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ORIGINAL ARTICLE

A study on the efficacy of recombinant human endostatin combined with apatinib mesylate in patients with middle and advanced stage non-small cell lung cancer

Jian Zhao[1], Haibing Yu[1], Tianci Han[1], Wei Wang[1], Wei Tong[1], Xiangyu Zhu[2]

[1]Department of Thoracic Surgery, Cancer Hospital of China Medical University, Shenyang 110042, China; [2]Department of General Medicine, Cancer Hospital of China Medical University, Shenyang 110042, China.

Summary

Purpose: *To explore the clinical efficacy of recombinant human endostatin combined with apatinib mesylate in patients with middle and advanced non-small cell lung cancer (NSCLC).*

Methods: *A total of 64 patients with middle and advanced NSCLC were randomly divided into the control group (n=32) and observation group (n=32). The patients in control group received paclitaxel monotherapy, while those in the observation group were treated with recombinant human endostatin combined with apatinib mesylate. The short-term efficacy, the lung function and levels of immunoglobulin and T lymphocyte subsets before and after treatment and the adverse drug reactions of patients were compared between the two groups. All patients were followed up for 5 years, and the survival rate in the two groups was observed.*

Results: *The short-term efficacy and lung function in observation group were better than those in control group ($p<0.05$). Compared with those in the control group, the levels of immunoglobulin G (IgG), IgA, IgM, cluster of differentiation 3$^+$ (CD3$^+$), CD4$^+$ and CD4$^+$/CD8$^+$ were increased, while the CD8$^+$ level was lowered in the observation group ($p<0.05$). The rate of adverse drug reactions in the observation group was lower than that in the control group ($p<0.05$). The 5-year survival rate was significantly higher in the observation group than that in the control group ($p<0.05$).*

Conclusion: *Recombinant human endostatin combined with apatinib mesylate achieves a better therapeutic effect in the treatment of middle and advanced NSCLC, with improved immune resistance of patients and less side effects. Therefore, it is worthy of popularization and application in clinical practice.*

Key words: *recombinant human endostatin, apatinib mesylate, non-small cell lung cancer*

Introduction

Lung cancer, a common respiratory malignancy in clinical practice, has high morbidity and mortality rates, severely threatening human health [1]. It can be classified into small cell lung cancer and non-small cell lung cancer (NSCLC), of which NSCLC accounts for 4/5 of the lung cancer cases [2,3]. As to the treatment of NSCLC, surgery, radiotherapy and chemotherapy are mainly adopted. Surgery is a preferred option for early-stage NSCLC. However, NSCLC is difficult to be definitely diagnosed and usually in the advanced stage once detected due to its atypical symptoms in the early stage and insidious onset. As a result, most patients miss the best opportunity for surgery [4]. Chemotherapy has a certain effect for patients with NSCLC, but its toxic side effects are relatively severe. In particular, the immune function of patients who did not respond to first- and second-line

Corresponding author: Xiangyu Zhu, MD. Department of General Medicine, Cancer Hospital of China Medical University, No. 44, Xiaoheyan Rd, Dadong District, Shenyang 110042, Liaoning, China.
Tel: +86 013352402122, Email: pjzhuxiangyu@126.com
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chemotherapy is largely weakened, thus leading to lack of effective drugs [5]. Recombinant human endostatin, a targeted drug against tumor neovascularization, has a significant effect on many malignant tumors [6]. Apatinib mesylate is a drug mainly used in the third-line and above treatment of advanced gastric cancer, but its efficacy on lung cancer is rarely reported. In this study, patients with middle and advanced NSCLC were treated with recombinant human endostatin combined with apatinib mesylate to observe the therapeutic effect, so as to provide new ideas for the treatment of middle and advanced NSCLC.

Methods

General data

A total of 64 patients with middle and advanced NSCLC treated in our hospital from October 2011 to September 2013 were selected and divided into the control group (n=32) and the observation group (n=32) using a random number table.

Inclusion criteria: 1) Patients definitely pathologically diagnosed with NSCLC [7]; 2) those with an estimated survival of >3 months; and 3) those signing the informed consent.

Exclusion criteria: 1) Patients complicated by severe liver and kidney dysfunction and chemotherapy contraindications; 2) those with mental illness; or 3) those severely allergic to the drugs used in this study. There were no statistically significant differences in general data between the two groups of patients (p>0.05; Table 1). This study was approved by the Ethics Committee of Cancer Hospital of China Medical University. Signed informed consents were obtained from all participants before the study entry.

Methods

Treatment

Paclitaxel monotherapy was administered in the control group: Paclitaxel (Cisen Pharmaceutical Co., Ltd., Jining, China, approval number: NMPN H20057404), which was diluted with 5% glucose saline and 0.9% sodium chloride solution, was intravenously infused for 3 h at a dose of 75 mg/m^2 for 3 days (once every 3 weeks), with 1 month as a treatment course. A total of 4 treatment courses were carried out.

Recombinant human endostatin combined with apatinib mesylate were administered in the observation group: The patients took orally apatinib mesylate tablet (Hengrui Medicine, Lianyungang, China, approval number: NMPN H20140103) at a dose of 850 mg (once a day), with 1 week as a course of treatment. A total of 4 courses were administered. Recombinant human endostatin (Shandong Simcere-Medgenn Bio-pharmaceutical Co., Ltd., Yantai, China, approval number: NMPN S20050088) was intravenously infused at a dose of 15 mg (once every other day), with 2 weeks as a course of treatment, and a total of 4 courses were administered.

Detection of various indicators

Before treatment and after 4 courses of treatment, venous blood (5 mL) was collected from patients and centrifuged at 3000 r/min for 15 min, and the supernatant was taken and stored in a refrigerator at -20°C for testing. Anti-human cluster of differentiation 3 (CD3), CD4 and CD8 antibodies were separately added to the samples, followed by incubation in the dark at 4°C for 30 min. Thereafter, the levels of T lymphocyte subsets $CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$ were measured using a flow cytometer (BD, USA). The levels of immunoglobulin G (IgG), IgA and IgM were detected through immunoturbidimetry using relevant kits (provided by Beijing Donggeboye Biological Technology Co., Ltd., Beijing, China) strictly according to the instructions. The detected turbidity of the reaction solution was compared with that of the standard, and the content of IgG, IgA and IgM in the samples was calculated.

Evaluation criteria

Evaluation criteria for short-term efficacy in patients [8]: 1) Complete response (CR): all lesions disappeared for 4 weeks and beyond; 2) partial response (PR): the maximum diameter of the tumor was reduced by over half for 4 weeks and beyond; 3) Stable disease (SD): non-CR and –PR; and 4) progressive disease (PD):

Table 1. Comparisons of general data between the two groups of patients

Data	*Control group (n=32)*	*Observation group (n=32)*	t/x^2	*p*
Gender (male/female)	18/14	20/12	0.065	0.799
Age (years old)	40-70	40-75		
Average age (years old)	56.29±6.49	55.87±6.58	0.082	0.762
Pathological type, (n%)				
Adenocarcinoma	23 (71.87)	25 (78.12)	0.337	0.845
Squamous carcinoma	5 (15.63)	4 (12.50)		
Alveolar carcinoma	4 (12.50)	3 (9.38)		
Clinical stage [(n)%]				
Stage IIIb	12 (37.50)	10 (31.25)	0.069	0.792
Stage IV	20 (62.50)	22 (68.75)		

new lesions were detected or there was a relative increase of more than 20% in tumor diameter. Objective response rate (ORR)=(CR+PR)/total number of cases, and disease control rate (DCR)=(CR+PR+SD)/total number of cases.

Fasting venous blood (5 mL) was collected from patients in the morning before and after treatment and centrifuged to collect the supernatant that was then stored at -20°C for testing. Immunoturbidimetry was utilized to detect the levels of immunoglobulins IgG, IgA and IgM. The changes in T lymphocyte subsets ($CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$) were determined through flow cytometry. The lung function indicators including forced expiratory volume in one second (FEV1), maximum ventilation volume (MVV) and diffusion capacity of carbon monoxide (DLCO) of patients were evaluated before and after treatment.

Post-chemotherapy adverse reactions including nausea and vomiting, anemia, liver function impairment and thrombocytopenia in the two groups of patients were counted. All patients were followed up for 5 years after discharge to observe their survival.

Statistics

SPSS 19.0 (SPSS Inc., Chicago, IL, USA) software was used for data analyses. Measurement data were expressed as mean ± standard deviation (x±s), and t-test was employed for their analysis. Efficacy was evaluated by rank-sum test. Enumeration data were expressed as ratio (%), and x^2 test was used. P<0.05 suggested that the difference was statistically significant.

Results

Comparison of efficacy between the two groups of patients

The ORR and DCR in the observation group (68.76%, 87.50%) were clearly higher than those in the control group (40.63%, 63.50%) (p<0.05) (Table 2).

Comparisons of lung function indicators before and after treatment between the two groups of patients

The lung function of patients was overtly improved in both groups, while the improvement in the observation group was more obvious compared with that in the control group (p<0.05) (Table 3).

Comparisons of immunoglobulin levels before and after treatment between the two groups of patients

After treatment, the levels of immunoglobulins IgG, IgA and IgM were increased in both groups, and the increases were more remarkable in the observation group than those in the control group (p<0.05) (Table 4).

Comparisons of T lymphocyte subsets in peripheral blood of patients between the two groups

After treatment, the levels of $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ were raised, while the $CD8^+$ level de-

Table 2. Comparison of efficacy between the two groups of patients, (n%)

Group	*n*	*CR*	*PR*	*SD*	*PD*
Observation group	32	13 (40.63)	9 (28.13)	6 (18.75)	4 (12.50)
Control group	32	6 (18.75)	7 (21.88)	7 (21.88)	12 (37.50)

Based on rank-sum test, Z=2.300, p=0.021. For abbreviations see text

Table 3. Comparisons of lung function indexes between two groups of patients

Group	*Time*	*n*	*FEV1 (%)*	*MVV (%)*	*DLCO (%)*
Observation group	Before treatment	32	1.45±0.38	62.62±3.23	78.23±3.46
	After treatment	32	1.78±0.32*#	73.57±3.24*#	67.58±3.34*#
Control group	Before treatment	32	1.43±0.37	62.53±3.26	78.18±3.37
	After treatment	32	1.54±0.35*	64.58±3.25*	71.42±3.56*

*p<0.05 vs. before treatment, #p<0.05 vs. control group. For abbreviations see text

Table 4. Comparisons of immunoglobulin levels between the two groups of patients

Group	*Time*	*n*	*IgG*	*IgA*	*IgM*
Observation group	Before treatment	32	9.62±1.08	1.52±0.15	0.97±0.06
	After treatment	32	14.56±1.43*#	2.17±0.14*#	1.39±0.13*#
Control group	Before treatment	32	9.58±1.04	1.51±0.13	0.96±0.04
	After treatment	32	12.58±1.15*	1.69±0.17*	1.17±0.08*

*p<0.05 vs. before treatment, #p<0.05 vs. control group.

Table 5. Comparisons of the levels of T lymphocyte subsets in patients between the two groups

Group	*Time*	*n*	*CD3⁺*	*CD4⁺*	*CD8⁺*	*CD4⁺/CD8⁺*
Observation group	Before treatment	32	48.75±3.18	26.82±2.37	28.53±2.16	1.14±0.16
	After treatment	32	63.18±3.23*#	36.45±2.46*#	19.16±2.04*#	1.86±0.24*#
Control group	Before treatment	32	48.82±3.14	26.72±2.34	28.67±2.16	1.15±0.17
	After treatment	32	53.23±3.26*	30.37±2.36*	23.54±1.89*	1.47±0.23*

*p<0.05 vs. before treatment, #p<0.05 vs. control group.

Table 6. Comparisons of adverse reactions of patients between the two groups, (n%)

Group	*n*	*Gastrointestinal reactions*	*Abnormal liver function*	*Thrombocytopenia*	*Anemia*	*Total incidence rate of adverse reactions*
Observation group	32	2 (6.25)	0 (0.00)	2 (6.25)	1 (3.13)	5 (15.63)
Control group	32	5 (15.63)	3 (9.38)	4 (12.50)	3 (9.38)	15 (46.88)
x^2						5.426
p						0.013

Table 7. Comparisons of 5-year follow-up results between the two groups of patients

Group	*n*	*5-year survival (n%)*	*Mean survival (months)*
Observation group	32	16 (50.00)	46.72±6.23
Control group	32	7 (21.88)	35.45±6.32
x^2/t		4.344	5.826
p		0.037	<0.001

clined in both groups. The observation group showed more evident changes in comparison with the control group (p<0.05) (Table 5).

Comparisons of adverse reactions of patients between the two groups

The total incidence rate of adverse reactions in the observation group was markedly lower than in the control group (p<0.05) (Table 6).

Comparison of patient survival between the two groups

The observation group exhibited a longer mean survival time and an obviously longer 5-year survival rate in comparison with the control group (p<0.05) (Table 7).

Discussion

As a malignant tumor with the highest morbidity and mortality rates in the clinic, lung cancer is affected by environmental pollution, tobacco exposure, occupational carcinogen and host characteristics, and its incidence rate shows an increasing trend [9,10]. At present, the pathogenesis of NSCLC has not been well clarified, but it is generally believed that with the influence of external factors, the carcinogenic factors invade the lungs damaging local cells, while the lung cells can be self-repaired normally, while local inflammation occurs if the factors causing the damage are not removed completely, thus resulting in poor micro-environment in which malignant proliferation of lung cells occurs, eventually inducing cancer [11,12]. In case of NSCLC, the peripheral lung tissues of patients are damaged, leading to the falling of lung tissues into the pleural cavity and triggering direct metastasis, thereby reducing the survival of patients [13]. With improvements in current screening technology and resident awareness of physical examination, the early detection rate of NSCLC is increased to some extent, but which is still unsatisfactory and most patients are in the middle and late stage and have distant metastasis once definite diagnosis is made [14]. Therefore, chemotherapy is the first treatment option, which relieves the symptoms of patients, improves the immune function and prolongs the survival. However, due to poor tolerance to chemotherapy in patients with NSCLC and toxic side effects of the drugs, the patient compliance is rather poor, resulting in unsatisfactory efficacy in some of them [15]. Therefore, finding suitable drug therapeutic regimens is of great significance for patients with middle and advanced NSCLC.

In this study, it was found that the efficacy was significantly higher in the observation group than in the control group, and the lung function was distinctly improved in the observation group after treatment compared with that in control group (p<0.05). This is because paclitaxel, an anticancer

drug extracted from the bark of yew, is capable of preventing the depolymerization of the microtubules, thereby suppressing the division of tumor cells and inducing apoptosis [16]. Apatinib is a VEGFR2 tyrosine kinase inhibitor that represses both neovascularization and the metastasis of cancer cells [17]. Recombinant human endostatin combined with apatinib mesylate can block neovascularization, thus inhibiting the progression of NSCLC, eventually achieving a more obvious effect on NSCLC. Besides, it can alleviate the damage of the chest wall muscles, effectively protect the lung function of patients, reduce tumor neovascularization at the same time and improve the nutritional supply to the lung tissues, thereby improving lung function [18].

Immunoglobulins are important participants in the body defense. IgG is an antibody playing a leading role in anti-infection. IgA forms a local immune system with surrounding cells to protect against infection. IgM, an antibody phagocytizing, aggregating and dissolving bacteria, is very effective against infection [19]. In patients with NSCLC, the levels of immunoglobulins IgG, IgM and IgA are low, and the lung tissues are damaged, leading to inflammation and mild infection, so that the resistance is generally reduced. T lymphocytes are important for the body's immune response. $CD3^+$ can reflect the number of total T lymphocytes. $CD4^+$ is a helper T lymphocyte, which is able to enhance the immune response. $CD8^+$, a suppressor T cell that damages and kills cells, can cause immune dysfunction [20]. In this study, the results revealed that the levels of IgG, IgA, IgM, $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ were elevated, while the level of $CD8^+$ was lowered in both groups after treatment, and the observation group displayed more significant changes ($p<0.05$), because the treatment with recombinant human endostatin combined with apatinib mesylate accelerates the apoptosis of tumor cells, inhibits the infiltration and metastasis of cancer cells, relieves the clinical symptoms of patients and has less immunosuppression, thus improving the immune function of patients. Recombinant human endostatin is non-cytotoxic, and can reduce the drug toxic side effects, enhance the chemotherapy tolerance, improve the therapeutic effect, and prolong the patient survival.

Conclusions

In conclusion, recombinant human endostatin combined with apatinib mesylate given to patients with middle and advanced NSCLC not only improves their immunologic competence, but it also reduces the toxic side effects of the drugs. It is safe and worthy of generalization and application in the clinic.

Conflict of interests

The authors declare no conflict of interests.

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