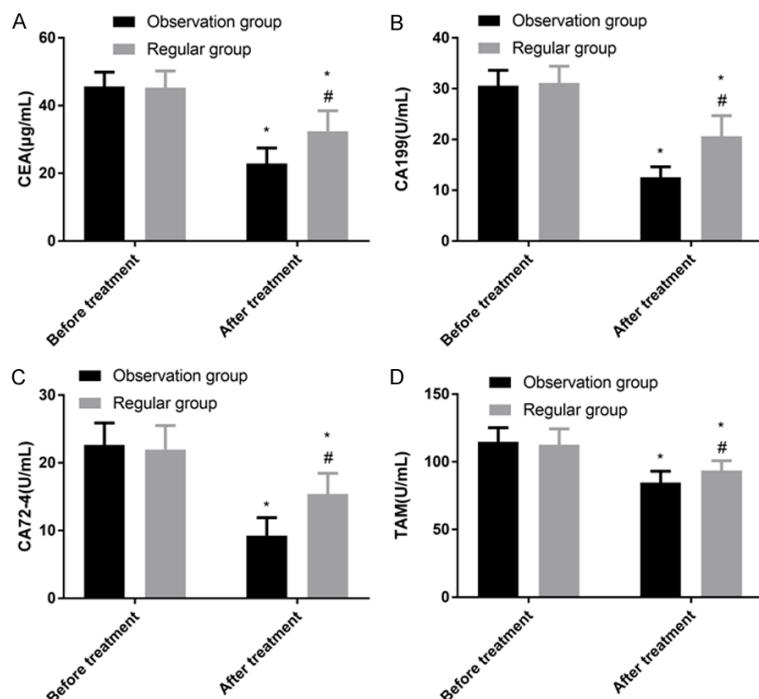


Figure 2. Comparison of tumor markers. A. Comparison of CEA between the two groups before and after treatment. B. Comparison of CA199 between the two groups before and after treatment. C. Comparison of CA72-4 between the two groups before and after treatment. D. Comparison of TAM between the two groups before and after treatment. * vs the same group, $P < 0.05$, # vs the observation group after treatment, $P < 0.05$.

Besides, both the two were deceased after treatment than before treatment ($P < 0.05$) (Figure 1).

Comparison of tumor markers

There was no difference in CEA, CA199, CA72-4 and TAM between the two groups before treatment ($P > 0.05$), and the four in the observation group were all lower than those in the regular group after treatment ($P < 0.05$). All the four markers were reduced after treatment in both groups compared to before treatment ($P < 0.05$) (Figure 2).

Comparison of prognosis for survival

During the 3-year follow-up, a total of 103 patients were successfully followed up, and the success rate of follow-up was 94.50%. Among them, 55 cases came from the observation group, and 48 cases came from the regular group. The results of follow-up showed that the 3-year survival rate in the observation group was higher than that in the regular group ($P < 0.05$) (Figure 3).

Comparison of quality of life

There was no difference between the sleep quality scores of the observation group and the regular group ($P > 0.05$), while physical function, social activity, and mental status

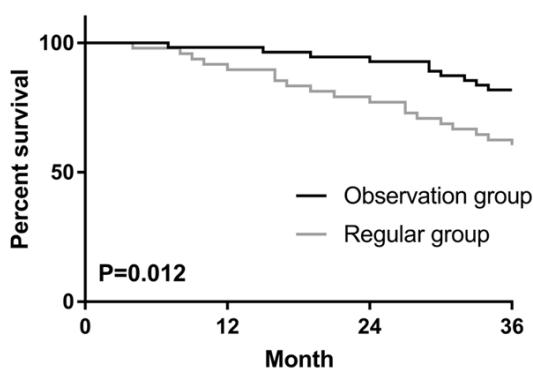


Figure 3. Prognostic survival curves of the two groups.

scores of the observation group were higher than those of the regular group ($P < 0.05$) (Figure 4).

Discussion

Malignant pleural effusion, as a common complication of patients with advanced lung cancer, seriously threatens the life and health of patients [16]. Evacuating the pleural fluid from the body is the most direct and effective method, but repeated evacuation not only brings great pain to the patient, but also may cause protein loss and accelerate the metastasis and infection of the patients [17, 18]. Therefore, intracavitary injection is one of the feasible methods at present, which can kill tumor cells while dredging blocked capillaries and lymphatic vessels [19]. In this case, the choice of injection drugs is particularly important.

In this study, we first investigated the clinical efficacy of the regular group (patients treated with oxaliplatin) and the observation group (patients treated with bevacizumab combined with oxaliplatin), and found that the cure rate of the observation group was higher than that of the regular group, suggesting that the use of bevacizumab combined with oxaliplatin can improve the curative effect of malignant pleural effusion. In previous studies, the efficacy of bevacizumab combined with oxaliplatin was superior to that of oxaliplatin [20, 21], which also supports our results. By comparing the incidence of adverse reactions between the two groups, we found no statistical difference between the two groups, which also indicated that the use of bevacizumab combined with oxaliplatin has higher safety and is worth recommendation for

future clinical practice. Malignant pleural effusion caused by tumor is mainly affected by chemotherapy drugs [22]. Oxaliplatin, as a common anti-tumor chemotherapy drug in clinic, is effective and safe [23]. On the basis of oxaliplatin, bevacizumab can further enhance the inhibitory effect on tumor cells. It is suggested that the combination of tumor VEGF and VEGFR reduces the division of vascular endothelial cells, thus weakening the ability of tumor blood vessel formation [24], or the blood supply to tumor focus is reduced by destroying the original tumor blood vessels [25]. In addition, bevacizumab may also play a certain part in promoting anti-tumor chemotherapy drugs, which increases the killing effect of oxaliplatin and improves the curative effect [26]. Therefore, we detected VEGF and VEGFR in two groups of patients, and found that the two in the observation group were significantly lower than those in the regular group, which indicated that bevacizumab combined with oxaliplatin has obvious inhibitory effect on tumor angiogenesis, and confirmed the above viewpoint. Subsequently, we also examined the tumor markers in the two groups, and found that CEA, CA199, CA72-4 and TAM in the observation group were significantly lower than those in the regular group, which further validated that bevacizumab combined with oxaliplatin has a more significant inhibitory effect on tumor. As the most sensitive marker of tumor diseases, tumor markers can reflect the development process and severity of diseases [27]. The decrease of its level also indicated that the development of tumor has been effectively controlled. The roles of CEA, CA199, CA72-4 and TAM in lung cancer have been supported by a number of studies, which are particularly sensitive to the progression of lung cancer, and also have an extremely accurate response ability to the deterioration of malignant pleural effusion of lung cancer [28-30]. Therefore, a reliable objective assessment of the progression of the disease can be made by detecting the changes in the level of the four. Through the follow-up investigation of prognosis, we found that the survival rate of the observation group was better than that of the regular group, indicating that the prognosis of patients was effectively improved after treatment with bevacizumab combined with oxaliplatin. Such above further laid a reliable foundation for the future treatment of malignant pleural effusion of lung cancer with bevacizumab.

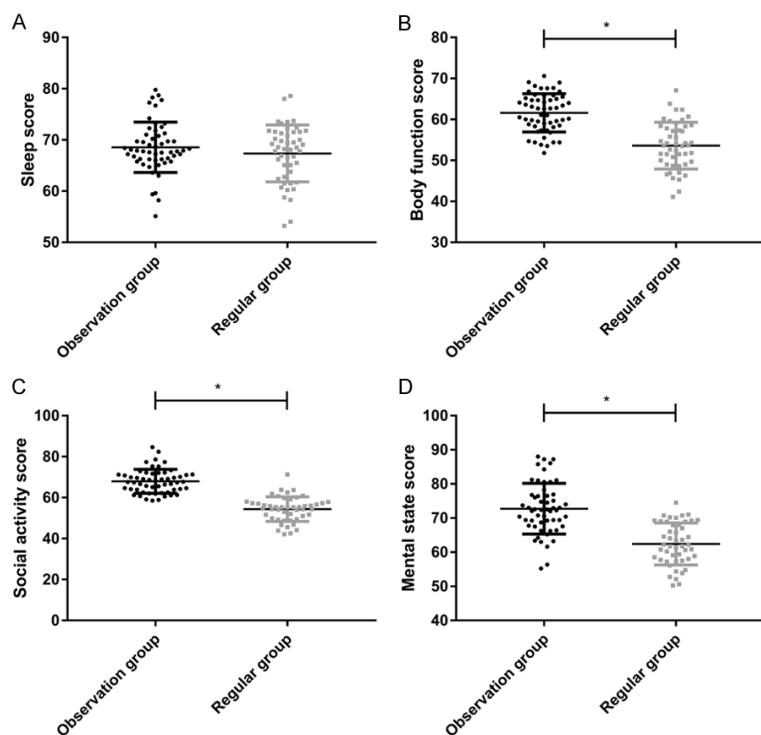


Figure 4. Comparison of quality of life between the two groups. A. Comparison of sleep quality scores between the two groups. B. Comparison of physical function scores between the two groups. C. Comparison of social activity scores between the two groups. D. Comparison of mental state scores between the two groups. * $P < 0.05$.

combined with oxaliplatin. Our observation also showed that the quality of life in the observation group was also better than that in the regular group, but there was no difference in sleep quality scores between the two groups, which may be caused by the fact that pleural effusion has little effect on sleep.

There are still some shortcomings in this experiment. For example, in previous studies, it was suggested that oxaliplatin combined with docetaxel and fluorouracil had better effects [31, 32], but in this study, only bevacizumab combined with oxaliplatin was analyzed. In the future, we need to make a more extensive comparison to determine the best drug choice for malignant pleural effusion of lung cancer. In addition, due to the small number of research objects included in this experiment, there was no difference in the statistical calculation of some results, but the actual number of people was obviously different. Such above suggests that we need to expand the base of research objects and analyze big data to obtain more rigorous results.

Finally, the trial period was too short to assess how bevacizumab combined with oxaliplatin affects the long-term prognosis of patients with lung cancer. We will conduct a more complete experimental analysis to address the above limitations and obtain more reliable results for clinical reference as soon as possible.

To sum up, bevacizumab combined with oxaliplatin intrathoracic injection is effective in the treatment of malignant pleural effusion of lung cancer, which can effectively inhibit the expression of VEGF and tumor markers, improve the prognosis and survival rate and quality of life of patients, and is worthy of clinical application.

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Disclosure of conflict of interest

None.

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