BEVACIZUMAB TREATMENT OF MALIGNANT PLEURAL EFFUSION

YAN GU, WANLING YANG, MIN ZHANG, XIAOLU YANG, XINHUA FU*
Department of Respiratory and Critical Care Medicine, the Affiliated Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia 010050, China

ABSTRACT

Objective*: To evaluation the efficacy and direct costs of Bevacizumab in managing of malignant pleural effusion (MPE) caused by lung adenocarcinoma.*

Methods*: Between December 2014 to December 2016, 60 untreated patients with MPE in lung adenocarcinoma were randomly assigned to one of two groups; intrapleural injection of Bevacizumab (n= 30) or intrapleural injection of OK-432 (n= 30). Adverse events were recorded and assessed. ELISA was applied to detect the serum vascular endothelial growth factor (VEGF) level.*

Results*: In the Bevacizumab group, fifteen (50%) and eleven (37%) patients achieved complete response (CR) and partial response (PR), respectively, 1 patient remained stable (3%), and 3 patients showed disease progression (10%). In the OK-432 group, thirteen (43%) and twelve (40%) patients achieved CR and PR, respectively, 2 patients remained stable (7%), and 4 patients showed progressed (13%). There was no statistically significant difference in the effective rate between the two groups (P> 0.05). Regarding the adverse effects, only 1 case experienced fever in the Bevacizumab group. However, for the patients in OK-432 group, chest pain, fever, dyspnea, fatigue, nausea, and anorexia were occurred in 16 (53%), 21 (70%), 5 (16.67%), 5 (16.67%), 1 (3.33%), and 7 (23.3%) cases, respectively. The incidence of adverse reactions of the patients in the OK-432 group was significantly higher than that in the Bevacizumab group (P< 0.05). In the Bevacizumab group, the serum VEGF concentration was 246.79± 179.51 pg/ml before treatment and 129.85± 113.09 pg/ml after treatment, suggesting the VEGF level was decreased in Bevacizumab group (P< 0.001). Median duration in hospital was 3 days in the Bevacizumab group, and less than 5 days in the OK-432 group (P< 0.001). The care cost was CNY 136.00±75.46 in the Bevacizumab group compared with CNY 201.33±66.00 in the OK-432 group (P< 0.001).*

Conclusion: *Intrapleural injection of Bevacizumab was effective and safe for MPE, and shortened the length of hospital stay, and reduced the cost of hospitalization and nursing care.*

Keywords: *Malignant Pleural Effusion, Bevacizumab, Vascular Endothelial Growth Factor.*

DOI: 10.19193/0393-6384_2021_5_406

Received *November 15, 2020;* ***Accepted*** *May 20, 2021*

Introduction

Malignant pleural effusion (MPE) is a type of pleural effusion caused by primary or secondary malignant pleural tumor[1]. Among metastatic tumors, metastatic adenocarcinoma is the most common[2]. Epidemiological data indicate that the incidence of lung cancer and breast cancer is increasing yearly[3]. In lung cancer patients, the incidence of adenocarcinoma is higher than squamous cell carcinoma[4].

MPE often occurs during the late stage of the lung adenocarcinoma. And the patient's median survival time is only 3~12 months. Clinical trials have demonstrated that controlling pleural effusion improves the quality of life for patients, and reduces the mortality caused by pleural effusion-induced respiratory distress[5].

There are a variety of treatments strategies for MPE, including thoracoscopic pleural dissection, intrathoracic drainage, pleurodesis.

However, according to the 2010 MPE guidelines, pleural fixation is the first choice of treatment[1]. Common types of drugs used in pleural fixation include chemotherapeutic agents, immunotherapy drugs, biological response regulators. For example, the injection of bleomycin, cisplatin, IL-2, and OK-432 has been applied to treat MPE in clinical trials[6]. OK-432 is a lyophilized streptococcal preparation used to treat MPE; the 30-day success rate for OK-432 and talc-s is 79%- 80.7%. Propensity score-matched analyses showed that OK-432 and talc-s demonstrated for pleurodesis demonstrated comparable efficacy and safety profiles in patients with lung adenocarcinoma. This indicates that OK-432 provides a viable alternative to talc-s this procedure[7,8]. However, OK-432 is associated with several adverse reactions, such as fever, chest pain, dyspnea, and other side effects, which lead to poor tolerance in patients and limit the use of the drug to a certain extent. Therefore, it is of great clinical significance to explore effective pleural perfusion drugs with fewer side effects.

Vascular Endothelial Growth Factor (VEGF) plays a significant role in promoting lung cancer metastasis[9]. Studies have shown that VEGF produced by lung cancer cells contributes to pleural effusion, tumor spread, and angiogenesis[10,11]. VEGF antagonists may play an active role in the treatment of MPE[12]. Bevacizumab is a kind of recombined humanized and human-mouse chimeric monoclonal antibody, a kind of VEGF repairing inhibitor. Angiogenesis inhibitors specifically bind to VEGF, prevent its binding to the receptor, induce tumor blood vessel degeneration, inhibit the neovascularization, and prevent the growth and metastasis of tumor cells[13,14]. Simultaneously, they reduce the permeability of blood vessels and the development of pleural effusion[15]. Therefore, the purpose of this study was to investigate the mechanism and role of bevacizumab in the local treatment of malignant pleural effusion of lung adenocarcinoma. VEGF is believed to function as a tumor angiogenesis factor being mitogenic for endothelial cells and has a potential pathogenic role in the development of pleural effusions[16]. Further elucidation of the pathogenic mechanisms and identification of novel local and/or systemic treatments targeting these pathways may improve the efficacy of current management strategies. Therefore, we investigated the pathophysiology, diagnosis, and management of MPEs focusing on the role of VEGF in the development of MPE and the rationale for VEGF-targeted treatment modalities.

Methods

General information

Based on a sample size calculation, this randomized study enrolled patients from the affiliated hospital of Inner Mongolia Medical University between December 2014 and December 2016. Sixty patients with MPE caused by lung adenocarcinoma confirmed by histology or cytology were enrolled, all patients were assessed by ultrasonography and CT scans. The size of the pleural effusion was defined as follows: massive, effusion volume > 75% of the hemithorax; large, effusion volume 50-75% of the hemithorax; and small ,effusion volume <25% of the hemithorax. The eligibility criteria were as follows: patients 18-75 years of age; an estimated survival duration of > 3 months, patients with normal major organ functions, and patients who provided written informed consent.

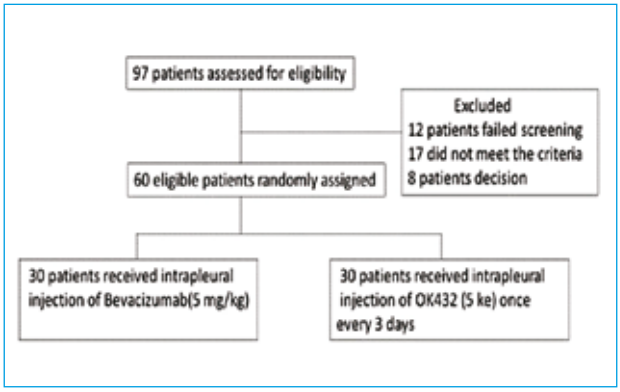

Fig. 1: Patient flowchart.

The exclusion criteria included the following: gastrointestinal perforation or tracheoesophageal fistula within the 2 months before enrollment, hemorrhage(cerebral hemorrhage, hemoptysis, hematuria); reversible posterior white matter encephalopathy syndrome; diagnosis of venous or arterial thromboembolism; severe congestive heart failure; uncontrolled hypertension after adequate antihypertensive treatment; a wound that did not heal within at least 28 days after major surgery; level 4 proteinuria; allergy to penicillin; pregnant, lactating, or possibly pregnant women; or multiple active cancer. (Fig 1; Table 1). Blood samples were collected 1week before and after treatment. Venous blood was collected into inter separation gel coagulation tube and immediately centrifuged for 10 minutes at 3000 rpm/min.

The supernatant was retained in EP tube and be frozen in-80 ˚C refrigerator. Reagents and drugs

used included a human VEGF ELISA kit (R&D Co, Ltd).

Characteristics	Bevacizumab Group (n= 30)	OK-432 Group (n= 30)	P value
Age (mean± sd, year)	64.33± 8.872	62.50± 9.062	0.432
Gender			0.438
Male Female	14 16	17 13	
Pretreatment ZPS score			0.125
0	2	5	
1	2	7	
2	14	11	
3	12	7	
Smoker Yes No	12 18	16 14	0.301

Table 1: Patient characteristics.

The VEGF concentration is proportional to the measured OD values at 450 nm. Therefore, the expression level of VEGF is determined based on the standard curve of know concentrations. To observe the changes in VEGF serum levels in patients treated before and after treatment with Bevacizumab, the relationship between the concentration of serum VEGF before treatment and the curative effect of Bevacizumab, we classified the curative effect on bevacizumab treatment group and correlated them with the VEGF concentration before treatment, and also recorded the concentration changes of VEGF before and after treatment.

This work was carried out in accordance with the the World Medical Association Declaration of Helsinki . This study was approved ethically by the Affiliated Hospital of Inner Mongolia Medical University (YKD2014051). All patients provided informed written consent. The trial is registered with chictr.org.cn.

Treatment programs

All patients were subjected to a routine blood test, liver function evaluation, renal function evaluation, urine analysis, ultrasound, CT scans, and electrocardiogram examination. In addition, all patients were confirmed to be without absolute contraindications of pleural perfusion treatment, thereby fulfilling the inclusion criteria without meeting any of the exclusion criteria. The Zubord Performance Status (ZPS) was determined before treatment. Sixty untreated lung adenocarcinoma patients with MPE were randomly assigned to one of the two groups received an intrapleural injection of Bevacizumab (5 mg/kg, once a day) (n= 30) and intrapleural injection of OK-432 (5 kg, once every 3 days) (n= 30). Adverse events were recorded and assessed. All patients in two groups with negative EGFR gene mutation were treated with pemetrexed combined with cisplatin after pleural perfusion. Tunneled pleural catheters were especially helpful in the management of trapped lungs in the setting of an MPE. The drainage tube was clamped for 24 hours after the drug was injected into the catheter. The intrapleural administration process was performed in accordance with standard operating procedures when the pleural effusion drainage was complete. The therapeutic effect of pleural effusion was evaluated for 4 weeks.

Safety and efficacy evaluation criteria

The therapeutic effect of pleural effusion was evaluated as follows (WHO standard): Complete Response (CR): the effusion completely disappeared and remained stable for more than 4 weeks, partial response (PR), the amount of effusion decreased by more than 50%, the symptoms improved, and the residual fluid did not increase within 4 weeks. Stable (SD), the hydrothorax decreased by < 50% or not more than 25% for over 4 weeks and progression, pleural effusion increased by more than 25% compared with the amount before treatment. The sum of the total remission rate and partial remission rate was defined as total efficiency. For adverse reactions, drug toxicity evaluation was performed in accordance with the NCI CTC version 3 (graded 0–IV). Chest pain was evaluated is in accordance with the WHO standard as follows: 0, no pain; I, mild pain, or intermittent pain and no medication; II, moderate pain or persistent pain affecting rest and requiring pain management; III, severe pain, persistent pain, or pain that could not be self-relieved; and IV, severe pain or severe persistent pain accompanied by changes in blood pressure, heart rate, pulse and others parameters.

Statistical analyses

SPSS13.0 statistical software was used for statistical analysis. The t-test and χ^2 test was used for comparison of measurement data or rates. The rank-sum test was used for grade data. $P \leq 0.05$ indicated that the difference was statistically significant.

Results

Adverse effects

The Bevacizumab group: Fifteen (50%) and eleven (37%) patients achieved CR and PR, respec-

tively, 1case was stable (3%), and 3 cases were progressed (10%). The OK-432 group: Thirteen (43%) and twelve (40%) patients achieved CR and PR, respectively, 2 cases were stable (7%), and 4 cases showed disease progressed (13%). There was no statistically significant difference between the effective rate in the two groups (P> 0.05). Among 30 patients who received bevacizumab intrapleural infusion, fever was reported in only 1 case, and no hemorrhage, high blood pressure, or other intravenous adverse was observed. Among thirty patients treated with OK-432, chest pain, fever, dyspnea, fatigue, nausea, and anorexia occurred in 16 (53%), 21 (70%), 5 (16.67%), 5 (16.67%), 1 (3.33%), and 7 (23.3%) cases, respectively. Among them, 2 patients had grade III–IV chest pain. One patient had grade IV fever. Although the adverse reactions in the OK-432 group were all relieved after symptomatic treatment, the incidence of adverse reactions in the OK-432 group was significantly higher than that in the bevacizumab-treated group. According to statistical analysis, the differences in the rates of adverse effects were statistically significant between the two groups (P< 0.05).

The effect of bevacizumab on the concentration of serum VEGF

	pre-treatment (mean± sd, pg/ml)	post-treatment (mean± sd, pg/ml)	t	*P*
VEGF	246.79± 179.51	129.85± 113.09	5.948	< 0.001

Table 2: Comparison of VEGF expression in serum before and after the use of bevacizumab.

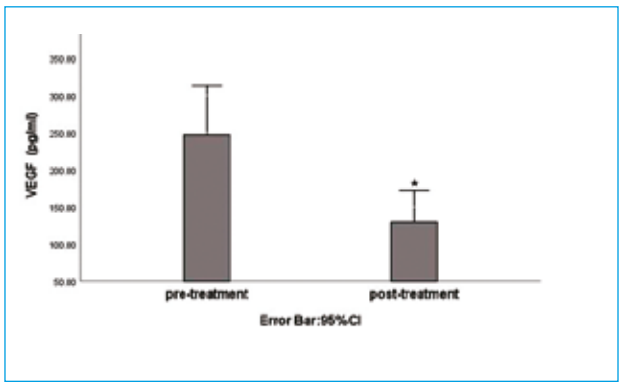

Fig. 2: Comparison of VEGF expression in serum before and after the use of bevacizumab.

The serum VEGF concentration in patients with lung adenocarcinoma was 246.79± 179.51 pg /ml before treatment, 129.85± 113.09 pg /ml after treatment, and the difference was statistically significant (P < 0.001). This indicated that Bevacizumab intrathoracic infusion reduced the serum VEGF concentration (Table 2, Fig 2).

Correlation between the serum VEGF level and the curative effect

The concentration of VEGF was 258.41± 187.93pg/ml in the Bevacizumab group and 171.25± 91.76pg/ml in the invalid group, and there was no significant difference (P= 0.375, P> 0.05). The VEGF concentration showed no correlation with efficacy of intrapleural perfusion treatment (Table 3).

	effectiveness (mean± sd, pg/ml)	Ineffectiveness (mean± sd, pg/ml)	t	*P*
VEGF	258.41± 187.93	171.25± 91.76	0.901	0.375

Table 3: Effect of VEGF expression in serum.

Correlation between the changes in serum VEGF before and after treatment and the curative effect

The changes in the VEGF serum concentration were 126.57±99.79 pg/ml for the complete remission group, 129.60± 118.54 pg/ml for partial remission group, and 45.99±104.98 pg/ml for the invalid group (P= 0.380, P> 0.05). The difference was not statistically significant. These results suggest that the effect of bevacizumab on pleural perfusion is not related to the change in serum VEGF concentrations (Table 4).

(mean± sd, pg/ml)	Curative effect grade (mean± sd, pg/ml)		
	CR (n= 15)	PR (n= 11)	NC+ PD (n= 4)
Pre-treatment	296.34± 211.06	206.69± 144.29	171.25± 91.76
Post-treatment	169.77± 144.14	77.09± 44.28	125.26± 43.90
P	0.380		

Table 4: Correlation between the change of serum VEGF before and after treatment and curative efficacy.

Cost and hospital duration

Group	Hospitalization Day $M(P_{25} \sim P_{75})$	Care fees	Direct cost
Bevacizumab	3(2.00 ~ 4.25)	136.00±75.46	62.00±10.95
OK-432	5(3.00 ~ 6.25)	201.33±66.00	154.00±34.09
Z	-3.826	-3.826	-6.919
p	<0.001	<0.001	<0.001

Table 5: Comparison of cost -effectiveness between the two groups.

The length of hospital stay in the bevacizumab group were 3 days (2.00 ~ 4.25). The care cost was

CNY 136.00±75.46 and operating cost was CNY 62.00±10.95. In the OK-432 group, the length of hospital stay was 3 days (3.00 ~ 6.25). The care cost was CNY 201.33±66.00, and Operating cost was CNY 154.00±34.09 ($P < 0.001$) (Table 5).

Discussion

Treatment effect

Bevacizumab is an inhibitor of VEGF that specifically binds to VEGF and prevents it from binding to receptor, thereby inhibiting tumor blood vessels formation. As a result, it inhibits the growth and metastasis of tumor cells[13,14], reduces VEGF blood vessels permeability, and decreases the development of serous cavity effusion[15]. Pichelmayer et al. first found that intravenous administration of bevacizumab (15 mg/kg) controlled malignant ascites[17]. Because the treatment of peritoneal effusion requires local high concentration of drugs, researchers have directly infused bevacizumab into the peritoneal cavity of patients with malignant peritoneal effusion. It was found that 5 mg/kg effectively controlled the development of effusions, reduced the level of VEGF in the abdominal cavity, and alleviated the adverse reactions caused by high concentration[18]. In this trial, intrapleural injection of Bevacizumab (5 mg/kg) was used to treat MPE and the overall effective rate in the bevacizumab group was 87%. The results indicated that bevacizumab therapy was an effective strategy for clinical treatment of MPE. The subjects included patients diagnosed with lung adenocarcinoma-induced MPE. A randomized study was conducted to compare the efficacy and side effects of OK-432 and in the treatment of chest perfusion, and the results showed that the clinical efficacy of both treatment strategies was similar.

Safety evaluation

Intravenous injection of Bevacizumab often causes increased blood pressure, gastrointestinal perforation, tracheoesophageal fistula, hemorrhage, reversible posterior leukoencephalopathy syndrome, thromboembolism, and other adverse reactions. In a previous study, the incidence of high blood pressure was 22.4%, the risk of thrombosis was 4.4%, and the incidence of hemorrhage was more than 16%[19]. In this trial, 30 patients treated with OK-432 experienced chest pain, fever, dyspnea, fatigue, nausea, and anorexia, with incidence rates of 16 (53%), 21 (70%), 5 (16.67%), 5 (16.67%), 1 (3.33%), and 7 (23.3%) respectively. Among them, 2 patients had chest pain of grades III-IV , and one patient had grade IV fever. Although the adverse reactions in the OK-432 group were all relieved after symptomatic treatment. the incidence of adverse reactions in the OK-432 group was significantly higher than that in the bevacizumab group. Therefore, bevacizumab therapy effectively controls MPE caused by lung adenocarcinoma and is safer than OK-432.

Effect of bevacizumab on the serum concentration of VEGF

Bevacizumab is a therapeutic drug targeting the VEGF signaling pathway. It inhibits VEGF signal transduction, thereby blocking tumor neovascularization and reducing the density of blood vessels. Bevacizumab also induces the "normalization" of survivaling vessels in the tumor, reduces the permeability of blood vessels and the interstitial pressure, improves the anoxic state of tumor blood vessels, and increases the delivery of drugs to tumor tissues. Furthermore, Bevacizumab causes degeneration of existing tumor vessels and cuts off the nutrient source to the tumor cells[20].

In this study, the serum VEGF concentration in lung adenocarcinoma patients with MPE was 246.79± 179.51 pg/ml before treatment, 129.85± 113.09 pg/ml after treatment, and the difference was statistically significant ($P< 0.05$). Hence, Bevacizumab decreased the level of serum VEGF with MPE caused by lung adenocarcinoma. he intrapleural infusion of bevacizumab effectively controlled MPE, suggesting that the mechanism is likely related to the inhibition of VEGF expression.

Correlation between the serum VEGF level and the curative effect

The results of our research and previous studies showed that MPE was significantly reduced by the monoclonal antibody Bevacizumab[21]. It was also found that baseline plasma VEGF levels were significantly higher in patients with disease control than those without control, indicating that the mechanism of bevacizumab in the treatment of malignant tumors was related to the VEGF pathway[22-24]. However, some studies have concluded that the relationship between the increased serum VEGF and the clinical benefit of bevacizumab therapy is not consistent. The stage III clinical analysis of 1816 patients with advanced malignant tumors conducted by Hegde et al. found that increased baseline levels of VEGF-A were associated with poor prognosis, but it was not possible to predict the benefit of anti-angiogenic

therapy(24). In our trail, the concentration of VEGF in bevacizumab group was 258.41± 187.93 pg/ml, and the concentration of VEGF in ineffective group was 171.25± 91.76 pg/ml (P> 0.05). There was no correlation between the expression of VEGF and the curative effect of thoracic perfusion. A recent Phase II clinical trial showed that the addition of bevacizumab to carboplatin-pemetrexed chemotherapy for non-small-cell lung cancer resulted in MPE control without pleurodesis[25].

Correlation between the changes in serum VEGF and the curative effect before and after treatment

Research on the role of VEGF in MPE formation and lung adenocarcinoma treatment has not been conclusive. In this study, the change in serum VEGF concentration in complete remission patients with pleural effusion was 126.57± 99.79 pg/ml, and the change in partial remission patients was 129.60± 118.54 pg/ml (P= 0.380, P> 0.05). Hence, the curative effect of single anti-pleural injection was not related to the change in serum VEGF concentration. We speculated that bevacizumab may have other mechanisms in the treatment of MPE.

Conclusion

Intrapleural injection of Bevacizumab treatment of MPE is not only effective, but also is safer than OK-432. Our result indicate that intervention with Bevacizumab improve the treatment of MPE by inhibiting VEGF production. The level of VEGF in pleural effusion and serum plays a guiding role in the treatment of MPE. Successful treatment of MPE represents an ongoing challenge in clinical practice. Recent scientific progress has shed light on the biological processes underlying the pathobiology of MPE. Recently, clinical studies reported in China showed that the administration of platinum chemotherapy drugs plus bevacizumab via intrapleural injection for treatment of MPE improved the clinical efficacy and increased the quality of life for these patients. The effective rate of bevacizumab combined with cisplatin in the treatment of MPE was 83.3-90%[26-30]. In contrast to the reported literature, this study showed that intrapleural injection of bevacizumab (one-time infusion dose of according to body weight) obtained good efficacy. The care cost in the OK-432 group was higher than that in the bevacizumab group, the length of hospitalization in the bevacizumab group was significantly shorter than that in the OK-432 group, and the drug expense was higher than that of the OK-432 group. With the reduced cost of bevacizumab compared with OK-432, the cost of thoracic perfusion therapy could be reduced by 1/2. Intrapleural injection of Bevacizumab was effictive and safe for MPE, with fewer side effects, shorter lengths of hospital stay, and reduced direct costs. Currently, there is a lack of high-quality randomized controlled clinical studies on the dose and course of intrathoracic perfusion drugs ,which need to be confirmed by large-scale multi-center clinical studies in the future.

References

1) Bibby AC, Dorn P, Psallidas I, Porcel JM, Janssen J, Froudarakis M, Subotic D, Astoul P, Licht P, Schmid R, Scherpereel A, Rahman NM, Cardillo G, Maskell NA.ERS/EACTS statement on the management of malignant pleural effusions.Eur Respir J. 2018, 52(1): 1800349.
2) Chen W, Zhang S, Zou X. Estimation and projection of lung cancer incidence and mortality in China. Zhongguo fei ai za zhi 2010, 13(5): 488-93.
3) Clive AO, Jones HE, Bhatnagar R, Preston NJ, Maskell N. Interventions for the management of malignant pleural effusions: a network meta-analysis2016. Cochrane Database Syst Rev. 2016, 2016(5): CD010529
4) Freddie Bray, Jacques Ferlay, Isabelle Soerjomataram, Rebecca L Siegel, Lindsey A Torre Ahmedin Jemal. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin.2018, 68(6): 394-424.
5) Antunes G, Neville E, Duffy J, Ali N, Pleural Diseases Group SoCCBTS. BTS guidelines for the management of malignant pleural effusions. Thorax. 2003, 58 Suppl 2: ii29-38.
6) Viallat JR, Rey F, Astoul P, Boutin C. Thoracoscopic talc poudrage pleurodesis for malignant effusions. A review of 360 cases. Chest. 1996, 110(6): 1387-93.
7) Kasahara K, Shibata K, Shintani H, Iwasa K, Sone T, et al. Randomized phase II trial of OK-432 in patients with malignant pleural effusion due to non-small cell lung cancer. Anticancer Res. 2006, 26(2B): 1495-9.
8) Nohara K, Takada K, Kojima E, Ninomiya K, Miyamatsu S, et al. A propensity score-matched comparison of the efficacies of OK-432 and talc slurry for pleurodesis for malignant pleural effusion induced by lung adenocarcinoma. Respiratory investigation. 2016, 54(5): 341-6.
9) Lee CG, Link H, Baluk P, Homer RJ, Chapoval S, et al. Vascular endothelial growth factor (VEGF) induces remodeling and enhances TH2-mediated sensitization and inflammation in the lung. Nature medicine. 2004, 10(10): 1095-103.
10) Ishii H, Yazawa T, Sato H, Suzuki T, Ikeda M, et al. Enhancement of pleural dissemination and lymph node metastasis of intrathoracic lung cancer cells by vascular

endothelial growth factors (VEGFs). Lung cancer. 2004, 45(3): 325-37.
11) Yano S, Shinohara H, Herbst RS, Kuniyasu H, Bucana CD, et al. Production of experimental malignant pleural effusions is dependent on invasion of the pleura and expression of vascular endothelial growth factor/vascular permeability factor by human lung cancer cells. The American journal of pathology. 2000, 157(6): 1893-903.
12) Bradshaw M, Mansfield A, Peikert T. The role of vascular endothelial growth factor in the pathogenesis, diagnosis and treatment of malignant pleural effusion. Current oncology reports. 2013, 15(3): 207-16.
13) Bose D, Meric-Bernstam F, Hofstetter W, Reardon DA, Flaherty KT, Ellis LM. Vascular endothelial growth factor targeted therapy in the perioperative setting: implications for patient care. The Lancet Oncology. 2010, 11(4): 373-82.
14) Prager GW, Lackner EM, Krauth MT, Unseld M, Poettler M, et al. Targeting of VEGF-dependent transendothelial migration of cancer cells by bevacizumab. Molecular oncology. 2010, 4(2): 150-60.
15) Kitamura K, Kubota K, Ando M, Takahashi S, Nishijima N, et al. Bevacizumab plus chemotherapy for advanced non-squamous non-small-cell lung cancer with malignant pleural effusion. Cancer chemotherapy and pharmacology. 2013, 71(2): 457-61.
16) Thickett DR, Armstrong L, Millar AB. Vascular endothelial growth factor (VEGF) in inflammatory and malignant pleural effusions. Thorax. 1999, 54(8): 707-10.
17) Pichelmayer O, Gruenberger B, Zielinski C, Raderer M. Bevacizumab is active in malignant effusion. Annals of oncology : official journal of the European Society for Medical Oncology. 2006, 17(12): 1853.
18) El-Shami K, Elsaid AA, El-Kerm Y. Open-label safety and efficacy pilot trial of intraperitoneal bevacizumab as palliative treatment in refractory malignant ascites. Journal of Clinical Oncology. 2007, 25(18): 9043.
19) Kabbinavar F, Hurwitz HI, Fehrenbacher L, Meropol NJ, Novotny WF, et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2003, 21(1): 60-5.
20) Huang G, Chen L. Tumor vasculature and microenvironment normalization: a possible mechanism of antiangiogenesis therapy. Cancer biotherapy & radiopharmaceuticals. 2008, 23(5): 661-7.
21) Shinkaruk S, Bayle M, Lain G, Deleris G. Vascular endothelial cell growth factor (VEGF), an emerging target for cancer chemotherapy. Current medicinal chemistry Anti-cancer agents. 2003, 3(2): 95-117.
22) Gianni L, Romieu GH, Lichinitser M, Serrano SV, Mansutti M, et al. AVEREL: a randomized phase III Trial evaluating bevacizumab in combination with docetaxel and trastuzumab as first-line therapy for HER2-positive locally recurrent/metastatic breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013, 31(14): 1719-25.
23) Miles DW, de Haas SL, Dirix LY, Romieu G, Chan A, et al. Biomarker results from the AVADO phase 3 trial of first-line bevacizumab plus docetaxel for HER2-negative metastatic breast cancer. British journal of cancer. 2013, 108(5): 1052-60.
24) Hegde PS, Jubb AM, Chen D, Li NF, Meng YG,et al. Predictive impact of circulating vascular endothelial growth factor in four phase III trials evaluating bevacizumab. Clinical cancer research : an official journal of the American Association for Cancer Research. 2013,19(4): 929-37.
25) Usui K, Sugawara S, Nishitsuji M, et al.A Phase II study of bevacizumab with carboplatin-pemetrexed in non-small-cell lung carcinoma patients with malignant pleural effusion: North East Japan Study Group Trial NEJ013.Lung Cancer.2016, 99: 131-136.
26) Du N, Li XS, Li F, et al. Intrapleural combination therapy with bevacizumab and cisplatin for non-small cell lung cancer-mediated malignant pleural effusion. Oncol Rep, 2013, 29(6): 2332-2340.
27) Dawei Chen, Xinyu Song, Fang Shi, Hui Zhu, Haiyong Wang, et al. Greater efficacy of intracavitary infusion of bevacizumab compared to traditional local treatments for patients with malignant cavity serous effusion. Oncotarget, 2017, 8(21): 35262-35271.
28) Sun ZW, Kong S, Zhao C, Fu T, Zhang Y, et al. Evaluation of efficacy and safety for bevacizumab in treating malignant pleural effusions caused by lung cancer through intrapleural injection. Oncotarget, 2017, 8(69): 113318-113330.
29) Chen DW, Song XY, Zhang Y, Kong L, Wang HY,et al. Optimizing intrapleural bevacizumab dosing in non-small-cell lung cancer-mediated malignant pleural effusion less is more. Future Oncol, 2018, 14(21): 2131-2138
30) Liu YJ, Tian PW. Progress of Bevacizumab in Malignant Pleural Effusion Caused by Non-small Cell Lung Cancer. Zhongguo Fei Ai Za Zhi, 2019, 22(2): 118-124.

Acknowledgements

This program was supported by research projects of the Affiliated Hospital of Inner Mongolia Medical University (NYFY ZD 2014001) and Science and technology project of Inner Mongolia Medical University (YKD2015KJBW018). The authors declare that there are no conflicts of interest. We thank Liwen Bianji (Edanz) (www.liwenbianji.cn/) for editing the English text of a draft of this manuscript.

Corresponding Author:

Xinhua Fu

Department of Respiratory and Critical Care Medicine, the Affiliated Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia 010050,China

Email: fuxinhua555@163.com

(China)