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ORIGINAL ARTICLE

A study on the efficacy of recombinant human endostatin combined with chemotherapy in treating advanced non-small-cell lung cancer

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Summary

Purpose: *To observe and compare the efficacy and safety between recombinant human endostatin combined with chemotherapy and chemotherapy alone in treating advanced non-small-cell lung cancer (NSCLC).*

Methods: *The clinical data of 136 patients with advanced NSCLC admitted and treated in the Department of Medical Oncology of our hospital from March 2014 to March 2016 were retrospectively analyzed. Among them, 68 patients received recombinant human endostatin combined with chemotherapy (experimental group), and 68 patients were treated with chemotherapy alone (control group). The clinical data of all the patients were collected to compare the short-term response rate, changes in Karnofsky performance status score and serum carcinoembryonic antigen (CEA) level before and after treatment as well as occurrence of adverse reactions between the two groups of patients. Moreover, the patients were followed up to record the overall survival (OS) rate and progression-free survival (PFS) rate.*

Results: *There were no statistical differences in general clinical characteristics between the two groups of patients. In the experimental group, the overall response rate (ORR) was 48.5% (33 cases), and the disease control rate (DCR) 91.2% (62 cases). In the control group, the ORR and DCR were 29.4% (20 cases) and 75.0% (51 cases), respectively. The Karnofsky performance status score was increased in both groups (72.92±7.44 points and 73.64±5.68 points) after treatment (p=0.527). After treatment, the serum CEA level declined remarkably in both groups (10.62±1.43 ng/mL and 11.07±2.02 ng/mL) (p=0.136). The proportion of patients with cardiac toxicity in the experimental group was higher than that in the control group, but the difference was not statistically significant (p=0.064). According to log-rank test, there were statistically significant differences in the OS rates and PFS rates between the two groups of patients (p=0.019, p=0.009).*

Conclusion: *Recombinant human endostatin combined with chemotherapy has favorable short-term efficacy in treating advanced NSCLC. It can prolong the OS and PFS rate of the patients, without increasing adverse reactions of chemotherapy, and therefore is worthy of clinical popularization.*

Key words: *recombinant human endostatin, chemotherapy, non-small-cell lung cancer, efficacy*

Introduction

Lung cancer ranks first in incidence and mortality rates among malignant tumors in urban residents in China, and the patients with non-small-cell lung cancer (NSCLC) account for 75-80%. Most patients are in advanced stage when they are diagnosed, so the treatment is dominated by systemic chemotherapy [1,2]. Although the efficacy of the third-generation cytotoxic drugs (such as gemcitabine, vinorelbine and docetaxel) combined with platinum drugs in treating advanced NSCLC has been improved, the 5-year survival rate is still very low [3,4]. In recent years, targeted agents for tumors such as gefitinib, erlotinib and bevacizumab, are increasingly applied to lung cancer patients,

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which can ameliorate the prognosis of patients with advanced NSCLC to some extent [5-7]. Recombinant human endostatin is a type of targeted agent capable of inhibiting neovascularization. The recombinant human endostatin (Endostar) produced using *Escherichia coli* as the protein expression system has higher purity and lower dose compared with natural endostatin [8,9]. A growing number of data have verified that recombinant human endostatin combined with chemotherapy can improve the therapeutic effect on advanced NSCLC and ameliorate the patient's quality of life [10].

In this research, 136 patients with advanced NSCLC admitted and treated in our department from March 2014 to March 2016 were retrospectively analyzed. Among them, 68 patients received recombinant human endostatin combined with chemotherapy, and the other 68 patients were treated with chemotherapy alone. The overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS) rate and overall survival (OS) rate in the two groups of patients were observed and recorded. The occurrence of common adverse reactions was recorded, and the clinical efficacy and safety of the two treatment regimens were compared.

Methods

General data

A total of 136 patients with advanced NSCLC admitted and treated in the Department of Medical Oncology of our hospital from March 2014 to March 2016 were collected. There were 82 males and 54 females aged 43-78 years (median 61). All the patients were definitely diagnosed through cytology or biopsy, with clinical stages IIIB-IV. Sixty-six patients were initially treated and 70 patients were retreated (the interval between the previous treatment and this treatment should be at least 3 months), with more than 1 measurable lesion. At the time of enrollment, the patients had a Karnofsky performance status score of ≥60 points, without dysfunction of vital organs and with basically normal blood routine as well as hepatic, renal and cardiac functions. Moreover, the life expectancy was >3 months. Sixty-eight of them received recombinant human endostatin combined with chemotherapy (experimental group), and 68 underwent chemotherapy alone (control group). The general characteristics of the two groups of patients before treatment are shown in Table 1, displaying no statistically significant differences (p>0.05). This research was approved by the Ethics Committee of our hospital. All the patients enrolled followed the Declaration of Helsinki and signed the informed consent.

Table 1. Baseline characteristics of the studied patients

Characteristics	*Experimental group N=68 n (%)*	*Control group N=68 n (%)*	*p value*
Age (years)	59.5±11.9	61.8±10.8	0.456
Gender			
Male	39 (57.4)	43(63.2)	0.572
Female	29 (42.6)	25(36.8)	
Pathological type			0.743
Squamous cell carcinoma	26 (38.2)	29 (42.7)	
Adenocarcinoma	37 (54.4)	33 (48.5)	
Others	5 (7.4)	6 (8.8)	
Clinical stage			0.257
IIIB	25 (36.8)	22 (32.4)	
IV	43 (63.2)	46 (67.6)	
Previous therapy			0.565
Yes	31 (45.6)	35 (51.5)	
No	37 (54.4)	33 (48.5)	
KPS score			0.344
80-90	38 (55.9)	34 (50)	
60-70	30 (44.1)	34 (50)	
Chemotherapy			
AP	29 (42.6)	25 (36.8)	
GP	33 (48.5)	35 (51.5)	
DP	4 (5.9)	5 (7.3)	
TP	2 (3.0)	3 (4.4)	

KPS: Karnofsky performance status, AP: pemetrexed+cisplatin; GP: gemcitabine+cisplatin, DP: docetaxel+cisplatin, TP: taxol+cisplatin

Treatment regimens

All the patients received double-agent chemotherapy combining Endostar with third generation platinum drugs, including pemetrexed + cisplatin (AP) (n=29 and 25), gemcitabine + cisplatin (GP) (n=33 and 35), docetaxel + cisplatin (DP) (n=4 and 5) and paclitaxel + cisplatin (TP) (n=2 and 3). The dosage of Endostar was 15 mg (intravenous infusion for days 1-14 or continuous infusion via venous pump days 1-9). The specific regimens were as follows: AP regimen: pemetrexed (500 mg/m^2 for 1 d) + cisplatin (25 mg/m^2 for 1-3 d). GP regimen: gemcitabine (1000 mg/m^2 for 1 d) + cisplatin (25 mg/m^2 for 1-3 d) on the 8th day. DP regimen: docetaxel (75 mg/m^2 for 1 d) + cisplatin (25 mg/m^2 for 1-3 d). TP regimen: paclitaxel (175 mg/m^2 for 1 d) + cisplatin (25 mg/m^2 for 1-3 d). The patients in the experimental group were treated with chemotherapy and received intravenous infusion of recombinant human endostatin (15 mg/injection, Shandong Simcere-Medgenn Bio-pharmaceutical Co., Ltd.) at 15 mg/d on the 1st-14th day of each chemotherapy cycle. Chemotherapy was administered for 2-6 cycles with 21 d interval in each cycle. Azasetron was routinely used for antiemesis, and granulocyte colony-stimulating factors were utilized as needed. The NCCN guideline was adopted for subsequent treatment after disease progression.

Observation indexes

Short-term efficacy

Routine blood tests were performed twice a week during chemotherapy. Hepatic and renal function and electrocardiogram examinations were performed before each chemotherapy cycle, and CT examination was performed after every 2 chemotherapy cycles. The short-term efficacy was evaluated after at least 2 chemotherapy cycles, which was classified into complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) according to Response Evaluation Criteria in Solid Tumors 1.0. ORR is the sum of CR and PR, while DCR refers to the percentage of PR, CR and SD cases after treatment to the total evaluable cases.

Adverse reactions

According to the WHO grading standards for acute and subacute adverse reactions of anti-tumor drugs, the adverse reactions were divided into grades 0-IV.

Quality of life

Karnofsky performance status score of the patients was assessed before chemotherapy and at 2-6 cycles after chemotherapy.

Detection of serum tumor marker carcinoembryonic antigen (CEA)

Before chemotherapy and at 2-6 cycles after chemotherapy, electrochemiluminescence assay was adopted to determine the change in serum CEA level (normal value: 0.00-5.00 ng/mL).

Follow-up of survival

OS and PFS of all the patients were followed up and recorded, and the patients lost to follow-up were recorded as censored from the day of loss to follow-up. OS refers to the time from randomization to death due to any cause. PFS refers to the time from randomization to tumor progression in any aspect or death due to any cause.

Statistics

SPSS 22.0 (IBM, Armonk, NY, USA) was used for statistical analyses. The measurement data were expressed by mean ± standard deviation (x±s), and two-sample *t*-test was performed for inter-group comparison. The enumeration data were presented as ratio (%), x^2 test was used for inter-group comparison, and $p<0.05$ suggested that the difference was statistically significant. Kaplan-Meier method was used for survival analysis, log-rank test was utilized for comparison of the OS and PFS rates between two groups and $p<0.05$ suggested that the difference was statistically significant.

Results

Comparison of short-term efficacy

The efficacy was evaluated after all the patients completed the chemotherapy cycles. The mean number of chemotherapy cycles was 2.34 in the experimental group and 2.41 in the control group. In the experimental group, there was 1 case (1.5%) of CR, 32 cases (47.1%) of PR, 29 cases (42.6%) of SD and 6 cases (8.9%) of PD. The ORR was 48.5% (33 cases), and the DCR was 91.2% (62 cases). In the

Table 2. Clinical effective rates of the two studied groups

Responses	*Experimental group n (%)*	*Control group n (%)*	*p value*
CR	1 (1.5)	0 (0)	
PR	32 (47.1)	20 (29.4)	
SD	29 (42.6)	31 (45.6)	
PD	6 (8.9)	17 (25.0)	
ORR	33 (48.5)	20 (29.4)	0.035
DCR	62 (91.2)	51 (75.0)	0.021

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, ORR: objective response rate, DCR: disease control rate

control group, the cases of CR, PR, SD and PD were 0, 20 (29.4%), 31 (45.6%) and 17 (25.0%), respectively, and the ORR and DCR were 29.4% (20 cases) and 75.0% (51 cases), respectively. The differences in ORR and DCR between the two groups were statistically significant (p=0.035, p=0.021) (Table 2).

Comparisons of quality of life and serum CEA level after treatment

The average Karnofsky performance status score was 71.41±6.13 points in the experimental group and 72.83±8.30 points in the control group before treatment, with no statistically significant difference (p=0.259). After treatment, the score was increased in both groups [(72.92±7.44) points and (73.64±5.68) points], but there was no statistically significant difference (p=0.527). Before treatment, the average serum CEA level was 27.11±1.09 ng/mL and 26.95±1.33 ng/mL in the experimental and control group, respectively, displaying no statistically significant difference (p=0.444). However, the serum CEA level declined remarkably in both groups [(10.62±1.43) ng/mL and (11.07±2.02) ng/mL] after treatment, but there was no statistically significant difference (p=0.136) (Table 3).

Comparison of adverse reactions

During this research, the major adverse reactions included hematologic toxicity, nausea and vomiting, fatigue, mild fever, mild renal and hepatic dysfunction, mild cardiac toxicity and neurotoxicity (Table 4). There was no statistically significant difference in the occurrence of adverse reactions between the two groups of patients after treatment (p>0.05). In the two groups the cases of neutropenia were 23 (22.8%) and 18 (26.5%) (p=0.455), of reduced hemoglobin were 22 (32.4%) and 17 (25.0%) (p=0.449), of thrombocytopenia were 19 (27.9%) and 13 (19.1%) (p=0.312), of nausea and vomiting were 28 (41.2%) and 21 (30.9%) (p=0.284), and of diarrhea were 7 (10.3%) and 10 (14.7%) (p=0.605), with no statistically significant differences. Grade III-IV adverse reactions dominated by bone marrow depression and digestive system responses.

Table 3. Comparison of KPS scores and serum CEA levels of patients in the two studied groups (mean±SD)

Comparisons	*Experimental group*	*Control group*	*p value*
KPS score			
Pretreatment	71.41±6.13	72.83±8.30	0.259
Posttreatment	72.92±7.44	73.64±5.68	0.527
Serum CEA level (ng/ml)			
Pretreatment	27.11±1.09	26.95±1.33	0.444
Posttreatment	10.62±1.43	11.07±2.02	0.136

KPS: Karnofsky performance status, CEA: carcinoembryonic antigen

Table 4. Comparison of adverse reactions of patients in the two studied groups

Adverse reactions	*Experimental group n (%)*	*Control group n (%)*	*p value*
Fever	9 (13.2)	12 (17.6)	0.636
Fatigue	6 (8.9)	8 (11.8)	0.779
Rash	3 (4.4)	1 (1.5)	0.619
Neutropenia	23 (33.8)	18 (26.5)	0.455
Thrombocytopenia	19 (27.9)	13 (19.1)	0.312
Anemia	22 (32.4)	17 (25.0)	0.449
Nausea, vomiting	28 (41.2)	21 (30.9)	0.284
Diarrhea	7 (10.3)	10 (14.7)	0.605
Liver dysfunction	14 (20.6)	9 (13.2)	0.361
Renal dysfunction	5 (7.4)	2(2.9)	0.441
Arrhythmia	9 (13.2)	6 (8.9)	0.585
Palpitation/ chest distress	8 (11.8)	5 (7.4)	0.561
ECG ST-T change	10 (14.7)	5 (7.4)	0.273
Neuropathy	10 (14.7)	8 (11.8)	0.801

ECG: electrocardiogram

The ratio of patients with cardiac toxicity in the experimental group was higher than that in the control group (electrocardiogram manifested ventricular premature beat, atrial premature beat and ST-T segment change, and clinical symptoms included palpitation and chest tightness), but the difference was not statistically significant (p=0.064). The experimental group had 1 case of atrial premature beat, 1 case of stopped administration of recombinant human endostatin due to frequent ventricular premature beat and 1 case of grade III hepatic dysfunction. Most adverse reactions were in the controllable range and improved after symptomatic therapy.

Follow-up results of patient survival

All the 136 patients were followed up for 3-36 months after treatment until March 2019. The mean follow-up time was 29.6±7.8 months in the experimental group and 27.3±9.5 months in the control group. During follow-up, the 1-year OS rate was 63.2% (43/68) and 41.2% (28/68) in the experimental group and control group, respectively, and the PFS rate was 45.6% (31/68) and 32.4% (22/68), respectively. The 2-year OS rate was 47.1% (32/68) and 28.0% (19/68) in the experimental and control group, respectively, with PFS rate 26.5% (18/68) and 19.1% (13/68), respectively. Moreover, in the experimental and control group, the 3-year OS rate was 22.1% (15/68) and 8.9% (6/68), respectively, and the PFS rate was 14.7% (10/68) and 3.0% (2/68), respectively. The Kaplan-Meier survival (Figure 1) and the log-rank test showed that there were statistically significant differences in OS and PFS rates between the two groups of patients (p=0.019, p=0.009) (Figure 1).

Discussion

Most NSCLC patients are in advanced stage when first diagnosed, missing thus the opportunity of surgical resection. In clinical practice, only chemotherapy-based comprehensive treatment can relieve the symptoms of the patients, improve the quality of life and extend the survival time [11]. The response rate of chemotherapy regimens combining platinum drugs with paclitaxel, gemcitabine, vinorelbine, etc. on advanced NSCLC is only 30-40% [12]. The key parts of tumor growth and metastasis are associated with neovascularization. Studies have revealed that the antiangiogenic agent Endostar combined with chemotherapy drugs can increase the efficacy of chemotherapy in advanced NSCLC, without triggering more adverse reactions of chemotherapy and improve the quality of life of the patients [13]. As a multi-target endostatin, recombinant human endostatin is able to specifically repress the migration of new vascular endothelial cells. It can control tumor angiogenesis through multiple routes such as regulating the expression of vascular endothelial growth factor in tumor cells, thus suppressing tumor growth [14,15]. The main mechanism of action of Endostar combined with chemotherapy drugs is to (1) organize neovascularization, which is conducive to the chemotherapy drugs entering into the tumor cells, (2) induce apoptosis of endothelial cells, and (3) affect nutrient supply to tumor and inhibit the growth of tumor and micrometastases, thereby reducing tumor recurrence and metastasis [16].

Since Endostar was successfully marketed in China in 2005, randomized controlled clinical studies on the treatment of advanced NSCLC

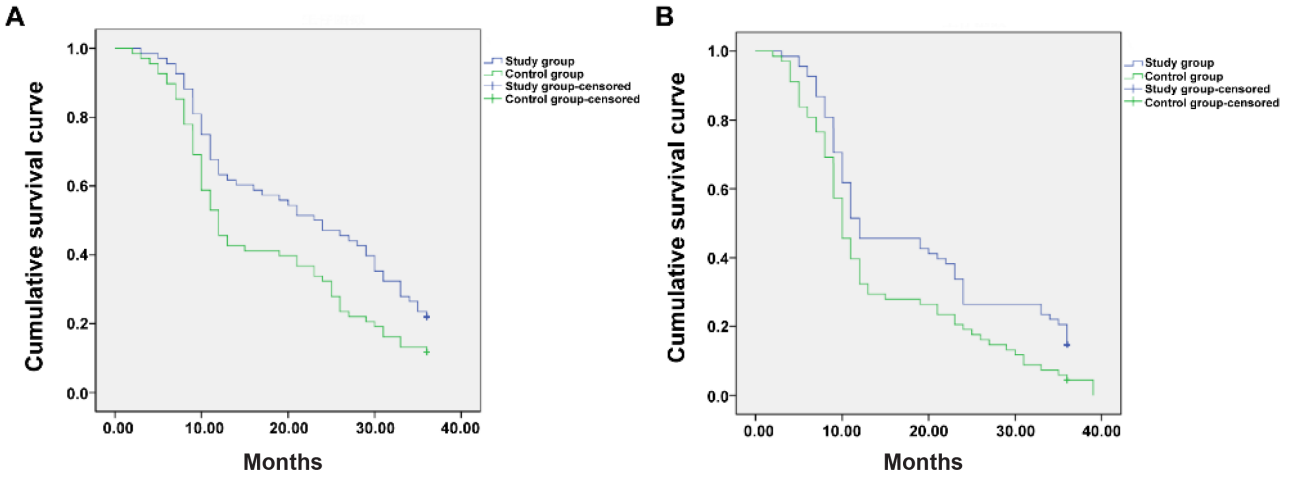

Figure 1. Kaplan-Meier survival curve of patients in the study and control group. **(A):** The overall survival rate of patients in the study group was significantly higher compared with those of the LARG group (p=0.019). **(B):** The progression-free survival rate of patients in the study group was significantly higher compared with those of the LARG group (p=0.009).

with recombinant human endostatin combined with other platinum-based regimens have been conducted one after the other, but the conclusions are not consistent. A majority of clinical studies have demonstrated that the combined therapies are capable of enhancing the short-term efficacy on advanced NSCLC, but their long-term efficacy is far from satisfactory, which needs to be clarified via large-sample randomized controlled trials [17]. The meta-analysis published by Rong et al. [18] in 2012 indicated that compared with those of platinum-based double-agent chemotherapy alone, the ORR and DCR of Endostar combined with chemotherapy are increased remarkably [ORR: odds ratio (OR)=1.69, 95% confidence interval (95% CI)=1.39 & 2.05, p<0.00001, DCR: OR=1.22, 95% CI=1.06 & 1.41, p=0.006]. Moreover, the quality of life is improved in experimental group, but the adverse reactions are similar to those in control group. In this research, it was discovered that after treatment, both the ORR and DCR in experimental group were superior to those in control group (p=0.035, p=0.021), the Karnofsky performance status score was raised in both groups, while the serum CEA level was lowered markedly, showing no statistically significant differences (p=0.444, p=0.136). The above results are basically consistent with those in previous studies except that the Karnofsky performance status score is quite different from literature reports in which the quality-of-life score is increased notably after treatment. The possible reason is the adverse reactions of chemotherapy [19].

The primary adverse reactions of recombinant human endostatin combined with chemotherapy include hematologic toxicity, gastrointestinal reaction, skin rash and cardiac toxicity. Several randomized controlled trials have revealed that the primary adverse reactions of Endostar combined with chemotherapy in treating advanced NSCLC resemble those of chemotherapy alone [17,18]. A few patients treated with Endostar may have toxic side effects in the heart, mainly manifested as myocardial ischemia, which is common in patients with a past history of coronary heart disease and hypertension. Those patients may have fatigue, chest tightness, palpitation and other manifestations. If the treatment is stopped, most patients will have sinus tachycardia, mild ST-T segment changes in electrocardiogram, atrioventricular block, atrial premature contraction and ventricular premature contraction. Those symptoms can return to normal after drug withdrawal or symptomatic therapy [20]. All the adverse reactions in this research were evaluable, and there was no treatment-related death. Most adverse reactions in the patients were mild, and grade III-IV adverse reactions mainly consisted of bone marrow depression and digestive system responses. The major manifestations of cardiac toxicity were on electrocardiogram, showing ventricular premature beat, atrial premature beat and ST-T segment change, and the primary clinical symptoms included palpitation and chest tightness. In the experimental group, 1 patient stopped receiving recombinant human endostatin due to frequent ventricular premature beat, but whether it was related to the drug remains unknown. According to this research, the incidence rate of adverse reactions was not increased by chemotherapy combined with recombinant human endostatin, the patients had good tolerance, and the adverse reactions were improved among all patients after the symptomatic therapy. The results of follow-up indicated that both OS and PFS rate had statistically significant differences between the two groups of patients (p=0.019, p=0.009), and the experimental group had evidently higher OS and PFS rate than the control group.

There were certain limitations in this research as it was a single-center retrospective study. The sample size was small, the follow-up time was short, and the potential impacts of different chemotherapeutic regimens on the efficacy in the two groups were not investigated. Therefore, large-sample, multi-center, prospective randomized controlled studies need to be further conducted in the future to testify the research results, thus providing references for selecting treatment protocols of advanced NSCLC in the clinic.

Conclusions

Recombinant human endostatin combined with chemotherapy has preferable short-term efficacy in treating advanced NSCLC. It can prolong the OS and PFS rate of the patients without increasing adverse reactions of chemotherapy, which makes it worth of clinical popularization.

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Conflict of interests

The authors declare no conflict of interests.

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