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Original Research Article

Efficacy and safety of the combination of paclitaxel, cisplatin and bevacizumab for the treatment of non-small cell lung cancer

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Abstract

Purpose: *To investigate the efficacy and safety of the combined use of paclitaxel, cisplatin, and bevacizumab for the treatment of non-small cell lung cancer (NSCLC).*

Methods: *98 NSCLC patients who received therapy at Hainan Hospital of Traditional Chinese Medicine, Changsha, China from January 2018 to December 2022 were retrospectively analyzed. The 45 patients who received paclitaxel and cisplatin injections were enrolled in a control group while 53 patients who received additional chemotherapy with bevacizumab injection were enrolled in a study group. Levels of vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (bFGF) were compared before and after treatment. Furthermore, the efficacy and incidence of adverse reactions were evaluated and compared between the two groups.*

Results: *There was no significant inter-group difference in VEGF and bFGF levels ($p > 0.05$) before treatment. There was a significant reduction in VEGF and bFGF levels in the study group compared to control group ($p < 0.05$). The study group showed a significantly higher total remission rate compared to control group ($p < 0.05$). Furthermore, there was no significant difference in the incidence of adverse reactions between the two groups ($p > 0.05$). Also, age, tumor, node, metastasis (TNM) stage, metastasis, and smoking history are risk factors that influence patient prognosis.*

Conclusion: *Combination of paclitaxel, cisplatin and bevacizumab demonstrates significant efficacy in the treatment of NSCLC. The combination lowers VEGF and bFGF levels without worsening adverse reactions. Future large population studies would be required to obtain a more detailed and comprehensive outcome on this combination in NSCLC.*

Keywords: *Paclitaxel, Cisplatin, Bevacizumab, Non-small cell lung cancer, VEGF, bFGF*

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INTRODUCTION

Lung cancer (LC) is a serious form of malignancy that has high incidence and mortality, consistently ranking as the leading cause of cancer-related morbidity and mortality [1]. The predominant sub-type of LC is characterized by high malignancy, sensitivity to radiotherapy and chemotherapy, and increased risk of recurrence [2]. Typical symptoms of NSCLC may manifest as persistent cough, low-grade fever, hemoptysis (bloody sputum), and chest pain. These

symptoms potentially lead to complications such as pericardial effusion, malignant pleural effusion, and lymph node metastasis, posing a significant threat to life [3]. Currently, NSCLC is usually treated using surgery, radiotherapy, and chemotherapy in clinical practice.

At present, platinum-based chemotherapy is considered the conventional treatment approach for NSCLC. However, the chemotherapy cycle is long, and large dosages of a single chemotherapy method often result in huge toxic and side effects. Therefore, a shift towards combination therapy regimens in the treatment of NSCLC becomes important. This change was driven by a comprehensive assessment of treatment efficacy as well as toxic and side effects associated with chemotherapy [4]. Cisplatin is combined with most anti-tumor drugs to achieve a strong synergistic effect [5].

Paclitaxel, a novel chemotherapy drug, is commonly used in combination with platinum-based agents due to its promising results, particularly in cases where tumor cells have developed resistance to platinum-based treatments [6]. Bevacizumab is a monoclonal antibody that functions as a highly safe anti-angiogenic agent by suppressing the proliferation and growth of tumor blood vessels [7]. Paclitaxel in combination with cisplatin chemotherapy is often the primary treatment approach for NSCLC. While this regimen effectively delays tumor growth, the overall therapeutic effect and prognosis may not always meet expectations [8].

Chemotherapy for NSCLC remains a significant focus of current research and clinical investigation, but there are limited studies on the effects of paclitaxel and cisplatin combined with bevacizumab on NSCLC. Therefore, this study investigated the efficacy and safety of combining paclitaxel and cisplatin with bevacizumab in treating NSCLC, with the goal of providing reliable and valuable information that may improve NSCLC treatment strategies.

METHODS

Patient data

The medical records of 98 NSCLC patients who underwent therapy at Hainan Hospital of Traditional Chinese Medicine, Changsha, China from January 2018 to December 2022 were analyzed retrospectively and assigned to control (45 patients) and study groups (53 patients). Diagnosis of NSCLC was based on NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) NSCLC [9]. Control group received chemotherapy with paclitaxel and cisplatin injections while study group received additional chemotherapy with bevacizumab injection. The study was conducted with approval from the Medical Ethics Committee (approval no. KY20230115A) and adhered to the guidelines in the Declaration of Helsinki [10].

Inclusion criteria

Patients who satisfied NSCLC diagnostic criteria [11], estimated survival time exceeding 90 days, no history of radiotherapy and chemotherapy and detailed clinical data.

Exclusion criteria

Patients with active heart, brain, or vascular diseases within the last 6 months; had suffered respiratory failure, had allergic history to the drugs adopted in this study, and patients who had received tumor treatment within the last month.

Therapeutic regimen

Control group received a weekly intravenous infusion of 135 mg/m^2 paclitaxel injection (Heilongjiang Fuhe Huaxing Pharmaceutical Group Co. Ltd, State Food and Drug Administration (SFDA) approval no. H20066442) in 5 % glucose and normal saline solution. In addition, control group received daily intravenous injection of 30 mg/m^2 cisplatin (Yunnan Biovalley Pharmaceutical Co. Ltd, SFDA approval no. H20043888) in 0.9 % sodium chloride injection (500 mL). This treatment was administered for three consecutive days, and repeatedly after 3 weeks. Study group received bevacizumab (15 mg/kg) injection (Qilu Pharmaceutical Co. Ltd, SFDA approval no. S20190040) in addition to paclitaxel and cisplatin injections for 3 weeks. Both groups were treated for 3 months.

To mitigate the risk of allergic reactions caused by paclitaxel, a pre-medication regimen was implemented. This involved intravenously administering 20 mg of dexamethasone (Guangdong Luofushan Sinopharm Co. Ltd, SFDA approval no. H44024841) 6 and 12 h before paclitaxel administration. Additionally, oral diphenhydramine (50 mg) (Grandpharma (China) Co. Ltd, SFDA approval no. H42021571) and 300 mg cimetidine (Shandong FANGMING Pharmaceutical Group Co. Ltd, SFDA approval no. H37023309) was administered 30 min before paclitaxel administration. Heart rate, blood pressure, as well as respiration, were measured every 15 min after administration, and any potential allergic reaction was identified.

Evaluation of parameters/indices

Treatment efficacy

After three months of treatment, efficacy was classified as complete remission (CR) in which case, all tumor lesions disappeared, and there were no signs of recurrence within three months; partial remission (PR) when tumor lesion volume dropped by over 50 % and remained stable within three-months; stable disease (SD) when tumor lesion volume decreased by less than 50 %, and no new lesions were generated; and progressive disease (PD) when none of the above criteria were met [12]. The overall response rate (OR) was calculated using Eq 1.

$$OR = ((CR+PR)/N)100 \quad \ldots\ldots\ldots\ldots\ldots (1)$$

where N is the total number of cases.

Prognosis

The prognosis of NSCLC patients within one year was analyzed, and independent risk factors for unfavourable prognoses were identified via multivariate logistics regression analysis.

Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF)

Levels of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) were compared between the two groups before and after treatment. Fasting venous blood (5 mL) was collected from every patient before therapy and 3 months after therapy, centrifuged, and levels of VEGF and bFGF were determined using VEGF (Wuhan Moshak Biotechnology Co. Ltd, Wuhan, China) and bFGF kits (NeoBioscience Technology Co. Ltd, Shenzhen, China), respectively.

Incidence of adverse reactions

Adverse reactions such as nausea and vomiting, leukopenia, thrombocytopenia, and bone marrow suppression in the two groups during treatment were recorded.

Statistical analysis

Statistical analysis was done using Statistical Packages for Social Sciences (SPSS Inc, Chicago, USA) for data analysis and GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA) for Figure presentations. Count data were presented as percentages and the chi-square test was used for comparison. Measurement data were presented as mean ± standard deviation (SD), and the independent sample t-test and paired t-test were used for inter-group and intra-group comparisons respectively. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline data of patients

There was no significant difference in baseline data between the two groups ($p > 0.05$) (Table 1).

Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) levels

There was no significant difference in VEGF and bFGF levels before treatment in both groups ($p > 0.05$).

Table 1: Baseline data of the two groups

Variable	Sub-factor	Study (n=53)	Control (n=45)	χ^2	*P*-value
Age	<55years old	20	15	0.206	0.650
	≥55 years old	33	30		
Gender	Male	36	30	0.018	0.895
	Female	17	15		
Body mass index	≥23kg/m^2	25	20	0.073	0.787
	<23kg/m^2	28	25		
TNM stage	Stage I-II	30	24	0.105	0.746
	Stage III-IV	23	21		
Metastasis	Yes	10	8	0.019	0.889
	No	43	37		
Smoking history	Yes	32	26	0.068	0.794
	No	21	19		
Drinking history	Yes	23	26	2.013	0.156
	No	30	19		

However, there was a significant reduction in VEGF and bFGF levels after treatment in study group compared to control group ($p < 0.05$; Figure 1).

Efficacy

Study group demonstrated significantly higher total remission rate compared to control group ($p < 0.05$) (Table 2).

Incidence of adverse reactions

There was no significant difference in the incidence of adverse reactions in both groups ($p > 0.05$; Table 3).

Related factors affecting prognosis

Patients who experienced recurrence or death within one year after treatment were categorized as having poor prognoses and were included in the unfavourable prognosis group (n = 33). Those who did not experience recurrence or death within one year were included in the favourable prognosis group (n = 65). Clinical data of the two groups were compared, followed by univariate analysis. Age, TNM stage, metastasis and smoking history were identified as risk factors affecting patient prognosis (Table 4). Significantly different indices were assigned (Table 5), and subjected to multivariate analysis. The result revealed that the TNM stage was the independent prognostic risk factor (Table 6).

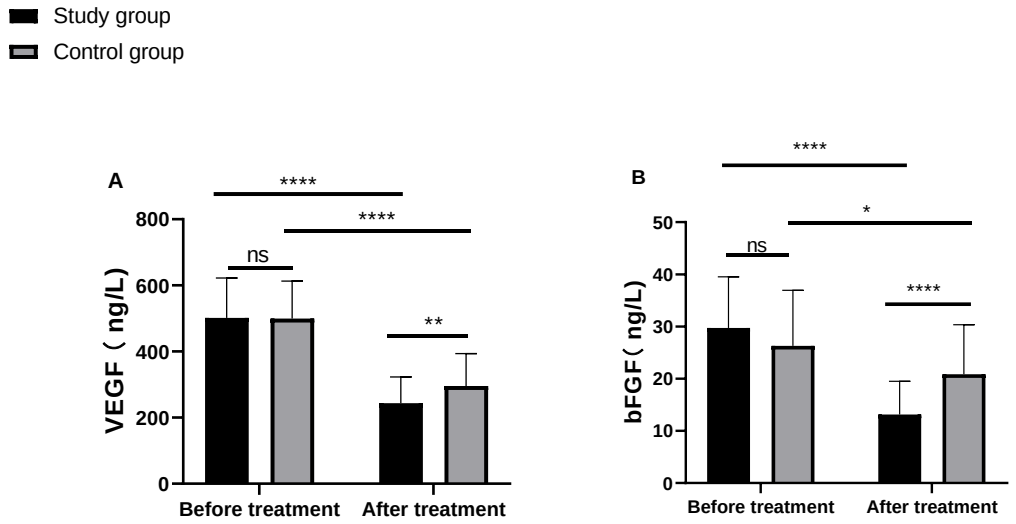

Figure 1: Comparison of VEGF and bFGF levels. A: VEGF levels before and after treatment, B: bFGF levels before and after treatment in study and control groups. ***Note:*** $^{ns}p > 0.05$ compared to control group; $*p < 0.05$ compared to before treatment, $**p < 0.01$ compared to control group, $****p < 0.0001$ compared to control group and before treatment. VEGF (vascular endothelial growth factor), bFGF (basic fibroblast growth factor)

Table 2: Efficacy in the two groups (n, %)

Group	Complete remission	Partial remission	Stable disease	Progressive disease	Total remission rate (%)
Study (n=53)	3(5.66)	25(47.17)	21(39.62)	4(7.55)	28(52.83)
Control (n=45)	1(2.22)	10(22.22)	26(57.78)	8(17.78)	11(24.44)
χ^2					7.723
***P*-value**					0.006

Table 3: Incidence of adverse reactions (n, %)

Group	Nausea and vomiting	Leukopenia	Thrombo-cytopenia	Myelo-suppression	Adverse reactions
Study (n=53)	2(3.77)	0(0.00)	1(1.89)	1(1.89)	4(7.55)
Control (n=45)	3(6.67)	1(2.22)	1(2.22)	0(0.00)	5(11.11)
χ^2					0.371
P-value					0.543

Table 4: Univariate analysis

Variable	Sub-factor	Favourable prognosis group (n=65)	Unfavourable prognosis group (n=33)	χ2	*P*-value
Age	*< 55 years old*	28	7	4.558	0.033
	≥55 years old	37	26		
Gender	*Male*	45	21	0.312	0.577
	Female	20	12		
Body mass index	*≥23kg/m²*	26	19	2.723	0.099
	<23kg/m²	39	14		
TNM stage	*Stage I-II*	50	4	37.151	<0.0001
	Stage III-IV	15	29		
Metastasis	*Yes*	6	12	10.751	0.001
	No	59	21		
Smoking history	*Yes*	30	28	13.571	0.0002
	No	35	5		
Drinking history	*Yes*	36	13	2.239	0.135
	No	29	20		

Table 5: Assignment of variables/indices

Variable	Assignment
Age	<55 years old=0, ≥55 years old=1,
TNM stage	Stage I-II=0, stage III-IV=1
Metastasis	No=0, Yes=1.
Smoking history	No=0, Yes=1.
Prognosis	Favourable prognosis=0, unfavourable prognosis=1.

Table 6: Multivariate analysis data

Factor	B	S.E	Wals	df	Sig.	Exp (B)	95% C.I for EXP(B).	
							Lower limit	*Upper limit*
Smoking history	0.070	0.462	0.023	1	0.879	1.073	0.433	2.655
Age	0.363	0.479	0.575	1	0.448	1.438	0.562	3.680
Metastasis	0.819	0.636	1.658	1	0.198	0.441	0.127	1.533
TNM stage	1.162	0.445	6.809	1	0.009*	3.196	1.335	7.648

**P* < 0.05. The TNM stage was the independent prognostic risk factor

DISCUSSION

Non-small cell lung cancer (NSCLC), which primarily affects middle-aged and elderly individuals, represents a common form of LC. Its occurrence is insidious and patients typically lack clinical manifestations in the early stage. With increasing environmental pollution and an aging population, the global incidence of NSCLC is on the rise each year [13]. Chemotherapy has been widely utilized in the treatment of NSCLC due to its effective elimination of tumor cells, control of metastasis and reduction of lesion recurrence risk. The use of chemotherapy in NSCLC has demonstrated significant and positive outcomes [14]. Cisplatin is a chemotherapy drug that has the ability to target and kill cells at various stages of the cell cycle. However, cisplatin induces drug resistance, with numerous side effects and short clearance half-life. Therefore, most of the current treatment schemes for NSCLC are platinum-based combined chemotherapy [15]. Paclitaxel is commonly used in the treatment of NSCLC and is effective when combined with cisplatin [16]. However, long-term use of paclitaxel and cisplatin in chemotherapy for NSCLC results in the development of drug resistance. As a result, in clinical practice, these two drugs are often combined with other agents to enhance treatment effectiveness. Bevacizumab, a novel anti-angiogenesis drug is effective in prolonging survival time of patients by blocking angiogenesis, formation of new blood vessels, and inhibiting tumor growth and metastasis. As a result, it has been extensively used against various types of tumors [17]. Therefore, this study investigated the efficacy and safety of paclitaxel and cisplatin combined with bevacizumab in treating NSCLC. Growth and metastasis of tumors depend on the formation of new blood vessels [18].

Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are pivotal growth factors that promote angiogenesis [19]. An increase in angiogenic factors in patients with NSCLC poses a robust capacity for tumor cells to proliferate and stimulate the formation of new blood vessels. [20]. In this study, there was no

significant difference in VEGF and bFGF levels in both study and control groups before treatment. However, after treatment, their levels dropped significantly in study group compared to control group. The results suggested that the combination of paclitaxel and cisplatin with bevacizumab lowered VEGF and bFGF levels in NSCLC, offering a better chemotherapeutic effect. This study also compared the efficacy in the two groups, and the results showed a significantly higher total remission rate in study group compared to control group. This finding further supported the evidence that combined treatment of paclitaxel, cisplatin, and bevacizumab was more effective than treatment with paclitaxel and cisplatin alone.

Similar to the results of this study, Chu *et al* [21] revealed that the efficacy of cisplatin combined with paclitaxel plus bevacizumab on advanced cervical cancer was better than that of cisplatin combined with paclitaxel, and prolonged life of patients. Additionally, there was no significant difference in the incidence of adverse reactions between the two groups. As a result, the addition of bevacizumab was safe and without worsening adverse reactions. Lastly, this study conducted a comprehensive analysis of factors influencing prognosis, and the findings revealed that age, TNM staging, metastasis, and smoking history were significant risk factors that influenced patient outcomes. Furthermore, it was demonstrated that TNM stage emerged as one independent risk factor of patient prognosis using a logistic regression model.

Limitations of this study

The small sample size may compromise the validity of the results. Furthermore, this study did not include long-term follow-up of patients to comprehensively investigate efficacy and long-term safety of the combination. Therefore, the sustained efficacy and potential impact on overall survival beyond the study period remain unclear.

CONCLUSION

The combination of paclitaxel and cisplatin with bevacizumab demonstrates significant efficacy in the treatment of NSCLC and reduces VEGF and bFGF levels without worsening adverse reactions. In addition, age, TNM stage, metastasis, and smoking history are risk factors impacting patient prognosis. Future large-scale studies to determine the sustained efficacy of this combination and the potential impact on the overall survival of NSCLC patients will be required.

DECLARATIONS

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None provided.

Ethical approval

The study was approved by the Medical Ethics Committee (approval no. KY20230115A).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Hui Zhang, Lei Fu, and LF conceived and designed the study, and drafted the manuscript. Hui Zhang, Lei Fu, Jingwen Jiang, Fangfang Fu, Aiying Chen and Hui Gong collected, analyzed, and interpreted the experimental data. Lei Fu and Hui Gong revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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