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ORIGINAL ARTICLE

Effect of thoracic hyperthermic perfusion with recombinant human endostatin plus nedaplatin in treating pleural effusion in patients with advanced non-small cell lung cancer

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Summary

Purpose: *To explore the efficacy and safety of thoracic hyperthermia perfusion with recombinant human endostatin plus nedaplatin in the treatment of pleural effusion in patients with advanced non-small cell lung cancer (NSCLC).*

Methods: *A retrospective analysis was conducted on the clinical data of 122 advanced NSCLC patients with pleural effusion, and among them, 61 received thoracic hyperthermic perfusion with recombinant human endostatin (ES) plus nedaplatin (Endostatin group), while the other 61 underwent thoracic hyperthermic perfusion with cisplatin alone (Cisplatin group). The short-term efficacy, changes in the pleural effusion and serum immunological indicators before and after treatment, quality of life, and incidence of adverse reactions were compared between the two groups of patients. Finally, the progression of pleural effusion in patients were followed up and recorded.*

Results: *After treatment, the overall response rate of patients in Endostatin group was considerably higher than that in Cisplatin group (p=0.030). At 2 weeks after treatment, the level of alanine transferase (ALT) rose notably, while that of carcinoembryonic antigen (CEA) declined dramatically in both groups of patients, and the patients in Endostatin group had markedly lower levels of ALT and CEA than those in Cisplatin group (p=0.007, p=0.003). After treatment, the Karnofsky Performance status (KPS) score of patients was prominently raised in the two groups, and Endostatin group exhibited considerably higher KPS scores than Cisplatin group (p=0.045). The incidence rates of nausea and vomiting as well as diarrhea in Endostatin group were prominently lower than those in Cisplatin group (p=0.039, p=0.048). According to the follow-up results, the median time to the progression of pleural effusion in Endostatin group was markedly longer than that in Cisplatin group (p=0.008).*

Conclusions: *Compared with the thoracic hyperthermic perfusion with cisplatin alone, the thoracic hyperthermic perfusion with recombinant human endostatin plus nedaplatin showed dramatically potential efficacy, decrease of the incidence rate of adverse reactions in the digestive system, improvement of quality of life of patients, and prolongation of progression of pleural effusion.*

Key words: *non-small cell lung cancer, pleural effusion, recombinant human endostatin, nedaplatin, hyperthermic perfusion*

Introduction

Malignant pleural effusion (MPE), also defined as cancerous pleural effusion and malignant pleural fluid, is the most common and uncontrollable complication of advanced lung cancer. When large amounts of pleural effusion are produced rapidly, chest tightness, cough and dyspnea will occur in patients, greatly decreasing their quality of life [1]. Moreover, the survival is only several months, and if no treatment measures are taken promptly, the mortality rate will be 29-50% and the median sur-

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vival will be no longer than 6 months. Therefore, reducing pleural effusion is the primary approach to improving the quality of life of advanced lung cancer patients [2,3]. Intraperitoneal chemoperfusion alone has limited efficacy, while intraperitoneal chemotherapy drugs combined with hyperthermic perfusion have the pharmacokinetics advantage of topically high effectiveness, and such combination has sensitizing and synergistic effects according to the studies [4,5].

Endostatin, an endogenous anti-angiogenic factor, specifically inhibits the migration and induces apoptosis of endothelial cells, especially microvascular endothelial cells, thereby repressing angiogenesis and tumor growth, which has become a novel strategy to treat tumors in recent years [6,7]. The present study, therefore, compared the thoracic hyperthermic perfusion with recombinant human endostatin plus nedaplatin with the thoracic hyperthermic perfusion with cisplatin alone in the treatment of pleural effusion in patients with advanced NSCLC, so as to explore the clinical efficacy and safety of the combination therapy and provide a potent basis for the options of clinical treatment regimens for such patients.

Methods

General data

A total of 122 NSCLC patients admitted to and treated in our hospital from January 2016 to December 2017 were enrolled based on the following criteria: Inclusion criteria: 1) Patients definitely diagnosed via histopathology; 2) those with clinical stage IV cancer based on the TNM staging criteria for lung cancer (IASLC 2009) after chest CT, contrast-enhanced whole-body MRI and fiberoptic bronchoscopy; 3) those with confirmed pleural effusion and positive for cancer cells in the pleural fluid; 4) those with predicted survival >3 months; and 5) those with Karnofsky Performance Scale (KPS) score ≥60 points. Exclusion criteria: 1) Patients with severe coagulation disorder; 2) those with systemic vasculitis, cardiovascular disease, diabetes, pulmonary hypertension or infectious diseases; 3) those with severe liver or lung dysfunction; 4) those with extensive adhesions in the thoracic cavity or encapsulated pleural effusion; or 5) those with obvious symptoms of brain metastasis or cognitive dysfunction.

The patients receiving thoracic hyperthermic perfusion with recombinant human endostatin plus nedaplatin were selected as the Endostatin group (n=61), whereas those undergoing thoracic hyperthermic perfusion with cisplatin alone as the Cisplatin group (n=61). Of them, there were 78 males and 44 females, with mean age of 54.16±7.05 years, and the pre-treatment baseline data were not statistically significantly different between two groups of patients (p>0.05) (Table 1). The present study was approved by the Ethics Committee of the Second Affiliated Hospital of Fujian Medical University. Moreover, the Declaration of Helsinki was strictly follow by, and all the patients were informed and signed the informed consent form.

Treatment schemes

After the preparations were completed before treatment, the patients underwent B ultrasound-guid-

Table 1. Baseline characteristics of the studied patients

Parameters	*Endostatin group (n=61)* n (%)	*Cisplatin group (n=61)* n (%)	*p value*
Age (years)	53.6±6.9	54.8±7.3	0.353
Gender			
Male	37 (60.7)	41(67.2)	0.572
Female	24 (39.3)	20(32.8)	
Pathological type			0.543
Squamous cell carcinoma	21(34.4)	19 (31.1)	
Adenocarcinoma	37 (60.7)	36(59.0)	
Others	3 (4.9)	6 (9.8)	
Smoking history			0.467
Yes	35 (57.4)	31 (50.8)	
No	26 (42.6)	30 (49.2)	
Volume of pleural effusion			0.332
Moderate	39 (63.9)	44 (72.1)	
Large	22 (36.1)	17 (27.9)	
KPS score			0.266
60-70	40 (65.6)	34 (55.7)	
70-80	21 (34.4)	27 (44.3)	

KPS: Karnofsky performance status

ed pleurocentesis and intubation. Then, a hyperthermic perfusion machine was connected to drain the pleural effusion, and the pleural cavity with effusions was rinsed using 1,000 mL of 0.9% sodium chloride heated to 42.5°C. The pleural effusion was drained at no more than 1,000 mL/time, after which drugs started to be injected into the pleural cavity and retained. After 2 days, no pleural effusion flowed out, and as confirmed by B-ultrasound examination, all the pleural effusions were drained out. Cisplatin group: First, 60 mg/m^2 cisplatin and 10 mg of dexamethasone were dissolved in 100 mL of normal saline, and the total solution was divided equally into two parts to be intrathoracically perfused into patients. Moreover, the patients were told to frequently change the posture to facilitate the full contact of drugs and foci within 30 min after the perfusion. The above treatment was performed twice/week for 2 courses, with 21 days as a treatment course. Two days after the treatment, the efficacy was evaluated. Endostatin group: The patients were intrathoracically perfused with two equal parts of the total solution containing 60 mg/m^2 nedaplatin, 45 mg of recombinant human endostatin and 10 mg of dexamethasone dissolved in 100 mL of normal saline, and they were asked to frequently change their postures to enable the drugs to fully contact foci within 30 min after the perfusion. This treatment was conducted twice/week for 2 courses, with 21 days as a treatment course. Two weeks after treatment, efficacy evaluation was performed. Additionally, the vital signs, routine blood parameters, liver and kidney function indicators, electrocardiographic responses and adverse reactions of the patients were closely monitored during the treatments.

Observation indicators

Short-term efficacy: The treatment outcomes of patients were assessed based on the evaluation criteria for the efficacy of MPE put forward by the World Health Organization. Complete remission (CR): Complete disappearance of pleural effusion for more than 4 weeks; partial remission (PR): a <50% decrease in pleural effusion for more than 4 weeks and no need for draining the pleural effusion within 1 month; stable disease (SD): a <5% decrease in pleural effusion for more than 4 weeks; and progressive disease (PD): No change or increase in the amount of pleural effusion. After treatment, the CR and PR of pleural effusion were regarded as response to treatment (CR+PR), while the progressive and stable MPE as no response to treatment (SD+PD). The time to the progression of pleural effusion was defined as the duration from the end of treatment to the progression of pleural effusion.

Before treatment and at 2 weeks after treatment, 10 mL of fasting venous blood was drawn from the patients in the morning. Then, the levels of carcinoembryonic antigen (CEA) and alanine transferase (ALT) were determined. The circulating endothelial cells (CECs) and activated CECs (aCECs) in the peripheral blood were counted via three-color flow cytometry as follows: Before and after treatment, 2 mL of fasting peripheral blood was collected from the patients in the morning, slowly infused into the lymphocyte extraction solution and centrifuged. The mononuclear cells were harvested, added with PBS (3:1) and centrifuged. Subsequently, 100 μL of cell suspension was taken into flow cytometry tubes, added with 300 μL of erythrocyte lysis buffer and subjected to water bath at 37°C for 10 min. Finally, the number of CECs and aCECs was measured using a flow cytometer.

Adverse reactions were evaluated based on the NCI Common Terminology Criteria for Adverse Events Version 4.0. During treatment, the adverse reactions, including myelosuppression, gastrointestinal reactions, fatigue, arrhythmia, and liver and kidney damage were monitored and recorded in all of the patients. Besides, the improvement in the quality of life of patients was assessed based on the KPS scores before and after treatment.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were presented as mean ± standard deviation, and the comparisons between the two groups were made using t-test. In addition, clinical data were compared via x^2 test or Fisher's exact test. A paired sample *t*-test was performed for the intragroup analysis of immunological indicators, while the intergroup comparisons were made via two-way analysis of variance. The comparison of the time to progression of pleural effusion was analyzed using the Kaplan-Meier method, and subjected to log-rank test. P<0.05 suggested statistically significant differences.

Results

Comparison of short-term efficacy

At 2 weeks after treatment, the efficacy was evaluated in all of the patients. Based on the results, the Endostatin group had 7 (11.5%) cases of

Table 2. Clinical effective rates of pleural effusion of the studied patients

	Endostatin group (n=61) n (%)	*Cisplatin group (n=61)* n (%)	*p value*
CR	7 (11.5)	3 (4.9)	
PR	30 (49.2)	22 (36.1)	
SD	15 (24.6)	19 (31.1)	
PD	9 (14.8)	17 (27.9)	
ORR	37 (60.7)	25 (41.0)	0.030

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: overall response rate

CR, 30 (49.2%) cases of PR, 15 (24.6%) cases of SD and 9 (14.8%) cases of PD, whereas there were 3 (4.9%) cases of CR, 22 (36.1%) cases of PR, 19 cases (31.1%) of SD and 17 (27.9%) cases of PD in the Cisplatin group. The overall response rate of patients in the Endostatin group [60.7% (37)] was notably higher than in the Cisplatin group [41.0% (25)] (p=0.030) (Table 2).

Comparisons of serum indicators and quality-of-life KPS scores before and after treatment between the two groups of patients

Before treatment, no statistically significant differences in the levels of ALT and CEA were observed between the two groups of patients (p>0.05). At 2 weeks after treatment, the level of ALT rose notably, while that of CEA declined dramatically in both groups of patients, and the patients in the Endostatin group had lower levels of ALT and CEA than those in the Cisplatin group, with statistically significant differences (p=0.007, p=0.003). Before treatment, the difference in the KPS score between the two groups of patients was not statistically significant (p>0.05). At 2 weeks after treatment, the KPS score was prominently elevated in the two groups of patients, and it was considerably higher in the Endostatin group than that in the Cisplatin group (p=0.045) (Table 3).

Comparison of number of peripheral blood CECs and aCECs between the two groups of patients

Before treatment, the number of peripheral blood CECs and aCECs was not statistically significantly different between the two groups (p>0.05). After treatment, the number of peripheral blood CECs and aCECs declined substantially in the two groups (p<0.05), and the patients in the Endostatin group had notably fewer CECs and aCECs in the peripheral blood than those in the Cisplatin group (p=0.005, p=0.022) (Table 4).

Comparisons of adverse reactions

During perfusion, none of the adverse reactions such as chest tightness, shortness of breath, palpitation and chest pain occurred in the patients. In the Endostatin group, fatigue appeared in 20 cases, nausea and vomiting in 17 cases, diarrhea in 13 cases, anemia in 9 cases, neutropenia in 8 cases, thrombocytopenia in 6 cases, and arrhythmia in 4 cases, whereas they appeared in 24, 29, 24, 11, 13, 3 and 6 cases, respectively in the Cisplatin group. All the adverse reactions occurring were of grade I-II and relieved after symptomatic treatments, without influence on the treatment. The incidence rates of nausea and vomiting as well as diarrhea in the Endostatin group were prominently lower than those

Table 3. Comparison of ALT and serum CEA levels of patients in the two studied groups

	Endostatin group	*Cisplatin group*	*p value*
ALT (U/L)			
Pretreatment	27.94±5.03	28.64±6.11	0.491
Posttreatment	67.62±7.47	71.68±8.90	0.007
Serum CEA level (ng/mL)			
Pretreatment	44.33±6.19	45.95±7.31	0.189
Posttreatment	26.88±5.93	30.07±5.82	0.003
KPS score			
Pretreatment	68.51±8.23	69.43±8.11	0.535
Posttreatment	75.72±8.24	72.65±8.53	0.045

ALT: alanine transaminase; CEA: carcinoembryonic antigen; KPS: Karnofsky performance status

Table 4. Comparison of pretreatment and posttreatment CECs and aCECs numbers of patients in the two studied groups

	Endostatin group	*Cisplatin group*	*p value*
CECs			
Pretreatment	3503±1234	3350±1381	0.523
Posttreatment	2562±1167	3177±1190	0.005
aCECs			
Pretreatment	1443±689	1495±730	0.496
Posttreatment	884±291	1069±552	0.022

CECs: circulating endothelial cells; aCECs: activated circulating endothelial cells

Table 5. Comparison of adverse reactions of patients in the two studied groups

Parameters	*Endostatin group (n=61)* *n (%)*	*Cisplatin group (n=61)* *n (%)*	*p value*
Fatigue	20(32.8)	24(39.3)	0.451
Neutropenia	8 (13.1)	13 (21.3)	0.231
Thrombocytopenia	6 (9.8)	3 (4.9)	0.299
Anemia	9 (14.8)	11 (18.0)	0.625
Nausea, vomiting	17(27.9)	29(47.5)	0.039
Diarrhea	13 (21.3)	24(39.3)	0.048
Liver dysfunction	1(1.6)	3 (4.9)	0.618
Renal dysfunction	1(1.6)	4(6.6)	0.365
Arrhythmia	4(6.6)	6 (9.8)	0.509

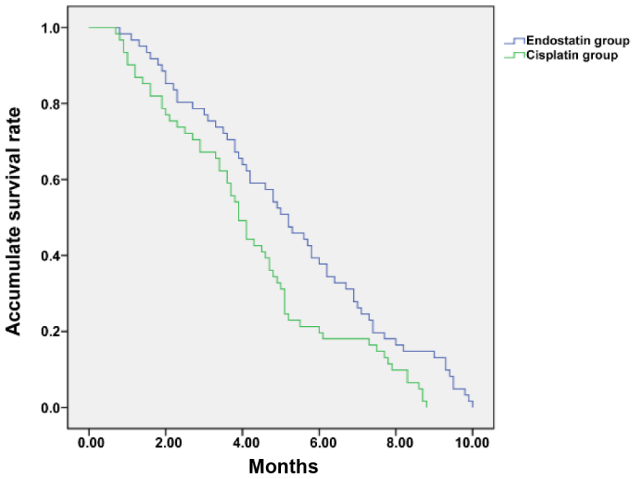

Figure 1. Kaplan-Meier progression-free curve of the studied patients. The pleural effusion progression-free rate of patients in the Endostatin group was significantly higher than in the Cisplatin group (p=0.008).

in the Cisplatin group (p=0.039, p=0.048), and no statistically significant differences in the incidence rates of the other adverse reactions were observed between the two groups (p>0.05) (Table 5).

Comparison of time to progression of pleural effusion in patients

According to the follow-up results, the median time to progression of pleural effusion in the Endostatin group was markedly longer than in the Cisplatin group (4.2 months *vs.* 3.6 months, p=0.008). Kaplan-Meier progression-free survival (PFS) is shown in Figure 1 and reveals that it was significantly higher in the Endostatin group compared with the Cisplatin group.

Discussion

Large amounts of pleural effusion, a common complication of end-stage lung cancer, can compress lung tissues and the heart to cause respiratory distress or circulatory dysfunction and even mediastinal shift in severe cases, endangering the life of patients [8]. In recent years, the combination of intrathoracic perfusion chemotherapy drugs and hyperthermia has achieved favorable efficacy in treating MPE in lung cancer patients [9,10]. Cisplatin is now the most extensively used chemotherapeutic drug for intrathoracic perfusion, with the most definite efficacy. Its concentration in the thoracic cavity is 20 times that in the plasma. The intrathoracic perfusion of cisplatin can directly kill the cancer cells on the pleura and in the thoracic cavity, and the resulting chemical pleurisy can induce pleural sclerosis, and decrease the further effusion of pleural fluid, thereby effectively controlling pleural effusion [11]. Hyperthermia and chemotherapy have synergistic effects. Hyperthermic chemoperfusion has the following advantages: 1) killing cancer cells by hyperthermia; 2) enhancing the permeability (up to 5 mm-direct penetration depth) and cytotoxicity of some chemotherapeutic drugs to induce tumor cell apoptosis; and 3) producing heat shock proteins, activating specific immune responses in the body and NK cells, and increasing DC cells to promote antigen-presenting effect [12]. However, cisplatin produces relatively obvious adverse reactions, and the promoting effect of tumor tissues on neovascularization fails to be repressed, so some patients experience recurrence of pleural effusion. Nedaplatin, as a new-generation platinum anticancer drug, causes distinctly milder adverse reactions in the treatment than cisplatin, and since the water-solubility of nedaplatin is far higher than that of cisplatin, the penetration depth and potency of nedaplatin in local tissues are also much higher than those of cisplatin [13,14]. Moreover, the application of nedaplatin tends to achieve preferable efficacy in some patients resistant or insensitive to cisplatin.

A growing number of studies has demonstrated that the growth and metastasis of malignant

tumors are associated with neovascularization [15]. Endostar, a self-researched and self-developed recombinant human endostatin injection in China, can suppress the activation of nitric oxide synthases in endothelial cells and the expressions of B-cell lymphoma 2 (Bcl-2) and Bcl-XL and block the signal transduction mediated by the vascular endothelial growth factor to restrain angiogenesis, thereby reppressing tumor cell growth and metastasis [16]. According to studies, endostar combined with cisplatin can considerably improve malignant pleural effusion in NSCLC patients, lower the levels of serum tumor markers such as vascular endothelial growth factor and hypoxia-inducible factor 1α. With extremely low toxicity, endostar has been found through numerous studies to be able to collaborate with chemotherapeutic drugs [17].

In the present study, the thoracic hyperthermic perfusion with endostar plus nedaplatin was compared with the thoracic hyperthermia perfusion with cisplatin alone in treating pleural effusion in advanced NSCLC patients, and the results showed that the overall response rate of patients in the Endostatin group was considerably superior to the Cisplatin group (60.7% *vs.* 41.0%, p=0.030). Compared with the thoracic hyperthermic perfusion with cisplatin alone, the thoracic hyperthermic perfusion with endostar plus nedaplatin dramatically decreased the incidence rate of the adverse reactions in the digestive system. Based on the follow-up results, the time to progression of pleural effusion in the Endostatin group was remarkably longer than in the Cisplatin group (p=0.008). Compared with cisplatin, nedaplatin has a wider anti-cancer spectrum and produces fewer adverse reactions in the digestive system, and the patient does not need to be hydrated before application due to its higher water-solubility, thereby simplifying the treatment procedures and improving the compliance of patients during treatment [18].

CECs serve as the specific and direct indicators for vascular injury in the body, and large numbers of studies have demonstrated that the content of peripheral blood is correlated with the growth of tumors to some extent. Mancuso et al found that the level of CECs in the peripheral blood in patients with breast cancer and lymphoma is higher than in normal people [19]. Monestiroli et al [20] researched the correlation between CECs and tumors through animal experiments and discovered that CECs are associated with tumor volume, indicating that the increase in CECs is correlated with tumor progression. Beerepoot et al [21] reported that the patients with progressive tumors have evidently more CECs in the body, while the number of CECs in the patients at the stable stage is nearly equal to that in normal people. Therefore, it can be inferred that the increase in the level of CECs is one of the markers for cancer progression in patients. The CECs in the peripheral blood of lung cancer patients can be taken as predictive indicators to evaluate the tumor angiogenesis and prognosis of lung cancer patients well. ACECs represent only a minority of mature CECs, while most mature CECs are dormant and apoptotic. ACECs can reflect the activity of tumor neovascularization, so they can be used as an ideal marker for predicting the anti-angiogenic effect and reflecting prognosis [22]. In the present study, it was found that the patients in the Endostatin group had markedly fewer CECs and aCECs in the peripheral blood than those in the Cisplatin group after treatment (p=0.005, p=0.22). Hence, in the present study it was held that the thoracic hyperthermic perfusion with endostar plus nedaplatin was safe and efficacious in the treatment of pleural effusion in advanced NSCLC patients, since this combination therapy effectively reduced the number of peripheral blood CECs and aCECs and inhibited neovascularization to prevent tumor cells from continuing to invade pleural tissues.

This single-center retrospective study has certain limitations: the sample size was not large enough, the follow-up time was shorter, and the follow-up content was not comprehensive enough. Therefore, large-scale prospective multi-center randomized controlled trials remain to be designed more vigorously and scientifically to corroborate the results of this study, so as to provide reference bases for the options of the treatment schemes for pleural effusion in advanced NSCLC patients.

Conclusions

Compared with the thoracic hyperthermic perfusion with cisplatin alone, the thoracic hyperthermic perfusion with recombinant human endostatin plus nedaplatin can dramatically potentiate the efficacy, decrease the incidence rate of adverse reactions in the digestive system, improve the quality of life of patients, and delay the progression of pleural effusion.

Conflict of interests

The authors declare no conflict of interests.

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