Original Article

Clinical efficacy of bevacizumab combined with cisplatin in the treatment of malignant pleural effusion and ascites caused by lung cancer: a randomized trial

Zhi Zhou[1#], Huiqing Li[1#], Daoqing Hu[2], Lanzhu Xie[1]

[1]Department of Palliative Medicine, Benq Hospital Affiliated to Nanjing Medical University, Nanjing, China; [2]Department of Oncology, Benq Hospital Affiliated to Nanjing Medical University, Nanjing, China

Contributions: (I) Conception and design: Z Zhou, H Li; (II) Administrative support: None; (III) Provision of study materials or patients: D Hu; (IV) Collection and assembly of data: L Xie; (V) Data analysis and interpretation: Z Zhou; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Zhi Zhou. Department of Palliative Medicine, Benq Hospital Affiliated to Nanjing Medical University, 71 Hexi Street, Jianye District, Nanjing 210000, China. Email: Zhouzhi9419@hotmail.com.

Background: To analyze the clinical effect of bevacizumab combined with cisplatin in the treatment of malignant pleural effusion and ascites.

Methods: A total of 86 patients with malignant pleural effusion and ascites admitted from June 2018 to September 2020 were selected as the research participants and randomly divided into a control group and observation group, with 43 cases in each group. The control group was given cisplatin intracavitary perfusion scheme, and the observation group was given bevacizumab combined with cisplatin intracavitary perfusion scheme. The Symptom Checklist 90 (SCL-90), Hamilton Depression Scale (HAM-D), and Hamilton Anxiety Scale (HAM-A) were used to evaluate participants' self-perceived negative symptoms, depression, and anxiety. The therapeutic effect and adverse reactions of the 2 groups were compared. The *t*-test was used for measurement data, and c2 test was used for enumeration data. Statistical significance was considered at P<0.05.

Results: After treatment, the serum levels of hypoxia inducible factor-1 (HIF-1α) and vascular endothelial growth factor (VEGF) in the observation group were significantly decreased and statistically lower than those in the control group (both P<0.05); the malignant pleural and abdominal water volume, average urine volume, and average chest circumference of the observation group were improved, and the difference was statistically significant compared with the control group (all P<0.05). The scores of each factor of SCL-90 in the observation group were decreased, among which the scores of somatization, interpersonal sensitivity, depression, anxiety, hostility, and terror in the observation group were significantly lower than those in the control group (all P<0.05); after treatment, the HAMD and HAMA scores of the observation group decreased, and the scores of HAMD (13.71±5.98) and HAMA (17.62±3.98) of the observation group were significantly lower than the score of (16.52±5.75) and (21.54±4.77) of the control group (both P<0.05).

Conclusions: In the clinical treatment of malignant pleural effusion and ascites, bevacizumab combined with cisplatin intracavitary perfusion can improve the clinical treatment effect, reduce the depression and anxiety of patients, optimize patient quality of life, and improve the safety of treatment.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2100048959.

Keywords: Lung cancer-associated malignant pleural effusion and ascites; bevacizumab; cisplatin intracavitary perfusion; vascular endothelial growth factor (VEGF)

Submitted Jul 30, 2021. Accepted for publication Oct 22, 2021.
doi: 10.21037/apm-21-2623
View this article at: https://dx.doi.org/10.21037/apm-21-2623

Introduction

Malignant pleural effusion and ascites is a common serious complication of advanced malignant tumor. Statistics show that about 50% of patients with advanced malignant tumor have malignant pleural effusion and ascites in the course of disease development (1). As a common malignant tumor, lung cancer has a high incidence rate in China. Most patients are at the middle and advanced stage when diagnosed, and the rates of survival and surgical cure are low. Early diagnosis and timely treatment of lung cancer can increase the patient survival rate (2). For patients at the middle and advanced stages, malignant pleural effusion and ascites caused by lung cancer will affect circulatory and respiratory functions, quality of life, and seriously threaten their lives (3). The main method of clinical treatment is to actively remove the pleural effusion and ascites caused by lung cancer and prevent further deterioration of the disease (4,5). At present, the main treatment is the thoracic perfusion of chemotherapy drugs, but the clinical effect is not obvious, and the recurrence rate is high (6).

In recent years, it has been found that vascular endothelial growth factor (VEGF) is expressed in malignant pleural effusion caused by many kinds of tumors such as lung cancer, breast cancer, and colorectal cancer. It can increase the permeability of blood vessels by inducing endothelium fenestration and damaging endothelial cell connection, which plays an important role in the formation of malignant pleural effusion. Bevacizumab is a humanized monoclonal antibody against VEGF (7). By specifically binding with VEGF and blocking VEGF pathway, bevacizumab can effectively inhibit neovascularization and reduce vascular permeability (8). In recent years, there have been many studies on bevacizumab thoracic infusion therapy at home and abroad, and the efficacy and safety of bevacizumab have been discussed from multiple perspectives and at multiple levels in single or combined use, local and systemic use (9). Therefore, this study compared the efficacy and safety of bevacizumab combined with cisplatin in the treatment of malignant pleural effusion and ascites caused by lung cancer, and explored the value of anti-VEGF in the treatment of malignant pleural effusion. We present the following article in accordance with the CONSORT reporting checklist (available at https://dx.doi.org/10.21037/apm-21-2623).

Methods

Subjects

A total of 86 patients with malignant pleural and ascites caused by lung cancer admitted to the Benq Hospital Affiliated to Nanjing Medical University from June 2018 to September 2020 were enrolled. The patients were confirmed by histology or pathology as lung cancer patients with stage IV or above; the pleural effusion was confirmed as malignant by exfoliative cytology and ultrasound examination; the expected survival time was more than 3 months, and no chemotherapy, targeted therapy, or other anti-tumor therapy was received during the month before enrollment. Before treatment, blood routine, liver function, kidney function, and electrocardiogram examinations were performed, and no abnormality was found; and all patients had no history of allergy to biological agents. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Benq Hospital Affiliated to Nanjing Medical University (No. 2021012).

All patients were numbered sequentially and randomly divided into control group and observation group with 43 cases in each group by computer generated random number. The allocation ratio of control group and observation group was 1:1. In the control group, there were 20 males and 23 females, aged 40–73 years old, with an average age of 62.43±2.55 years old; In the observation group, there were 21 males and 22 females, aged 41–74 years old, with an average age of 61.34±2.68 years old. There was no significant difference in gender and age between the two groups (both $P>0.05$). Patients and their families were informed of the study, and all participants provided written informed consent before the study commenced.

Research methods

Under the guidance of B-ultrasound, the drainage tube was placed into the thoracic cavity of the participants in both groups, the pleural effusion and ascites were drained as much as possible within 48 h, and then the thoracic perfusion was implemented. The control group was given 60 mg cisplatin intraperitoneal or thoracic perfusion; the observation group was given bevacizumab combined

with cisplatin intracavitary perfusion, that is, 200 mg bevacizumab + 60 mg cisplatin intraperitoneal or thoracic perfusion. Both groups were given liver protection, antiemetic, stomach protection, and other precautionary measures before perfusion. After intracavitary perfusion, the participant was asked to rest in bed and adjust their position every 15 minutes to facilitate the full capacity of the drug in the chest and abdominal cavity. Before and after perfusion, 5 mg dexamethasone and 5 mL lidocaine were given to reduce the adverse reaction of perfusion. Every 2 weeks was a course of treatment, and the curative effect was evaluated after 3 courses.

Research indicators and efficacy evaluation

The content of hypoxia inducible factor (HIF-1α) and VEGF in pleural fluid and the quality of life score of participants before and after treatment was recorded, and the clinical index level, total remission rate, and adverse reactions after treatment were also analyzed.

Efficacy evaluation: According to the pleural effusion efficacy evaluation standard of the World Health Organization (WHO) (10,11), the amount of pleural effusion was determined by B-ultrasound or computed tomography (CT). Complete remission (CR): the patient had no clinical symptoms, the effusion completely disappeared and was maintained for more than 4 weeks; Partial remission (PR): clinical symptoms improved, effusion decreased by more than 1/2, and pleural effusion drainage was not needed for more than 4 weeks; Stable disease (SD): no obvious improvement of symptoms, effusion decreased by less than 1/2 or increased by less than 1/4 or had no change; Progressive disease (PD): the amount of effusion increased significantly, the fluid needed to be pumped again within 4 weeks, and further treatment was needed (overall remission rate = complete remission rate + partial remission rate).

Quality of life assessment:

(I) The Symptom Checklist 90 (SCL-90) was used to evaluate participants' symptoms (12). The scale was divided into 5 grades of 1–5 (no, light, medium, heavy, and severe), with a total of 90 items and 10 factors. In this study, 9 factors were analyzed before and after treatment, including somatization, obsessive-compulsive symptoms, interpersonal sensitivity, depression, anxiety, hostility, terror, paranoia, and psychoticism.

(II) Hamilton Depression Scale (HAM-D) (13) contains 24 items, such as guilt, difficulty in falling asleep. Each item was scored according to the frequency of occurrence, with a total score of 4 (0: none; 1: mild; 2: moderate; 3: severe; 4: heavy). The higher the score was, the more serious the depression was. More than 14 points indicated that the depressive symptoms had clinical significance. The Hamilton Anxiety Scale (HAM-A) (14) includes 14 items, such as tension, anxiety. More than 14 points indicated that anxiety symptoms had clinical significance. The scoring rules are consistent with those of HAM-D.

Statistical analysis

The software SPSS 23.0 (IBM Corp., Armonk, NY, USA) was used to analyze the data. Measurement data were expressed as mean ± standard deviation ($\bar{x}$±s) and analyzed by *t*-test. The enumeration data were expressed by percentage (%), and the differences were compared by c2 test. A P value <0.05 was considered statistically significant.

Results

Baseline patient data

Patients with malignant pleural effusion caused by lung cancer admitted to our hospital from June 2018 to September 2020 were selected. The baseline data of patients are shown in *Table 1*. The clinical data of the two groups were comparable. All the 86 patients completed the treatment (*Figure 1*). Every two weeks for a course of treatment, a total of three courses.

HIF-1α and VEGF levels before and after treatment

Before treatment, there was no significant difference in HIF-1 and VEGF levels between the 2 groups. After treatment, the HIF-1 and VEGF content of both groups decreased significantly, and the HIF-1α and VEGF content (49.34±3.85, 38.54±4.01 ng·L^{-1}) of the observation group were significantly lower than those of the control group (62.72±8.09, 684.31±25.33 ng·L^{-1}) (both P<0.001). The results showed that compared with before treatment, the treatment methods of both the control group and the observation group reduced the levels of HIF-1α and VEGF in abdominal and pleural effusion, and the treatment group method significantly reduced the levels of HIF-1α and

Table 1 Baseline patient data

Clinical variables	Control group (n=43)	Observation group (n=43)	P
Gender			>0.999
Male	20	21	
Female	23	22	
Age	62.43±2.55	61.34±2.68	0.057
Disease types			0.884
Adenocarcinoma	25	22	
Squamous cell carcinoma	11	15	
Large cell lung cancer	7	6	

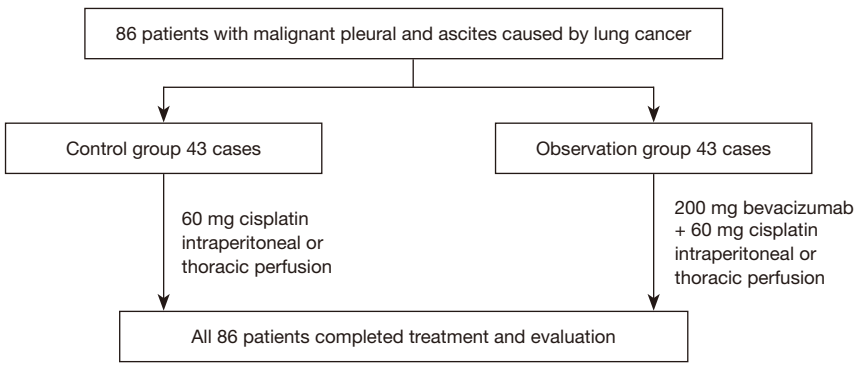

Figure 1 Participant flow.

Table 2 Changes of HIF-1α and VEGF levels before and after treatment in two groups ($\bar{x}$±s)

Before or after	Clinical indicator (ng·L^{-1})	Control group (n=43)	Observation group (n=43)	*t*	P value
Before treatment	HIF-1α	62.72±8.09	62.85±7.93	–0.08	0.940
	VEGF	688.25±22.56	684.31±25.33	0.76	0.448
After treatment	HIF-1α	49.34±3.85	38.54±4.01	12.74	<0.001
	VEGF	528.67±20.34	413.21±23.14	–79.72	<0.001

HIF-1α, hypoxia inducible factor-1α; VEGF, vascular endothelial growth factor.

VEGF in pleural effusion (*Table 2*).

Malignant pleural effusion and ascites, average urine, and average chest circumference of the 2 groups after treatment

As shown in *Table 3*, the malignant pleural and abdominal water volume, average urine volume, and average chest circumference of the observation group were 47.68±5.98, 866.59±9.45, and 82.32±5.69, respectively, which were better than those of the control group (68.31±6.56, 679.54±7.67, and 95.61±7.32, respectively). The results of *t*-test showed that the differences between the 2 groups were statistically significant (all P<0.01), and the symptoms of all participants were improved after treatment.

Comparison of quality of life between the 2 groups after treatment

SCL-90 symptom checklist

Before treatment, the quality of life of both groups was low,

Table 3 Comparison of clinical indicators between the 2 groups after treatment ($\bar{x}$±s)

Clinical indicators	Control group (n=43)	Observation group (n=43)	*t*	P value
Malignant pleural effusion (mL)	68.31±6.56	47.68±5.98	15.24	<0.001
Mean urine volume (mL)	679.54±7.67	866.59±9.45	−100.78	<0.001
Average chest circumference (cm)	95.61±7.32	82.32±5.69	9.4	<0.001

Table 4 SCL-90 symptom checklist of 2 groups after treatment ($\bar{x}$±s)

Group	Control group (n=43)	Observation group (n=43)	*t*	P value
Somatization	2.45±0.64	1.58±0.62	6.40	<0.001
Obsessive-compulsive symptoms	1.74±0.75	1.60±0.56	0.98	0.330
Interpersonal sensitivity	2.16±0.61	1.88±0.54	2.25	0.027
Depression	1.99±0.74	1.63±0.68	2.35	0.021
Anxiety	2.80±0.87	2.11±0.70	4.05	<0.001
Hostility	2.58±0.66	1.78±0.71	5.41	<0.001
Terror	3.04±0.74	2.68±0.68	2.35	0.021
Paranoia	2.99±1.01	2.94±0.97	0.23	0.815
Psychoticism	1.42±1.21	1.36±1.02	0.25	0.804

SCL-90, Symptom Checklist 90.

Table 5 Comparison of HAM-D and HAM-A scores between the two groups after treatment ($\bar{x}$±s)

Group	Evaluation index	Control group (n=43)	Observation group (n=43)	*t*	P value
Before treatment	HAM-D	18.35±4.65	18.55±5.31	−0.19	0.853
	HAM-A	34.36±3.24	35.21±3.54	−1.20	0.233
After treatment	HAM-D	16.52±5.75	14.21±5.98	2.22	0.029
	HAM-A	21.54±4.77	17.62±3.98	4.138	<0.001

HAM-D, Hamilton Depression Scale; HAM-A, Hamilton Anxiety Scale.

and there was no significant difference in the distribution of symptom factor scores of SCL-90 (P>0.05); After treatment, the quality of life of both groups was improved. The somatization (1.58±0.62 *vs.* 2.45±0.64), interpersonal sensitivity (1.88±0.54 *vs.* 2.16±0.61), depression (1.63±0.68 *vs.* 1.99±0.74), anxiety (2.11±0.70 *vs.* 2.80±0.87), hostility (1.78±0.71 *vs.* 2.58±0.66), and terror (2.68±0.68 *vs.* 3.04±0.74) symptom factor scores in the observation group were all lower than those in the control group (all P>0.05). There was no significant difference in the scores of obsessive-compulsive symptoms, paranoia, and psychoticism between the 2 groups (all P>0.05; *Table 4*).

Comparison of HAM-D and HAM-A scores between the 2 groups before and after treatment

According to *Table 5*, there was no significant difference in HAM-D score and HAM-A score between the 2 groups before treatment (both P>0.05). After treatment, the HAM-D and HAM-A scores of the observation group were 13.71±5.98 and 17.62±98, respectively, which were significantly lower than those of 16.52±5.75 and 21.54±4.77, respectively, before treatment (both P<0.05).

Table 6 Comparison of remission after treatment between the two groups

Clinical efficacy	Control group (n=43), n (%)	Observation group (n=43), n (%)	c^2	P value
CR	12 (27.91)	20 (46.51)	–	–
PR	17 (39.53)	18 (41.86)	–	–
SD	8 (18.61)	3 (6.98)	–	–
PD	6 (13.95)	2 (4.65)	–	–
Overall remission rate	29 (67.44)	38 (88.37)	5.47	0.019

CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.

Table 7 Comparison of adverse reactions between the 2 groups after treatment

Adverse reactions	Control group (n=43), n (%)	Observation group (n=43), n (%)	c^2	P value
Myelosuppression	17 (39.53)	15 (34.89)	0.20	0.656
Vomiting and diarrhea	19 (44.19)	16 (37.21)	0.43	0.510
Fever and fatigue	4 (9.30)	8 (18.60)	1.55	0.213
Liver function damage	3 (6.98)	4 (9.30)	0.16	0.693

The remission of the 2 groups after treatment

After treatment, the efficacy of the control group was mainly concentrated in partial remission (39.53%), while the observation group was mainly concentrated in complete remission (46.51%), followed by partial remission (41.85%). Further analysis showed that the total remission rate of the observation group was 88.37% (38/43), which was significantly higher than 67.44% (29/43) of the control group (c2=5.47, P=0.019; *Table 6*).

Adverse reactions of two groups after treatment

Adverse reactions after treatment included myelosuppression, vomiting and diarrhea, fever and fatigue, and liver function damage. The main adverse reactions in the control group and the observation group were vomiting and diarrhea (44.19% *vs.* 37.21%) and myelosuppression (39.53% *vs.* 34.89%). A few patients had fever, fatigue, and liver function damage. There was no statistical significance in adverse reactions between the 2 groups (P>0.05, *Table* 7).

Discussion

Malignant pleural effusion and ascites is the main cause of death in patients with advanced lung cancer, and its formation mechanism is related to tumor invasion of serosa, blockage of lymphatic vessels and mural serosa vessels, enhancement of permeability of thoracic and abdominal capillaries caused by inflammation, blockage of reflux caused by lymph node metastasis, and other factors (15). The main characteristics are that the appearance is often nonspecific, and can be bloody, light yellow or milk like, and often exudative (16). The main clinical manifestations are cough, chest tightness, dyspnea, abdominal distension, and so on. Malignant pleural effusion and ascites have a very serious negative impact on the quality of life of patients, and further accelerate the disease progression of advanced malignant tumor (17).

Malignant pleural effusion and ascites mostly occur in patients with advanced lung cancer, the majority of whom have limited survival time. At this time, the main goal of treatment is to improve the quality of life of patients, and only a few patients can prolong their survival time after treatment. Patients with malignant pleural effusion and ascites do not have the conditions for surgical treatment, and systemic chemotherapy and radiotherapy make it difficult for patients with poor tolerance (18). Thoracic perfusion is a well-tolerated treatment, making it the first choice for lung cancer patients with malignant pleural effusion and ascites. Pleural perfusion can directly act on the pleura and conform to the blood flow of pleura and tumor tissue. It has good pharmacokinetics and can effectively alleviate the clinical symptoms of patients and reduce

abdominal hydrops (19,20). A study by Masago *et al.* in 2003 showed that VEGF plays an important role in tumor angiogenesis (21). The secretion of VEGF can promote the production of malignant serous effusion. It exists widely in tumor cells, and can interact with its receptor and exert a significant biological effect. At the same time, it is a representative vascular permeability agent, which can enhance vascular permeability and promote tumor cell invasion and metastasis. Bevacizumab is a humanized monoclonal antibody against VEGF, which can specifically block the binding of VEGF and its receptor, promote tumor vascular degeneration, and ensure the normalization of the remaining vessels. At the same time, it can block the growth, proliferation, and metastasis of tumor cells, inhibit tumor angiogenesis, and promote the normalization of other blood vessels (22).

The results of this study showed that the overall remission rate of the observation group (88.39%) was significantly higher than that of the control group (67.44%). The results of SCL-90, HAM-D, and HAM-A showed that after bevacizumab treatment, the scores of somatization, interpersonal sensitivity, depression, anxiety, hostility, and terror in the observation group were lower than those before treatment and in the control group, indicating that bevacizumab treatment further alleviated the psychological pressure of patients and enhanced their confidence in life. After treatment, the conditions of malignant pleural and abdominal water volume, average urine volume, and average chest circumference of the observation group were significantly improved; the HIF-1α and VEGF level decreased significantly, and the observation group was significantly better than the control group. In terms of adverse reactions, there was no significant difference in the incidence of myelosuppression, vomiting and diarrhea, fever and fatigue, liver function damage, and other adverse reactions between the 2 groups (all $P>0.05$), suggesting that the combination regimen was well tolerated and had strong feasibility. The quality of life score of the observation group was significantly higher than that of the control group, and there was no significant difference in adverse reactions after treatment. The above results suggest that bevacizumab can significantly reduce the levels of HIF-1α and VEGF in pleural effusion, which is similar to the existing research results (23), indicating that the expression of VEGF in pleural effusion and ascites plays an important role in the prediction of curative effect of bevacizumab in the treatment of malignant pleural effusion, and that bevacizumab can effectively inhibit tumor cells and VEGF synthesis, reduce pleural effusion, and improve the quality of life of patients.

This clinical observation found that the curative effect of the bevacizumab combined with cisplatin group in the treatment of malignant pleural effusion and ascites was higher than that of the traditional cisplatin control group, and there were no significant clinical adverse events. Platinum is the most commonly used chemotherapy drug for malignant pleural effusion, and cisplatin, as the first generation of platinum, has a significant inhibitory effect on the formation of pleural effusion. However, leukopenia, renal toxicity, and nausea and vomiting are most common in patients with cisplatin pleural infusion. Bevacizumab is an anti-angiogenesis targeted drug, which also has an obvious inhibitory effect on malignant pleural effusion, and the most likely side effect is bleeding. Close attention should be paid to the patient during treatment.A combination of two drugs is a combination of chemotherapy drugs and antiangiogenesis that has a synergistic effect. It is suggested that bevacizumab is safe and effective in the treatment of malignant ascites, which is worthy of further clinical study. The possible mechanism is that bevacizumab can improve vascular permeability, and then relieve the osmotic pressure between tumor tissues, so that cisplatin can directly act on tumor lesions, strengthen local drug level, and improve the quality of treatment compared with drug alone. However, the prognosis of patients is closely related to the molecular biological characteristics of the malignant tumor, the general physical status of patients, the severity of complications, nutritional status, and the process of tumor treatment. The sample size of this study was relatively small, there was no further evaluation and grouping statistics on the physical and nutritional status of patients, and there were no further statistics on overall survival and progression-free survival, which were the limitations of this study.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-2623

Data Sharing Statement: Available at https://dx.doi.org/10.21037/apm-21-2623

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-2623). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Benq Hospital Affiliated to Nanjing Medical University (No. 2021012). Patients and their families were informed of the study, and all participants provided written informed consent before the study commenced.

References

1. Lu ZW, Lu G, Huang SM, et al. Clinical observation of the treatment of malignant body cavity effusion with cisplatin perfusion in body cavity. Drug Evaluation and Analysis in Chinese Hospitals 2014;10:870-2.
2. Huang HS, Yang XM, Fu JM, et al. The effect of hyperthermia combined with intracavity chemotherapy in the treatment of abdominal cancer with malignant pleural and ascites. China Medical Herald 2019;16:91-4.
3. Luo J, Zhu ZP, Jia GF, et al. Application of Moc-31, EMA, CEA in the differential diagnosis of benign and malignant pleural and ascites. Journal of Clinical and Experimental Pathology 2015;31:1177-9.
4. Wen ZZ, Zhang Y. Clinical observation of perfusion chemotherapy combined with deep hyperthermia in the treatment of malignant pleural and ascites. Strait Pharmacy 2018;30:162-4.
5. Su ZH, Tan LP, Que LL, et al. Application of continuous hyperthermic perfusion chemotherapy in the treatment of malignant pleural and ascites. Chinese Journal of Clinical Oncology and Rehabilitation 2013;20:1015-7.
6. Chen D, Song X, Zhang Y, et al. Optimizing intrapleural bevacizumab dosing in non-small-cell lung cancer-mediated malignant pleural effusion: less is more. Future Oncol 2018;14:2131-8.
7. Chen Y, Mathy NW, Lu H. The role of VEGF in the diagnosis and treatment of malignant pleural effusion in patients with non-small cell lung cancer (Review). Mol Med Rep 2018;17:8019-30.
8. Hu WB, Chen ZL, Chen J, et al. Observation on the effect of cisplatin perfusion combined with chemotherapy in the treatment of malignant pleural effusion of lung cancer. Modern Oncology Medicine 2015;23:3115-7.
9. Du N, Li X, Li F, et al. Intrapleural combination therapy with bevacizumab and cisplatin for non-small cell lung cancer-mediated malignant pleural effusion. Oncol Rep 2013;29:2332-40.
10. Thomas M, Fischer J, Andreas S, et al. Erlotinib and bevacizumab versus cisplatin, gemcitabine and bevacizumab in unselected nonsquamous nonsmall cell lung cancer. Eur Respir J 2015;46:219-29.
11. Chen D, Song X, Wang H, et al. Previous Radiotherapy Increases the Efficacy of IL-2 in Malignant Pleural Effusion: Potential Evidence of a Radio-Memory Effect? Front Immunol 2018;9:2916.
12. Chen IH, Lin CY, Zheng X, et al. Assessing Mental Health for China's Police: Psychometric Features of the Self-Rating Depression Scale and Symptom Checklist 90-Revised. Int J Environ Res Public Health 2020;17:2737.
13. Zimmerman M, Martinez JH, Young D, et al. Severity classification on the Hamilton Depression Rating Scale. J Affect Disord 2013;150:384-8.
14. Vehling S, Kissane DW, Lo C, et al. The association of demoralization with mental disorders and suicidal ideation in patients with cancer. Cancer 2017;123:3394-401.
15. Wang B, Hou W, Zhao B, et al. Application and research of external application of traditional Chinese medicine in the treatment of malignant pleural effusion. Chinese Journal of Information on Traditional Chinese Medicine 2013;20:100-2.
16. Xue DF, Zhao XJ. The therapeutic effect of bevacizumab combined with cisplatin on non-small cell lung cancer pleural effusion. China Medical Guide 2017;19:377-8.
17. Prado-Garcia H, Romero-Garcia S, Rumbo-Nava U, et al. Predominance of Th17 over regulatory T-cells in pleural effusions of patients with lung cancer implicates a proinflammatory profile. Anticancer Res 2015;35:1529-35.

18. Tao W, Li J. The application value of cellular DNA quantitative analysis in the identification of benign and malignant pleural and ascites fluid. Journal of Anhui Medical University 2015;50:1016-9.
19. Li CH, Li P. The effect of constant temperature thermal cycle intraperitoneal infusion chemotherapy on related tumor markers and prognosis of patients with ovarian cancer with ascites. Clinical Journal of Medical Officer 2017;45:848-50.
20. Xie SL, Yang MH, Chen K, et al. Efficacy of Arsenic Trioxide in the Treatment of Malignant Pleural Effusion Caused by Pleural Metastasis of Lung Cancer. Cell Biochem Biophys 2015;71:1325-33.
21. Masago K, Fujimoto D, Fujita S, et al. Response to bevacizumab combination chemotherapy of malignant pleural effusions associated with non-squamous non-small-cell lung cancer. Mol Clin Oncol 2015;3:415-9.
22. Novello S, Pinto C, Torri V, et al. The Third Italian Consensus Conference for Malignant Pleural Mesothelioma: State of the art and recommendations. Crit Rev Oncol Hematol 2016;104:9-20.
23. Novello S, Pinto C, Torri V, et al. The Third Italian Consensus Conference for Malignant Pleural Mesothelioma: State of the art and recommendations. Crit Rev Oncol Hematol 2016;104:9-20.
24. Natsume M, Honda T, Haruyama T, et al. A Case of Lung Adenocarcinoma with Marked Improvement of Pulmonary Lymphangitic Carcinomatosis by Adding Bevacizumab to Cisplatin and Pemetrexed. Case Rep Oncol 2017;10:1065-9.

(English Language Editor: J. Jones)

Cite this article as: Zhou Z, Li H, Hu D, Xie L. Clinical efficacy of bevacizumab combined with cisplatin in the treatment of malignant pleural effusion and ascites caused by lung cancer: a randomized trial. Ann Palliat Med 2021;10(10):10575-10583. doi: 10.21037/apm-21-2623

