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Original Article

Efficacy of continuous i.v. infusion of recombinant human vascular endothelial growth inhibitor in combination with chemotherapy in patients with advanced lung cancer

Wenli Li[1*], Ya Wu[1*], Haiying Wang[2], Lili Dai[3], Wei Wang[4], Yang Zhu[1]

[1]Department of Respiratory Medicine, Fuyang Hospital of Anhui Medical University, Fuyang, Anhui, China; [2]Department of Respiratory, Affiliated Hospital of Nantong University, Nantong, Jiangsu, China; [3]Department of Endocrinology, Funan County People's Hospital, Fuyang, Anhui, China; [4]Department of Respiratory Medicine, Funan County People's Hospital, Fuyang, Anhui, China. [*]Equal contributors and co-first authors.

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Abstract: Objective: This study aimed to observe the efficacy of continuous i.v. infusion of Recombinant Human Vascular Endothelial Growth Inhibitor (rhVEGI) in combination with chemotherapy in patients with advanced lung cancer (ALC). Methods: Eighty-six patients with ALC treated at our hospital between November 2018 and May 2020 were divided into two groups of 43 patients each according to a random number table. The control group (CG) was treated with routine chemotherapy, and the experimental group (EG) was treated with continuous i.v. Infusion of rhVEGI plus chemotherapy. The two groups were compared in terms of clinical efficacy, toxic side effects, immune function (T-lymphocyte subsets $CD4^+$, $CD8^+$, $CD4^+/CD8^+$), changes in neovascular parameters (serum bFGF, VEGF, MMP-9), quality of life, and survival rate within 6 months between two groups. Results: The response rate (81.40%) was higher in the EG (60.47%) than in the CG ($P<0.05$). After treatment, $CD4^+$ and $CD4^+/CD8^+$ increased in both groups, while $CD8^+$, serum bFGF, VEGF, and MMP-9 levels decreased, and the improvement in the EG was better than that in the CG ($P<0.05$). Three months after treatment, all quality of life scores increased in both groups, and were higher in the EG than in the CG ($P<0.05$). The mortality rate (32.56%) was lower in the EG (32.56%) than in the CG (67.44%) ($P<0.05$). Conclusion: Continuous i.v. infusion of rhVEGI combined with chemotherapy can effectively enhance clinical treatment efficacy, inhibit tumor cell growth, improve immune function, reduce mortality, and improve quality of life without increasing adverse effects in patients with ALC.

Keywords: Recombinant human vascular endothelial inhibitor, chemotherapy, advanced lung cancer, continuous i.v. infusion, immune function, quality of life

Introduction

According to the data by the World Health Organization, there were about 1.825 million new cases of lung cancer worldwide in 2012, accounting for 13.0% of all newly diagnosed cases of tumors, and 1.59 million lung cancer deaths, accounting for 19.4% of all deaths caused by tumors. Lung cancer ranked first in both incidence rate and mortality rate [1]. Lung cancer begins in bronchial epithelial cells. The clinical manifestation included dyspnea, cough, haemoptysis and expectoration, and the early symptoms are subtle. Some patients are already in advanced stages when diagnosed, missing the best time for treatment [2]. Most patients with advanced lung cancer (ALC) have a short survival period and a poor prognosis, so how to effectively prolong the survival time, improve the prognosis, and enhance the quality of life of patients with ALC is a pressing issue [3]. Clinical treatment for patients with ALC is based on chemotherapy regimens such as gemcitabine in combination with cisplatin, which showed certain efficacy but has little impact on the patients' survival, as well as bringing more toxic side effects, which is not conducive to the patients' prognosis [4, 5].

rhVEGI has been gradually applied in the clinical treatment of malignant tumors, which can

effectively inhibit tumor neovascularization and tumor cell proliferation [6, 7]. It has been found [8] that the disease control rate of advanced colorectal cancer treated with rhVEGI plus chemotherapy is 71.2%, which is significantly higher than 50.0% of chemotherapy alone. In the clinical treatment of ALC, the efficacy of continuous i.v. infusion of rhVEGI with chemotherapy still needs to be validated. Based on this, this study investigated the effects of continuous i.v. infusion of rhVEGI combined with chemotherapy on immune function, neovascular parameters and quality of life of patients with ALC, with the aim of providing reference for the clinical exploration of drug therapy for ALC.

Material and methods

Clinical data

Eighty-six patients with ALC treated at our hospital between November 2018 and May 2020 were enrolled and divided into two groups (n=43 for each group) according to a random number table method. Inclusion criteria: patients who meeting the diagnostic criteria for lung cancer in the Diagnostic and Treatment Code for Common Malignancies [9] and confirmed by examination of pathological tissues; TNM stage IIIb or IV; expected survival ≥3 months; functional status KPS score >60; age: 40 and 80 years; signed informed consent. Exclusion criteria: history of allergy to serum and vaccine; comorbid with other tumors; psychiatric disorders; concomitant other antitumor treatments such as radiotherapy and bioimmunotherapy; chemotherapy intolerance; comorbid with severe cardiac, hepatic, and renal dysfunction; history of thrombosis or a tendency to bleeding. This study was approved by Fuyang Hospital of Anhui Medical University.

Methods

(1) Control group (CG). Administration of GP chemotherapy: 1000 mg/m^2 gemcitabine (Yuanda Pharmaceutical Huangshi Feiyun Pharmaceutical Co., Ltd., H20133194) was administered intravenously on 1st and 8th day; 25 mg/m^2 cisplatin (Yunnan Biogu Pharmaceutical Co., Ltd., H20043889) was administered intravenously on 2nd and 4th day, with 21 days as one cycle of chemotherapy. During chemotherapy, conventional treatment such as hepatoprotective, antiemetic drugs, and acid suppressive therapy were given.

(2) Experimental group (EG). In addition to the regimen of the CG, 15 mg of rhVEGI (Shandong Simcere Biopharmaceutical Co., Ltd., S20050088) + 250 ml of 0.9% sodium chloride injection (Wanbond Pharmaceutical Group Co., Ltd., H33021775) was administered on the 1st-14th day for continuous I.V. infusion at a rate of q.d.11 ml/h, with 21 d as one treatment cycle, and 4 cycles were completed. Routine treatment such as anti-allergy, antiemetic drugs and acid suppression therapy were given during the treatment.

Outcome measurements

Primary observation indicators: (1) Clinical efficacy. The treatment efficacy was assessed as follows, including complete remission (complete disappearance of the lesion for >4 weeks), partial remission (lesion reduction ≥50% for >4 weeks), stable disease (lesion reduction <50% or increase <25%), and disease progression (appearance of new lesions or enlargement of lesions ≥25%). The response rate is the sum of the partial remission rate and the complete remission rate.

(2) Toxic side effects. The occurrence of toxic side effects in both groups, including fatigue, leukopenia, gastrointestinal reactions, hepatic and renal function impairment, and thrombocytopenia was recorded.

(3) Mortality. The patients were followed up for 18 months, and the mortality of the two groups was statistically analyzed.

Secondary observation indicators: (1) Immune function. Fasting venous blood in the morning was extracted from the two groups before and after treatment, and EDTA was used as the anticoagulation. Two test tubes were added with the combined antibody and monoclonal antibody, respectively, and then anticoagulant and PBS buffer were added, shaken and mixed, and incubated at room temperature in the dark for 15 min. After that, hemolysin was added, shaken and mixed, and incubated in the dark for 10 min, followed by adding PBS buffer for washing and centrifuged at 1000 r/min. PBS buffer was added to detect $CD4^+$ and $CD8^+$ subsets of T lymphocytes, and $CD4^+/CD8^+$ was calculated. The detection instrument was the flow cytome-

Table 1. Comparison of baseline data (n/$\bar{X}$ ± SD)

Grouping	Gender (men/ women)	Average age (years)	Average duration of illness (years)	Pathotyping	TNM Staging	Number of lesions
				Adenocarcinoma/squamous cell carcinoma/adenosquamous carcinoma	Phase IIIb/IV	Single/ multiple
Control group (n=43)	26/17	57.85±8.02	5.21±2.20	5.21±2.20	27/16	37/6
Experimental group (n=43)	28/15	57.23±7.39	5.33±2.14	18/14/11	29/14	38/5

Table 2. Comparison of the clinical efficacy [n (%)]

Grouping	CR	PR	SD	PD	Response rate
Control group (n=43)	6 (13.95)	20 (46.51)	9 (20.93)	8 (18.60)	26 (60.47)
Experimental group (n=43)	11 (25.58)	24 (55.81)	6 (13.95)	2 (4.65)	35 (81.40)#

Note: Compared with the control group, #*P*<0.05.

Table 3. Comparison of toxic side effects n (%)

Grouping	Fatigue	Leukopenia	Gastrointestinal reactions	Liver and kidney damage	Thrombocytopenia	Total
Control group (n=43)	3 (6.98)	2 (4.65)	1 (2.33)	2 (4.65)	3 (6.98)	11 (25.58)
Experimental group (n=43)	2 (4.65)	3 (6.98)	3 (6.98)	2 (4.65)	4 (9.30)	14 (32.56)

ter supplied by Shanghai Ranger Apparatus Co., Ltd.

(2) Indicators of neovascularization. The serum levels of basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF) and matrix metalloproteinase-9 (MMP-9) were detected by enzyme-linked immunosorbent assay (ELISA) before and after treatment. The kits of bFGF (Item No. 1534690851), VEGF (Item No. 1533815948), and MMP-9 (Item No. 1534721292) were provided by Shanghai Yuanye Bio-technology Co., Ltd.

(3) Quality of life. After 6 months of follow-up, the quality of life of the two groups was assessed before and at 3 months after treatment using the Quality of Life Scale (Chinese version of FACT-L) in 4 dimensions: emotional status, physical status, functional status and social/family status, with high scores for good quality of life.

Statistical analysis

The SPSS 22.0 was the analytic tool. Graphpad Prism 8.0 was used as the graphic software to prepare for the statistical charts. The measurement data (immune function, neovascularization index, quality of life) were expressed as $\bar{x}$ ± s, the comparison between groups and within groups were performed by independent samples t and paired sample t tests, respectively. Count data (clinical efficacy, side effects, survival rate) is expressed as percentages and compared using χ^2 test. P<0.05 indicated that the difference is statistically significant.

Results

Baseline data

Both groups showed no significant difference in terms of gender, mean age, disease duration, pathological type, TNM stage, and number of lesions (*P*>0.05), which were comparable (**Table 1**).

Clinical efficacy

The response rate (81.40%) of the EG was higher than that of the CG (60.47%) (*P*<0.05), which showed the combined therapy was effective for ALC (**Table 2**).

Toxic side effects

The difference in the incidence of toxic side effects between the two groups (32.56% vs 25.58%) was not different (*P*>0.05), indicating that combined treatment ALC did not increase toxic side effects (**Table 3**).

Immune function

Before treatment, the difference in immune function between the two groups was not sig-

nificantly different (P>0.05); after treatment, $CD4^+$, $CD4^+/CD8^+$ increased, while $CD8^+$ decreased, and they were better in the EG than that in the CG (P<0.05), showing that combined treatment can effectively improve the immune function of patients with ALC (**Figure 1**; **Table 4**).

Neovascular indicators

After treatment, the serum levels of bFGF, VEGF and MMP-9 decreased in the two groups, and were better in EG than in CG (P<0.05), suggesting that combined therapy can effectively suppress the tumor neovascularization of patients with ALC (**Figure 2**).

Quality of life

Before treatment, the differences in the quality of life scores between the two groups were not significantly different (P>0.05); 3 months after treatment, quality of life scores of the two groups increased, and were better in the EG than in the CG (P<0.05), which showed combined therapy can effectively improve the quality of life of patients with ALC (**Figure 3**).

Mortality rate

All deaths occurred within 7 months of treatment, and the mortality rate in the EG (32.56%) was lower than that in the CG (67.44%) (P< 0.05), indicating combined therapy can effectively reduce mortality in patients with ALC (**Table 5**).

Discussion

The incidence of lung cancer has been increasing, and it has the highest incidence and mortality rates in China. Over 70% of patients are in the middle and advanced stage when diagnosed, which increases the difficulty of treatment [10]. For patients with ALC, the main purpose of treatment is to inhibit the proliferation of tumor cells, extend the survival, and improve the quality of life. Chemotherapy is the main treatment option for ALC, and GP chemotherapy is the first-line regimen, in which cisplatin is the commonly used drug that is capable of destroying tumor cell DNA and preventing the invasion and proliferation of tumor cells [11, 12]. As a cytidine derivative, gemcitabine decreases the degradation of cellular metabolites and inhibits a variety of solid tumors [13]. However, patients with advanced lung showed little response to GP chemotherapy regimens. Some patients will have recurrence and metastasis after chemotherapy, resulting in high mortality rate [14].

rhVEGI is a novel vascular endothelial inhibitor, which can inhibit tumor cell proliferation by inducing endothelial apoptosis and inhibiting endothelial cell migration [15, 16]. In this study, 43 patients with ALC were given rhVEGI combined with chemotherapy, and the results showed that the response rate was higher and the mortality rate was lower in the EG than in CG; the difference in the incidence of toxic side effects between the two groups was not different. After treatment, the $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ and quality of life scores of the two groups were significantly improved, and they were better in the EG than in the CG. In the study by Zheng et al. [17], the overall remission rate of advanced lung squamous cell carcinoma treated with recombinant human vascular endothelial inhibitor combined with chemotherapy was 55.00%, which was significantly higher than the 32.50% of GP chemotherapy regimen, which was basically consistent with the results of the present study. This study suggested that combined therapy can effectively enhance the clinical efficacy, improve immune function, reduce mortality, and improve quality of life of patients with ALC.

It has been found [18] that the proliferation, differentiation and metastasis of lung cancer are closely associated with tumor neovascularization. Tumor neovascularization provides tumor cells with the nutrients and oxygen they need for growth, and also accelerates the excretion of metabolic products. VEGF is a pro-angiogenic factor that binds to endothelial cell receptors to increase vascular permeability and promote inflammatory exudation and stromal lysis [19]. Evidence showed [20] that VEGF expression level is closely related to the severity of lung cancer, and the decrease of VEGF expression level can effectively inhibit the growth of tumor cells and improve the prognosis of patients. bFGF is a multifunctional cell growth factor that promotes the division of vascular endothelial cells [21]. MMP-9 belongs to the family of matrix metalloproteinases that promote metastasis of tumor cells [22]. The

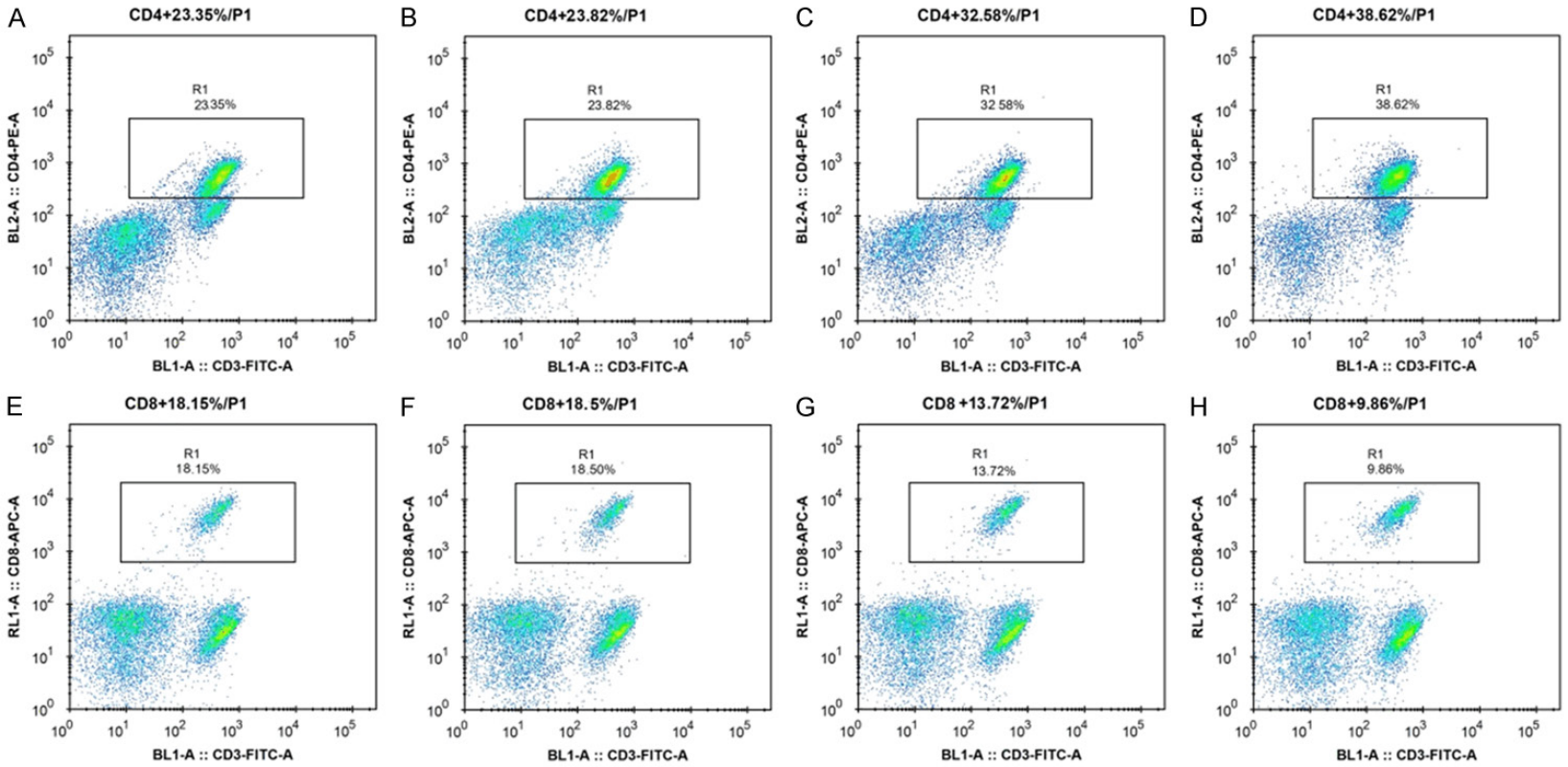

Figure 1. Comparison of immune function between the two groups before and after treatment. Note: A: $CD4^+$ level in the control group before treatment; B: $CD4^+$ level in the experimental group before treatment; C: $CD4^+$ level in the control group after treatment; D: $CD4^+$ level in the experimental group after treatment; E: $CD8^+$ level in the control group before treatment; F: $CD8^+$ level in the experimental group before treatment; G: $CD8^+$ level in the control group after treatment; H: $CD8^+$ level in the experimental group after treatment.

Table 4. Comparison of immune function between the two groups before and after treatment ($\bar{X}$ ± SD)

Grouping	$CD4^+$ (%)		$CD8^+$ (%)		$CD4^+/CD8^+$	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=43)	21.02±1.45	32.98±1.47***	17.51±1.52	13.39±1.42***	1.21±0.21	2.45±0.17***
Experimental group (n=43)	21.18±1.36	38.81±1.51###,***	17.42±1.55	10.40±1.48###,***	1.24±0.26	3.74±0.25###,***

Note: Compared to the control group, ###P<0.001; compared to the group before treatment, ***P<0.001.

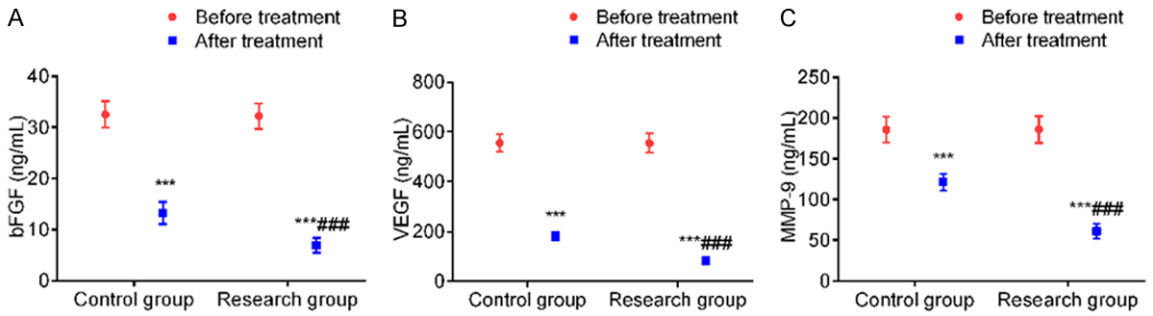

Figure 2. Comparison of neovascular parameters between the two groups before and after treatment. Note: A: bFGF (ng/mL); B: VEGF (ng/mL); C: MMP-9 (ng/mL). Compared to the control group, ###P<0.001; compared to the group before treatment, ***P<0.001.

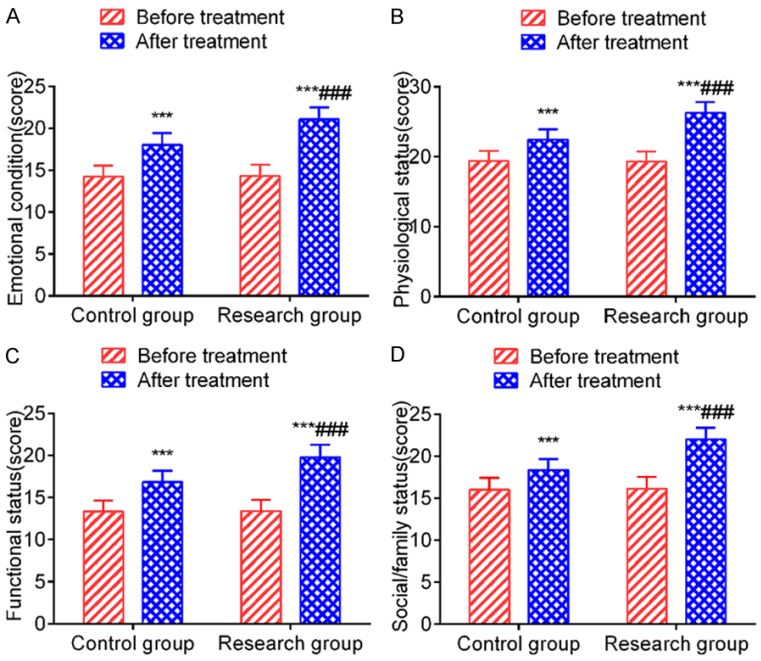

Figure 3. Comparison of quality of life scores between the two groups before and 6 months after treatment. Note: A: Emotional status score (points); B: Physiological status score (points); C: Functional status score (points); D: Social/family status (points). Compared to the control group, ###P<0.001; compared to the group before treatment, ***P<0.001.

results of this study showed that after treatment, the serum levels of bFGF, VEGF, and MMP-9 decreased in both groups, and the improvement in the EG was better than that in the CG, which was basically consistent with the results of other relevant studies, suggesting that combined therapy can effectively lower the serum levels of bFGF, VEGF, and MMP-9 and inhibit the growth of tumor neovascularization in patients with ALC. The underlying reason may be that rhVEGI can effectively inhibit the expression of anti-apoptosis genes, induce endothelial cell apoptosis, block angiogenic signaling pathways, reduce cell adhesion, and inhibit the growth, proliferation, and metastasis of endothelial cells [23, 24]. Meanwhile, rhVEGI can modify the internal vascular network of tumors in patients with ALC, prevent vascular leakage, reduces swelling so that the hydrostatic pressure keeps decreasing, leaving space for chemotherapeutic drugs to function on tumor cells

Table 5. Comparison of mortality n (%)

Grouping	Death	Survival
Control group (n=43)	24 (55.81)	19 (44.19)
Experimental group (n=43)	14 (32.56)#	29 (67.44)#

Note: Compared with the control group, #P<0.05.

[25]. In addition, rhVEGI can effectively improve the anoxic state of tumor cells, further improve its sensitivity to chemotherapy, and thus enhance the therapeutic effect.

However, due to the small sample size, the results may be biased, and the long-term efficacy of rhVEGI combined with chemotherapy has not been evaluated, which will be improved by increasing the number of cases and extending the follow-up time for in-depth discussion in future studies. In addition, it has been indicated in the results that all the deaths occurred at 7 months after treatment. Therefore, the survival curve and survival analysis of the patients at 6 months after treatment were not performed, which is also a deficiency of this study and will be further discussed in the next study.

In summary, rhVEGI for the treatment of ALC can effectively enhance the clinical efficacy, inhibit the growth of tumor cells, improve immune function, reduce mortality, improve quality of life, and its mechanism may be related to the inhibition of tumor neovascularization.

Disclosure of conflict of interest

None.

Address correspondence to: Yang Zhu, Department of Respiratory Medicine, Fuyang Hospital of Anhui Medical University, No. 99 Huangshan Road, Fuhe Modern Industrial Park, Yingzhou District, Fuyang 236000, Anhui, China. Tel: +86-17756860293; E-mail: zhuyang196@163.com

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