ORIGINAL RESEARCH

Effects of Brucea Javanica Oil Combined with Chemotherapy on Serum CYFRA21-1, Immune Mechanism and Prognosis in Lung Cancer Patients

Yaokai Ma, MB; Xiyi Yang, MB; Wu Agudamu, MB; Xuan Liu, MD; Baocheng Zhao, MB

ABSTRACT

Objective • To investigate the effect of Brucea javanica Oil combined with chemotherapy on serum cytokeratin 19 fragment antigen 21-1 (CYFRA21-1), immune mechanism, and prognosis in patients with lung cancer and provide a reference for its clinical diagnosis and treatment.

Methods • This study involved 112 lung cancer patients from June 2019 to January 2022 at Shanghai Guanghua Hospital. They were randomly divided into two groups: control (chemotherapy only) and observation (chemotherapy + Brucea javanica oil emulsion). Each treatment lasted three weeks for a total of four courses. Pre- and post-treatment comparisons were made for tumor markers, immune function, and quality of life. Clinical outcomes and adverse reactions were analyzed.

Results • The clinical efficacy of the observation group was significantly higher than that of the control group ($P < .05$). Compared to the pre-treatment levels, both groups exhibited significant decreases in serum levels of carcinoembryonic antigen (CEA), cytokeratin fragment 21-1 (CYFRA21-1), cancer antigen 125 (CA125), phosphorylated extracellular signal-regulated kinase (pERK), neuron-specific enolase (NSE), and vascular endothelial growth factor (VEGF). The reduction in these serum markers was more pronounced in the observation group ($P < .05$). After treatment, both groups demonstrated significant increases in CD8+ and CD3+ lymphocyte levels, as well as CD4+ lymphocyte levels and the CD4+/CD8+ ratio. However, the improvement in these immune indicators was more significant in the control group ($P < .05$). Furthermore, the quality of life, as assessed by the Quality-of-Life Questionnaire-Lung Cancer Module 13(QLQ-LC13) questionnaire, showed significant improvements in both groups after treatment. The observation group exhibited a more significant decrease in the QLQ-LC13 scores, indicating a better quality of life post-treatment ($P < .05$).

Conclusion • Brucea javanica oil combined with GP chemotherapy can effectively reduce the synthesis and secretion of tumor-related markers, improve immune function, reduce the incidence of adverse reactions, improve the prognosis and quality of life, and enhance the curative effect, which has a certain clinical application value. (*Altern Ther Health Med.* [E-pub ahead of print.])

Yaokai Ma, MB; Xiyi Yang, MB; Wu Agudamu, MB; Xuan Liu, MD; Baocheng Zhao, MB; Oncology Department of Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western medicine, Shanghai, China.

Corresponding author: Baocheng Zhao, MB
E-mail: 1245646656@qq.com

Lung cancer is a common malignant tumor in clinics, with relatively high mortality and incidence rate.[1] According to the survey, there were about 4.3 million new malignant tumor cases in China in 2015, of which lung cancer accounted for about 15%, accounting for the highest proportion among male malignant tumors, and the incidence rate among women was only second to breast cancer.[2] Once most patients are found to be in an advanced stage, they lose the best opportunity for surgical treatment. Therefore, chemotherapy is currently the common method for treating lung cancer in clinical practice, especially for patients without surgical indications.[3] Chemotherapy can not only kill tumor cells but also inevitably damage the immune function of the body, causing adverse effects on the prognosis of patients. Relevant studies show that,[4] the positive rate of CD4+, CD3+, and CD8+cells is an important indicator of the body's immunity. The stronger the immunity, the higher the positive rate of CD4+ and CD8+ cells in the patient's serum, and the stronger the body's immune function. For patients in the advanced stage, chemotherapy will reduce the positive rate of CD4+ and CD8+ cells in the serum, trigger the immune dysfunction of the body, and have a direct impact on the prognosis and development of lung cancer patients. In addition, chemotherapy can also cause bone marrow suppression and severe adverse reactions in the digestive

system and interrupt the treatment plan.[5] Therefore, for patients with advanced lung cancer, improving the prognosis and improving immune function has become a hot research topic. As a traditional Chinese medicine, Brucea javanica oil can kill cancer cells in vitro and improve the body's immune function. It has been initially used in the clinical adjuvant treatment of colon cancer, gastric cancer, lung cancer, and other drugs and has achieved good efficacy. However, there are relatively few clinical reports on the effect of Brucea javanica oil on lung cancer.[6] Therefore, Shanghai Guanghua Hospital selected 112 patients with lung cancer admitted to the oncology department from June 2019 to January 2022 as the research object to explore the influence of Brucea javanica oil combined with chemotherapy on the serum CYFRA21-1, immune mechanism and prognosis of lung cancer patients, so as to provide reference for their clinical diagnosis and treatment.

DATA AND METHODS

General information

112 patients with lung cancer admitted to the Interventional department of our hospital from June 2019 to January 2022 were selected as the research objects, and they were randomly divided into two groups: the control group and the observation group, with 56 patients in each group. In the control group, there were 30 males and 26 females, aged 43-77 years, with an average age of (54.85 ± 4.81) years. The size of the lesions was (4.13 ± 0.98) cm. The pathological classification was squamous cell carcinoma in 17 cases, adenocarcinoma in 19 cases, and large cell carcinoma in 20 cases; tumor node metastasis (TNM) staging: 17 cases in stage IV, 21 cases in stage III, and 18 cases in stage II. The observation group consisted of 32 males and 24 females, aged 45-78 years, with an average age of (54.88 ± 4.69) years. The size of the lesions was (4.22 ± 1.01) cm. The pathological classification was squamous cell carcinoma in 18 cases, adenocarcinoma in 21 cases, and large cell carcinoma in 15 cases; TNM staging: 18 cases in stage IV, 17 cases in stage III, and 21 cases in stage II. There was no significant difference in age, sex, lesion size, pathological type, and TNM classification between the two groups, which was comparable ($P > .05$).

Inclusion and exclusion criteria

Inclusion criteria: 1. All patients met the diagnostic criteria for lung cancer in the Guidelines for Clinical Diagnosis and Treatment of Lung Cancer of the Chinese Medical Association (2018 Edition)[7] and were confirmed by cytology and pathology; 2. Those who refuse operation or have no indication for operation; 3. The survival period is not less than 3 months; 4. No history of radiotherapy or chemotherapy; 5. Patients and their families agree and sign an informed agreement; 6. Approved by the hospital's Ethics Committee.

Exclusion criteria: 1. Those allergic to the study drug; 2. Coagulation dysfunction; 3. Severe liver and kidney dysfunction and cardiovascular disease; 4. Pregnant and lactating patients; 5. Mental system diseases, autoimmune diseases, and malignant tumors; 6. Recent severe electrolyte disorder and severe infection; 7. History of organ transplantation; 8. Poor compliance and quitting halfway.

Methods

The control group was treated with a GP regimen as follows: on the first and eighth days, gemcitabine (registration certificate No. H20160224; Vianex S.A. Plant C) with a dose of 1000 mg/m^2 was dissolved in 100 ml of normal saline for 30min intravenous drip. On the first and third days, a dose of 25 mg/m^2 of cisplatin (GYZZ H20043888; Yunnan Biocereal Pharmaceutical Co., Ltd.) was given to dissolve it in 250ml of normal saline for 60min intravenous drip. One treatment cycle is weeks, and a total of 4 courses of treatment are carried out. Based on the above treatment, the observation group added Brucea javanica oil emulsion (30ml of Brucea javanica oil lotion was added to 250 ml of normal saline, GYZZ Z20044247, Jiangsu Jiuxu Pharmaceutical Co., Ltd.) by intravenous drip, once a day, 100 ml per time. After each chemotherapy, the treatment lasted for 21 days. A total of 4 courses of treatment were conducted.

Observation indicators

Collect 5 ml of fasting elbow venous blood from patients in both groups before and after treatment with serum tumor markers and centrifuge the supernatant for later use. The serum carcinoembryonic antigen (CEA) level of patients was detected by chemiluminescence, the serum carbohydrate antigen 125 (CA125) was detected by double antibody sandwich method, and the serum CYFRA21-1 level was detected by enzyme-linked immunosorbent assay. The kit was purchased from Wuhan Saipei Biotechnology Co., Ltd., and the operation method was strictly by the instructions.

Serum-related markers were measured by enzyme-linked immunosorbent assay for the levels of serum vascular growth factor (VEGF) and neuron-specific enolase (NSE) phosphorylated extracellular signal-regulated enzyme (p-ERK). The kit was purchased from Wuhan Saipei Biotechnology Co., Ltd., and the operation method was strictly in accordance with the instructions.

Immune function Take the above serum and use flow cytometry (BeamCyte-1013M; Changzhou Bidaco Biotechnology Co., Ltd.) to measure the positive rate of CD4+, CD3+, and CD8+ Cells before and after treatment and calculate the CD4+/CD8+ Ratio.

The quality of life of patients was measured with the lung cancer-specific scale (QLQ-LC-13),[8] which included 13 items of lung cancer-related symptoms and side effects (peripheral neuritis, dysphagia, oral inflammation, dyspnea, hemoptysis, cough, etc.).

The adverse reactions were observed and recorded, including leukopenia, liver function damage, nausea and vomiting, bone marrow transplantation, renal function damage, and other adverse reactions.

Efficacy evaluation criteria Refer to RECIST 1.1 Solid tumor efficacy evaluation criteria to evaluate the treatment

effect of patients.[9] If the growth of the focus exceeds 25%, it is progress (PD). The lesion is stable (CD) when it increases by no more than 25%, shrinks by no more than 50%, and maintains the status quo for no less than 1 month. Partial remission (PR) refers to the reduction of the lesion not less than 50% and the maintenance time not less than 1 month; The time of disappearance of the lesion is not less than 1 month, which means complete remission (CR). Total effective rate=(CR+PR)/total amount/100%.

Statistical analysis

SPSS 20.00, a special statistical software, was used to sort out and analyze the above data. The counting data was expressed by n (%), the chi-square test was performed, the measurement data was expressed by ($\bar{x} \pm s$), and the t test was performed. The difference was statistically significant ($P < .05$).

RESULTS

Comparison of clinical efficacy between two groups

The clinical efficacy of the observation group was significantly higher than that of the control group ($P < .05$). As shown in Table 1.

Changes of serum tumor markers in two groups before and after treatment

Compared with those before treatment, the serum CEA, CYFRA21-1, and CA125 levels in the two groups were significantly lower, and the serum tumor markers in the observation group were significantly lower ($P < .05$). As shown in Table 2.

Changes of serum-related markers in two groups before and after treatment

Compared with those before treatment, the levels of serum pERK, NSE, and VEGF in the two groups were significantly lower, and the levels of serum-related markers in the observation group were significantly lower ($P < .05$). As shown in Table 3.

Comparison of changes in immune function indexes between two groups before and after treatment

Compared with those before treatment, the levels of CD8+in the two groups were significantly higher after treatment, and the levels of CD3+, CD4+and CD4+/CD8+were significantly lower, and the above indicators in the control group were improved more significantly ($P < .05$). As shown in Table 4.

Comparison of quality of life scores between two groups before and after treatment

Compared with that before treatment, the QLQ-LC13 scores of patients in both groups were significantly reduced after treatment, and the above indicators of patients in the observation group were significantly reduced ($P < .05$). As shown in Table 5.

Table 1. Comparison of clinical efficacy between two groups of patients n (%)

	PD	SD	PR	CR	Effective
Control group (n=56)	12 (21.43)	15 (26.79)	12 (21.43)	17 (30.36)	29 (51.79)
Observation group (n=56)	3 (5.36)	8 (14.29)	12 (21.43)	33 (58.93)	45 (80.36)
χ^2					10.196
P value					.001

Table 2. Changes of serum tumor markers in patients of two groups before and after treatment

		CEA (ng/ml)	CYFRA21-1 (ng/ml)	CA125 (U/ml)
Control group (n=56)	Before treatment	20.86±3.69	7.88±1.26	64.87±5.85
	After treatment	15.49±3.31	5.31±0.87	50.33±4.26
Observation group (n=56)	Before treatment	20.91±3.73	7.93±1.19	65.02±5.97
	After treatment	11.04±2.89	4.01±0.56	41.26±5.17
$t/P_{\text{Intra-control group values}}$		8.107/<.001	12.560/<.001	15.035/<.001
$t/P_{\text{Observed intra-group values}}$		7.578/<.001	22.305/<.001	22.514/<.001
$t/P_{\text{Post-treatment inter-group values}}$		7.578/<.001	9.403/<.001	10.132/<.001

Table 3. Changes of serum-related markers in two groups before and after treatment

		pERK (ug/ml)	NSE (ng/ml)	VEGF (ng/ml)
Control group (n=56)	Before treatment	3.05±0.36	23.33±3.45	36.35±4.87
	After treatment	1.89±0.28	18.68±2.97	23.69±3.44
Observation group (n=56)	Before treatment	3.01±0.33	23.41±3.42	36.42±4.74
	After treatment	1.32±0.22	13.42±2.51	16.95±3.26
$t/P_{\text{Intra-control group values}}$		19.034/<.001	7.644/<.001	15.889/<.001
$t/P_{\text{Observed intra-group values}}$		31.887/<.001	17.622/<.001	25.327/<.001
$t/P_{\text{Post-treatment inter-group values}}$		11.979/<.001	10.123/<.001	10.642/<.001

Table 4. Comparison of changes in immune function indexes between the two groups before and after treatment

		$CD8^+$ (%)	$CD3^+$ (%)	$CD4^+$ (%)	$CD4^+/CD8^+$
Control group (n=56)	Before treatment	23.65±3.51	57.23±5.65	54.36±5.59	1.89±0.21
	After treatment	33.84±3.59	47.33±5.12	41.68±5.13	1.28±0.19
Observation group (n=56)	Before treatment	29.37±3.49	57.15±5.58	54.39±5.47	1.85±0.16
	After treatment	30.58±3.86	52.04±5.26	47.63±4.95	1.59±0.17
$t/P_{\text{Intra-control group values}}$		15.188/<.001	9.716/<.001	12.506/<.001	16.119/<.001
$t/P_{\text{Observed intra-group values}}$		1.740/.042	4.987/<.001	6.857/<.001	8.334/<.001
$t/P_{\text{Post-treatment inter-group values}}$		4.628/<.001	4.802/<.001	6.246/<.001	9.099/<.001

Table 5. Comparison of quality of life scores between the two groups before and after treatment ($\bar{x} \pm s$)

		QLQ-LC13 Rating (points)
Control group (n=56)	Before treatment	23.69±3.25
	After treatment	16.28±2.87
Observation group (n=56)	Before treatment	23.74±3.19
	After treatment	10.39±2.55
$t/P_{\text{Intra-control group values}}$		12.789/<.001
$t/P_{\text{Observed intra-group values}}$		24.462/<.001
$t/P_{\text{Post-treatment inter-group values}}$		11.481/<.001

Table 6. Comparison of adverse reactions between the two groups

	Leukopenia	Liver function impairment	Nausea and vomiting	Bone marrow suppression	Renal impairment	Incidence
Control group (n=56)	6 (10.71)	4 (7.14)	6 (10.71)	4 (7.14)	6 (10.71)	26 (46.43)
Observation group (n=56)	1 (1.79)	1 (1.79)	1 (1.79)	0 (0.0)	1 (1.79)	4 (7.14)
χ^2						22.036
P value						<.001

Comparison of adverse reactions between the two groups

The incidence of adverse reactions in the observation group was significantly lower than that in the control group ($P < .05$). As shown in Table 6.

DISCUSSION

For patients with intermediate and advanced lung cancer, the rapid metastasis and development of cancer cells miss the opportunity of radical surgery and intervene through the use of chemotherapy drugs.[10] Among them, the GP chemotherapy scheme is the most commonly used method, which is composed of cisplatin and gemcitabine and has a good effect in killing cancer cells.[11] Among them, gemcitabine mainly affects the process of DNA repair and synthesis.[12] The main target of cisplatin is DNA, which is cross-linked within and between DNA chains to form DNA cisplatin complex, which interferes with the combination of cancer cell cytoplasmic protein and nucleoprotein with DNA and also affects DNA replication, with a good killing effect.[13] However, clinical studies have shown that,[14] the use of GP chemotherapy alone can cause a variety of serious adverse reactions, such as decreased immune function and bone marrow suppression and affect the prognosis. Because the clinical treatment of such malignant tumors is mainly aimed at improving the quality of life and prolonging survival time, traditional Chinese medicine is usually used as an auxiliary treatment to reduce the side effects caused by chemotherapy and improve the prognosis.

In the process of lung cancer formation, there are many abnormal expressions of cytokines. CEA, CYFRA21-1, and CA125 are commonly used clinical markers that are highly expressed in many malignant tumors. In particular, CYFRA21-1 is a typical marker specifically indicating lung cancer.[15] VEGF is closely related to the invasive growth of blood vessels in lung cancer, abnormal angiogenesis, and other biological behaviors, and its high level of expression often indicates that the tumor cells in focus have relatively high activity.[16] NSE is an important marker for specific diagnosis of lung cancer and an important indicator for prognosis evaluation. PERK is a new type of marker that shows abnormally high expression, mainly in extrapulmonary metastasis or local metastasis of lung cancer. In this paper, compared with the control group after treatment, the levels of serum CEA, CYFRA21-1, CA125, pERK, NSE, and VEGF in the observation group after treatment were significantly lower ($P < .05$). It is suggested that Brucea javanica oil emulsion combined with GP chemotherapy can better improve the expression of the above serum indicators. The reduction of relevant serum indicators may be caused by two factors: one is that the drugs in the observation group have an indirect or direct killing effect on tumor cells, and the other is that the drugs in the observation group can regulate the immune function of the body, so as to control and monitor tumor cells and tissues.[17] In this article, the clinical efficacy of the observation group is significantly higher than that of the control group, which may be due to the Chinese medical research showing that Brucea javanica has the efficacy of increasing efficacy and reducing toxicity. It originated from the Compendium of Materia Medica and has the functions of clearing the liver, dispersing the knot, and corroding warts. Brucea javanica oil emulsion is mainly prepared with natural soybean phospholipid as an emulsifier and glycerol as raw material. It has a high affinity for tumor cell membranes and can directly kill tumor cells. Its main components are oleic acid and linoleic acid, which are widely used in adjuvant treatment of cancer.[19] Modern pharmacological research shows that[20] Brucea javanica oil emulsions can induce and inhibit cell apoptosis and proliferation and also show varying degrees of concentration and time dependence. At the same time, it can also induce the rate of cell apoptosis by activating enzyme activity to enhance the therapeutic effect. In addition, some studies have shown that[21] Brucea javanica oil has a good inhibitory effect on tumor angiogenesis. It can inhibit tumor angiogenesis by reducing the synthesis and secretion of VEGF. The immune function of the patients in the observation group improved more significantly after treatment. This may be because the small oil emulsion particles in Brucea javanica oil emulsion can specifically bind with tumor cells and have a strong affinity. They can be adsorbed around tumor cells for a long time, delay the further development of tumors, and enhance the efficacy. At the same time, they can also better prevent chemotherapy drugs from damaging normal tissue cells, prevent the immune function of the body from being damaged by related cytokines, and protect the immune function of tumor patients.[22] In this article, the QLQ-LC13 score of patients in the observation group decreased more significantly after treatment, suggesting that Brucea javanica oil emulsion combined with GP chemotherapy can effectively improve the quality of life of patients with prognosis. This may be because, from the perspective of TCM syndrome differentiation and treatment, Brucea javanica oil can regulate the viscera and meridians, yin and yang qi and blood of the body, so as to improve the prognosis, survival treatment, enhance the body's resistance to disease, and achieve the purpose of strengthening the body and removing diseases and pathogens. In addition, Brucea javanica oil emulsion can also induce the P-glycoprotein on the cell membrane of the body so as to reverse the drug resistance, enhance the drug properties of other drugs, and reduce the side effects of chemotherapy drugs to a certain extent.

To sum up, Brucea javanica oil combined with GP chemotherapy can effectively reduce the synthesis and secretion of tumor related markers, improve immune function, reduce the incidence of adverse reactions, improve the prognosis and quality of life, and enhance the efficacy, which has certain clinical application value.

AUTHOR CONTRIBUTIONS

Baocheng Zhao designed the study; Wu. Agudamu & Xuan Liu contributed to the analysis of the manuscript; Yaokai Ma & Xiyi Yang involved in the data and writing of this article; and all authors have read and approved the final manuscript.

REFERENCE

1. Minegishi Y, Gemma A, Homma S, et al. Acute exacerbation of idiopathic interstitial pneumonias related to chemotherapy for lung cancer: nationwide surveillance in Japan. *ERJ Open Res*. 2020;6(2):184-193. doi:10.1183/23120541.00184-2019
2. Powell SF, Rodríguez-Abreu D, Langer CJ, et al. Outcomes With Pembrolizumab Plus Platinum-Based Chemotherapy for Patients With Non–Small-Cell Lung Cancer and Stable Brain Metastases: pooled Analysis of KEYNOTE-021, 189, and 407. *J Thorac Oncol*. 2021;16(11):1883-1892. doi:10.1016/j.jtho.2021.06.020

3. Moik F, Zöchbauer-Müller S, Posch F, Pabinger I, Ay C. Systemic Inflammation and Activation of Haemostasis Predict Poor Prognosis and Response to Chemotherapy in Patients with Advanced Lung Cancer. *Cancers (Basel)*. 2020;12(6):169-175. doi:10.3390/cancers12061619
4. van de Garde EMW, van Bedaf LR, Hurkmans DP, van den Heuvel MM. Antibiotic use and reduced effectiveness of second-line immunotherapy for lung cancer: all the time or just at the start of treatment? *Ann Oncol*. 2020;31(12):1779-1780. doi:10.1016/j.annonc.2020.09.007
5. Judd J, Borghaei H. Combining Immunotherapy and Chemotherapy for Non-Small Cell Lung Cancer. *Thorac Surg Clin*. 2020;30(2):199-206. doi:10.1016/j.thorsurg.2020.01.006
6. Shen DP, Zhang ZX, Cheng L, et al. Clinical study on the treatment of advanced gastric cancer with Brucea javanica oil emulsion injection combined with Tegio and Apatinib. *Journal of Clinical and Experimental Medicine*. 2022;21(9):945-948.
7. Chinese Medical Association, Chinese Medical Association Oncology Branch, Chinese Medical Association Journal Guidelines for Clinical Diagnosis and Treatment of Lung Cancer of the Chinese Medical Association. (2018 Edition). *Chin J Cancer*. 2018;40(12):30.
8. WQ Dai. Evaluation and clinical application of QLQ-C30 and QLQ-LC13 Chinese versions of the quality of life scale for lung cancer patients. *Sun Yat sen University*. 2006.
9. Lu B, Lu H, Yu J, et al. Effect of Fuzheng Jiedu Decoction and Brucea javanica oil emulsion injection on immune function, lung function and blood lipids in patients with advanced non-small cell lung cancer. *World J Tradit Chin Med*. 2020;15(9):1317-1321.
10. Li T, Xing P, Wang S, et al. P16.06 Exploration of Efficacy and irAEs of Pembrolizumab Plus Chemotherapy for Advanced NSCLC as 1st Line Treatment in Real World. *J Thorac Oncol*. 2021;16(3):S350-S359. doi:10.1016/j.jtho.2021.01.552
11. Li J, Zhu GH, Liu TT, Xu BW, Li J. Comparative efficacy of Chinese herbal injections combined with GP regimen chemotherapy for patients with advanced NSCLC: A protocol for systematic review and network meta-analysis. *Medicine (Baltimore)*. 2020;99(28):e21041. doi:10.1097/MD.0000000000021041
12. Tan HM, Tan CM, Feng XL, et al. Efficacy of GP chemotherapy combined with Aidi injection in the treatment of elderly patients with advanced non-small cell lung cancer and its impact on immune function and quality of life. *Journal of Practical Cancer*. 2020;35(8):1327-13301346.
13. Li H, Wang JY, Wang MM, et al. Meta analysis of the therapeutic effect of Kanglaite injection combined with GP chemotherapy on advanced non-small cell lung cancer. *Journal of Pharmacoepidemiology*. 2022;31(6):363-370.
14. Zhang XY, Hou XH, Shi BX. Effect of Zhenqi Fuzheng Capsule combined with gemcitabine and cisplatin chemotherapy regimen on serum neurociliatin 1 and B7-H3 levels in patients with advanced non-small cell lung cancer. *Cancer Progress*. 2020;18(18):1896-18981902.
15. Svaton M, Blazek J, Krakorova G, et al. Prognostic Role for CYFRA 21-1 in Patients With Advanced-stage NSCLC Treated With Bevacizumab Plus Chemotherapy. *Anticancer Res*. 2021;41(4):2053-2058. doi:10.21873/anticanres.14974
16. Nilsson MB, Robichaux J, Herynk MH, et al. Altered regulation of HIF-1α in the nave- and drug-resistant EGFR mutant NSCLC: implications for a VEGF-dependent phenotype- ScienceDirect. *J Thorac Oncol*. 2020;16(3):439-451. doi:10.1016/j.jtho.2020.11.022
17. Yuan F, Xue HK, Zhou JJ. Effect of Brucea javanica oil emulsion injection combined with vinorelbine tartrate and cisplatin chemotherapy on postoperative rehabilitation of lung cancer patients. *Chinese Journal of Cancer Clinical and Rehabilitation*. 2020;(3):299-302.
18. Li CG, Liu XC, Zhang XH, et al. CT perfusion evaluation of the efficacy of NP chemotherapy combined with Brucea javanica oil emulsion in the treatment of non-small cell lung cancer. *Hebei Medical Journal*. 2021;27(9):1508-1512.
19. Xie YY, Hu HF. Effect of Brucea javanica oil emulsion injection combined with bronchial artery infusion chemotherapy on immune function of patients with advanced lung cancer. *Modern Journal of Integrated Traditional Chinese and Western Medicine*. 2020;29(33):3711-3714.
20. Li ZL, Yang D, He WJ, et al. Effect of Brucea javanica oil emulsion injection combined with pemetrexed+cisplatin chemotherapy in non-small cell lung cancer. *Cancer Progress*. 2022;20(7):672-675.
21. Peng YY, Chen Z, Kong XB, et al. Meta-analysis of the efficacy and safety of Brucea javanica oil emulsion injection combined with chemotherapy in the treatment of advanced colorectal cancer. *J Tradit Chin Med*. 2020;26(7):78-83.
22. Li Q, Xi Y. Effect of Brucea javanica oil emulsion injection on immune function and quality of life of elderly patients with cervical cancer after radiotherapy. *Modern Journal of Integrated Traditional Chinese and Western Medicine*. 2020;29(23):2603-2606.