Effect of Endostar combined with Paclitaxel on the proliferation and migration of metalloproteinases and tumor cells in NSCLC patients

Qi Yong-Jian¹, Zeng Xue-Hua¹, Lai Ju-Ju², Zha Wang-Jian³

¹ Department of Respiratory Medicine, Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing 210029, Jiangsu, China  
² Department of Cardiology Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210000, Jiangsu, China  
³ Department of Respiratory & Critical Care Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210000, Jiangsu, China

ARTICLE INFO

Objective: To explore the effect of endostar combined with taxol on tumor markers, vascular endothelial growth factor, neuron-specific enolase, metalloproteinase and tumor cell proliferation and migration in NSCLC patients. Methods Patients with advanced NSCLC were studied. The patients in the control group received chemotherapy with paclitaxel combined with cisplatin. Patients in the combination group received intravenous infusion of endostar on the basis of treatment of patients in the control group. 21 days was a cycle, and all patients were treated for 2 cycles. Fasting venous blood 3mL of all patients before and after treatment was collected, and CEA and saccharide antigen (CA50) were detected by radioimmunoassay. Vascular endothelial growth factor (VEGF), neuron-specific enolase (NSE), serum matrix metalloproteinase (MMP-2, MMP-9), high-mobility family protein at-hook 2 (HMGA 2) and high-mobility family protein B 1 (HMGB 1) were detected by ELISA. Results There were no significant differences in serum CA50, CEA, VEGF, NSE, MMP-2, MMP-9, HMGB 1, and HMGA 2 between the two groups before treatment (P>0.05). After two courses of chemotherapy, CA50, CEA, VEGF, NSE, MMP-2, MMP-9, HMGB 1, and HMGA 2 in the combination group and control group were significantly lower than before treatment (P<0.05), and the combination group was significantly lower than the control group (P<0.05). Conclusion Endostar combined with paclitaxel can enhance the chemotherapy effect of NSCLC patients, reduce the level of serum tumor markers, neuronal specific enolase and vascular endothelial growth factor, and inhibit the proliferation and migration of tumor cells.

1. Introduction

Non-small cell lung cancer (NSCLC) is the main type of clinical lung cancer. The early clinical symptoms are not obvious. It is already in the advanced stage at the time of diagnosis. It has lost the best time for surgery. Therefore, conservative treatment has become the main treatment for patients with advanced NSCLC [1]. And chemical drugs can significantly inhibit the progress of cancer, and even kill tumor cells, but the effect of chemotherapy alone is limited [2]. Endostar is a targeted drug against tumor blood vessels, and its combination with chemotherapy for malignant tumors has a significant clinical effect and is a first-line treatment for malignant tumors [3, 4]. However, there are few reports on the effects of Endostar and paclitaxel on angiogenesis, metalloproteinases and neurological function in patients with NSCLC. Therefore, this study selected patients with advanced NSCLC as a research object to investigate the effect of Endostar combined with paclitaxel angiogenesis, metalloproteinases and neurological functions in patients with NSCLC.

2 Materials and methods

2.1 Clinical data

NSCLC patients who were treated in our hospital from June 2014 to February 2019 were enrolled in the study. Totally 81 patients with...
NSCLC who were included in the study were randomly assigned to the Endostar group and the control group, and 39 patients in the Endostar group, there were 25 males, 14 females, 13 patients in stage III, 26 cases in stage IV, 20 cases of adenocarcinoma, 12 cases of squamous cell carcinoma, 7 cases of adenosquamous carcinoma, aged 49-78 years, and 42 cases in the control group, including 27 males, 15 females, 14 cases of stage III, 28 cases of stage IV, 21 cases of adenocarcinoma, 13 cases of squamous cell carcinoma, and 8 cases of adenosquamous carcinoma, aged 47-79 years old. There were no significant differences in gender, TNM stage, pathological type, age and other general data between the two groups (P>0.05). All patients were informed to the study and the Medical Ethics Committee approved the study.

Inclusion criteria: (1) in accordance with NSCLC diagnostic criteria; (2) pathological biopsy confirmed as NSCLC; (3) TNM staging is stage III-IV; (4) estimated survival > 3 months; (5) No other related treatment has been provided (tumor resection, radiotherapy and chemotherapy, etc.); (6) those who can tolerate chemotherapy; (7) those who received treatment for the first time; (8) KPS scores > 60 points.

Exclusion criteria: (1) those who took anticoagulant drugs before enrollment; (2) those with other malignant tumors; (3) who were allergic to the study; (4) those with severe organ dysfunction such as liver and kidney; (5) Those with bleeding tendency; (6) those with severe cardiovascular and cerebrovascular diseases; (7) those with acute or chronic infectious diseases.

### 2.2 Treatment

The patients in the control group were treated with paclitaxel plus cisplatin. On the first day of the chemotherapy cycle, paclitaxel injection (Yangtongjiang Pharmaceutical Group Co., Ltd., Approval number H20058719) diluted in 500 mL of normal saline was intravenously infused with 150 mg/m2. The time was not less than 3 hours; cisplatin (Qilu Pharmaceutical Co., Ltd., Approval number H37021362) diluted in 500 mL of normal saline was intravenously injected 75 mg/m2, and dispensed in 3 days, respectively, from the first day to the third day of the chemotherapy cycle, and 21 days is a chemotherapy cycle. On the basis of the treatment of the control group, the patients in the Endostar group were treated with intravenous infusion of recombinant human endostatin injection (Shandong Xiansheng Bio-Pharmaceutical Co., Ltd., approval number S20050088), from the first day to 14th day in the chemotherapy cycle, 15 mg of endostar diluted in 500 mL of normal saline was instilled every day, the intravenous infusion time was not less than 3 h, and 21 days was 1 cycle, and all patients were treated for 2 cycles.

### 2.3 Detection method

3 mL of the patient's fasting venous blood was collected before and after treatment. Carcinoembryonic antigen (CEA) and carbohydrate antigen (CA50) were detected by radioimmunoassay after centrifugation. Neuron-specific enolase (NSE) assay. Serum matrix metalloproteinases (MMP-2, MMP-9), vascular endothelial growth factor (VEGF), high mobility group protein AT-hook 2 (HMGA 2) and high mobility group protein B 1 (HMGB 1) were detected by ELISA. The kit used in this study was provided by Beijing Putian Tongchuang Biotechnology Co., Ltd. and Beijing Zhongshang Jinqiao Bioengineering Co., Ltd.

### 2.4 Statistical methods

Statistical analysis was performed using SPSS 20.0. The measurement data in the text were indicated by (X±s). The independent t test was used to compare the two groups of patients. The paired t test was used before and after treatment in the same group. The test level was α =0.05.

### 3 Results

#### 3.1 Comparison of tumor markers before and after treatment of NSCLC patients in two groups

There was no significant difference in serum CA50 and CEA between the two groups before treatment (P>0.05). After 2 courses of treatment, the CA50 of the Endostar group and the control group were (21.09±4.17) U/mL and (18.34±4.30) U/mL, respectively, which were significantly lower than before treatment (P<0.05), and the degree of endostar combined group was significantly lower than that of the control group (P<0.05). The CEA of the endostar combined group and the control group were (14.63±3.15) ng/mL and (17.34±3.86) ng/mL, respectively, which were significantly lower than before treatment (P<0.05), and the Endostar group was dramatically lower than the control group (P<0.05). See Table 1.

### Table 1

Comparison of tumor markers before and after treatment between two groups of NSCLC patients (X±s)

<table>
<thead>
<tr>
<th>Group</th>
<th>Cases</th>
<th>CA50 (U/mL)</th>
<th>CEA (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td><strong>t</strong></td>
<td>1.287</td>
<td>2.916</td>
<td></td>
</tr>
<tr>
<td><strong>P</strong></td>
<td>0.202</td>
<td>0.005</td>
<td></td>
</tr>
</tbody>
</table>

| **t**          | 7.310 | 6.753       |              |               |               |
| **P**          | 0.000 | 0.000       |              |               |               |

There was no significant difference in serum CA50 and CEA between the two groups before treatment (P>0.05). After 2 courses of treatment, the CA50 of the Endostar group and the control group were (21.09±4.17) U/mL and (18.34±4.30) U/mL, respectively, which were significantly lower than before treatment (P<0.05), and the degree of endostar combined group was significantly lower than that of the control group (P<0.05). The CEA of the endostar combined group and the control group were (14.63±3.15) ng/mL and (17.34±3.86) ng/mL, respectively, which were significantly lower than before treatment (P<0.05), and the Endostar group was dramatically lower than the control group (P<0.05). See Table 1.
3.2 Comparison of tumor cell migration factors before and after treatment of NSCLC patients in two groups

There was no significant difference in serum HMGB 1 and HMGA 2 between the two groups before treatment ($P>0.05$). After 2 courses of treatment, the HMGB 1 of the Endostar group and the control group were (1.01±0.32) ng/mL and (1.41±0.24) ng/mL, respectively, which were significantly lower than before treatment ($P<0.05$). The Endostar group was significantly lower than the control group ($P<0.05$). The HMGA 2 in the combined group and the control group were (0.93±0.15) ng/mL and (1.16±0.13) ng/mL, respectively, which were significantly lower than before treatment ($P<0.05$), and the Endostar group was significantly lower than the control group ($P<0.05$). See Table 2.

3.3 Comparison of metalloproteinases in patients with NSCLC before and after treatment of both group

There were no significant differences in serum MMP-2 and MMP-9 between the two groups before treatment ($P>0.05$). After 2 courses of treatment, MMP-2 in the Endostar group and the control group were (76.53±9.52) ng/mL and (93.79±14.06) ng/mL, respectively, which were significantly lower than before treatment ($P<0.05$). The Endostar group was significantly lower than the control group ($P<0.05$). The MMP-9 in the combined group and the control group were (364.48±32.78) pg/mL and (457.87±46.02) pg/mL, respectively, which were significantly lower than before treatment ($P<0.05$), and both significantly lower than before treatment ($P < 0.05$), and the Endostar group was significantly lower than the control group ($P<0.05$). See Table 3.

3.4 Comparison of VEGF and NSE before and after treatment in two groups of NSCLC patients

There was no significant difference in serum VEGF and NSE between the two groups before treatment ($P>0.05$). After 2 courses of treatment, the VEGF of the Endostar group and the control group were (364.48±32.78) pg/mL and (457.87±46.02) pg/mL, respectively, which were significantly lower than before treatment ($P<0.05$), and the degree of combined group was significantly lower than that of the control group ($P<0.05$). The NSE of the combined group and the control group were (19.69±3.10) ng/L and (25.61±5.60) ng/L, respectively, both significantly lower than before treatment ($P < 0.05$), and the Endostar group was significantly lower than the control group ($P<0.05$). See Table 4.

4 Discussion

At present, chemotherapy, surgery, molecular targeted therapy are the main treatment methods for clinical NSCLC, but for patients who have lost the optimal timing of surgery, conservative treatment with chemotherapy and molecular targeted therapy has become the main treatment method [5]. Tumor internal angiogenesis is the basis for the development of NSCLC, which can promote tumor cell migration and invasion [6]. The vascular manifestations, endothelial cell expression, and interstitial cell space of tumors are different from those of normal cells and blood vessels, which may cause insufficient blood perfusion inside the tumor, forming an oxygen-deficient environment and reducing the sensitivity of chemotherapy.
Related reports show that anti-angiogenic drugs can effectively inhibit the angiogenesis of tumor cells, and combined with chemotherapy has synergistic sensitization effect, clinical treatment of NSCLC is significant. Therefore, anti-angiogenesis has become a research hotspot for targeted therapy of NSCLC molecules. Endostar is a novel endostatin that inhibits tumor angiogenesis, normalizes tumor vasculature, blocks tumor cell nutrient channels, enhances tumor cell sensitivity to chemotherapy, and promotes tumor cell apoptosis [8]. According to related reports [9], Endostar combined with chemotherapy for advanced NSCLC can obtain a higher clinical benefit rate, long-term application can prolong the disease progression time, does not increase the toxicity of chemotherapy, safe and effective.

Tumor markers are serological indicators that change with the occurrence and development of malignant tumors, and are closely related to the degree of malignant tumors. Among them, CEA is an acidic glycoprotein with human embryonic antigen characteristics. The CEA value of patients with advanced cancer is significantly higher than that of the early stage. When the tumor metastasizes or the condition deteriorates, the concentration of CEA will increase. When the condition improves, the CEA concentration will decrease [10-11]. CA50 is a sugar chain antigen with a high positive detection rate in malignant tumors. It is generally not present in normal tissues. The presence of CA50 suggests the nature of the tumor, and its changes can be used to reflect the therapeutic effect of cancer [12, 13]. The results of this study showed that there was no significant difference in serum CA50 and CEA between the two groups before treatment. After two courses of chemotherapy, the CA50 and CEA of the Endostar group and the control group were significantly lower than before treatment, and the Endostar group was significant lower than the control group. It is suggested that paclitaxel combined with cisplatin is effective in the treatment of patients with advanced NSCLC. The combination of Endostar and paclitaxel can significantly enhance the therapeutic effect of patients with NSCLC. Ling Minwen [13] also showed that recombinant human endostatin combined with chemotherapy can effectively reduce serum tumor markers in patients with NSCLC.

Malignant tumors not only can cause changes in tumor markers, but also cause changes in the expression levels of factors related to tumor development. MMP-2 and MMP-9 belong to the matrix metalloproteinase family, which has the function of dissolving extracellular matrix and basement membrane. It can also participate in tumor angiogenesis by releasing VEGF, and promote the infiltration and metastasis of tumor cells to surrounding healthy tissues. It can indicate the degree of malignancy and invasiveness of the tumor [14, 15]. HMGB 1 and HMGA 2 are proteins involved in tumor cell migration. When cells undergo cancer, HMGB 1 and HMGA 2 are highly expressed, which is closely related to tumor invasion and metastasis [16-18]. The main pathological basis of tumor is VEGF. Therefore, by inhibiting VEGF, the expression of MMP-2, MMP-9, HMGB 1 and HMGA 2, which promote tumor invasion and migration, can be down-regulated, thereby inhibiting the proliferation, invasion and transfer of tumor cells. This study explored the effects of Endostar combined with paclitaxel and cisplatin chemotherapy on VEGF, MMP-2, MMP-9, HMGB 1, and HMGA 2 in patients with NSCLC. The results showed that there was no difference in serum VEGF, MMP-2, MMP-9, HMGB 1 and HMGA 2. After 2 courses of chemotherapy, VEGF, MMP-2, MMP-9, HMGB 1, and HMGA 2 were significantly lower than those before treatment, and the Endostar group was significantly lower than the control group. It is suggested that the combination of Endostar and paclitaxel chemotherapy can effectively reduce the levels of serum VEGF, MMP-2, MMP-9, HMGB 1 and HMGA 2 in NSCLC patients. The results of Xiaojing [19] showed that the levels of serum VEGF, MMP-2, and MMP-9 in patients treated with Endostar were significantly lower than those in the control group. The results of Zang Ye [20] showed that Endostar combined with chemotherapy can reduce the expression levels of HMGA 2 and HMGB 1 in serum of NSCLC patients, which are similar to the above.

NSE is an enolase distributed in neurons and neuroendocrine cells. The detection of serum NSE can be used for disease monitoring and efficacy evaluation of small cell lung cancer [21]. However, there are few reports on the changes of NSE in the treatment of NSCLC patients. Some scholars believed that NSE can be used as a sensitive indicator to evaluate the chemotherapy effect and disease progression of NSCLC [22]. Therefore, this study investigated the effect of Endostar combined with paclitaxel and cisplatin on serum NSE in patients with NSCLC. The results showed that there was no significant difference in serum NSE between the two groups before treatment. After treatment, the NSE levels of the two groups were significantly reduced, and the Endostar group was lower than the control group. It is indicated that can reduce serum NSE levels and reduce neuronal damage in patients with NSCLC. Xue Shan et al [22] found that NSE levels in patients with stage IIIb-IV non-small cell lung adenocarcinoma were significantly lower than those before chemotherapy, which was similar to the results of this study.

In summary, Endostar combined with paclitaxel chemotherapy can significantly alleviate the progress of NSCLC, reduce serum tumor markers and metalloproteinase levels, reduce damage to neurons, and inhibit angiogenesis and migration of tumor cells.

References


