Effects of recombinant human endostatin on therapeutic effect, angiogenesis, tumor cell proliferation and migration in patients with non-small cell lung cancer

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ABSTRACT

Objective: To investigate the effects of recombinant human endostatin on therapeutic effect, angiogenesis, tumor cell proliferation and migration in patients with non-small cell lung cancer. Methods: A total of 100 patients with non-small cell lung cancer treated in our hospital from September 2015 to March 2018 were selected as research subjects. They were randomly divided into observation group and control group, 50 cases in each group. The control group was treated with gemcitabine plus cisplatin, while the observation group was combined with Endostar treatment on the basis of the control group. Observed and compared the expression of the therapeutic effect (including cytokeratin 19 fragment (CYFRA21-1), carcinoembryonic antigen (CEA) and carbohydrate antigen (CA50)), angiogenesis (including vascular endothelial growth factor (VEGF) and hypoxia inducible factor (HIF-1 alpha)), tumor cell proliferation (including insulin-like growth factor (IGF-1) and insulin-like growth factor receptor -7 (IGFBP-7)) and migration (including high mobility group protein AT-hook2 (HMGA2) and high mobility group protein B1 (HMGB1)) in two groups. Results: The two groups showed significant changes in the therapeutic effect, angiogenesis, proliferation and migration of tumor cells. Before treatment, there was no significant difference in all levels between the two groups. After treatment, the levels of CYFRA21-1, CEA, CA50, VEGF, HIF-1a, IGF-1, HMGA2 and HMGB1 in the two groups were significantly lower than those before treatment, while the levels of IGFBP-7 were significantly higher than those before treatment. After treatment, the levels of CYFRA21-1, CEA, CA50, VEGF, HIF-1a, IGF-1, HMGA2 and HMGB1 in the observation group were significantly lower than those in the control group, while the levels of IGFBP-7 were significantly higher than those in the control group. Conclusions: Recombinant human endostatin can enhance the therapeutic effect of non-small cell lung cancer patients, reduce angiogenesis, inhibit tumor cell proliferation and migration and has a higher degree of malignancy. It is difficult to diagnose in the early stage, and most of them are in the middle and late stage of diagnosis[5,6], and metastasis has already occurred in the body. Even after surgery, the recurrence rate is higher[7]. For patients with advanced NSCLC, mainly chemoradiotherapy, but the effect is poor[8,9]. Recombinant human endostatin (Endo) is a synthetic endogenous anti-angiogenic substance that prevents tissue endothelial cell migration, inhibits tumor angiogenesis, and inhibits NSCLC well[10,11]. In view of this, this study mainly explored the effect of Endo on the efficacy, angiogenesis, tumor cell proliferation and migration of patients with NSCLC.
2. Materials and methods

2.1 Clinical data

One hundred patients with non-small cell lung cancer who were treated in our hospital from September 2015 to March 2018 were randomly divided into observation group and control group, with 50 cases in each group. The observation group included 33 males and 17 females; aged 53-75 years; Clinical stage IIIB 27 cases, stage IV 23 cases; adenocarcinoma 32 cases, squamous cell carcinoma 10 cases, and other 8 cases. The control group included 32 males and 18 females; aged 52-73 years; clinical stage IIIB, 24 cases, stage IV, 26 cases; adenocarcinoma, 31 cases, squamous cell carcinoma, 12 cases, and other 7 cases. There were no significant differences in the general data of gender, age, clinical stage and pathological type between the two groups. The difference was not statistically significant ($P>0.05$) and could be compared and analyzed. This study has been approved by the ethics Committee of our hospital, and patients or their families have signed informed consent.

Inclusion criteria: (1) patients were in accordance with the diagnostic criteria for non-small cell lung cancer [12], and confirmed by pathological biopsy; (2) TNM staging was III B-IV; (3) had not received other related surgery, radiotherapy and chemotherapy. Exclusion criteria: (1) exclude cancer metastasis patients with other malignant tumors; (2) exclude patients with severe organ dysfunction; (3) exclude patients who are allergic to the drug used in this study.

2.2 Treatment

The control group was treated with gemcitabine plus cisplatin, and the first day and the eighth day were intravenously infused with gemcitabine (Jiangsu Haosen Pharmaceutical Co., Ltd., approval number: Guoyao Zhunzi H201030104, specification 0.2 g) 1 000-1 250 mg/m$^2$; on the first day, intravenous infusion of cisplatin (Jiangsu Haosen Pharmaceutical Co., Ltd., National Pharmaceutical Standard H20110812) 75 mg/m$^2$. On the first to the fourteenth day of the observation group, Endo (Dongshen Maidjin Bio-Pharmaceutical Co., Ltd., Guoji Zhunzi S20050088) was given 7.5 mg/m$^2$ for treatment once a day. A 14-day cycle, both groups of patients were treated for one cycle.

2.3 Observation indicators

Sample collection: 5 mL of fasting venous blood was collected from the two groups before and after treatment, and centrifuged for 10 min to collect serum.

Observed indicators: cytokeratin 19 fragment (CYFRA21-1) was detected by electrochemical method; carcinoembryonic antigen (CEA) and carbohydrate antigen (CA50) were measured by radioimmunoassay; vascular endothelial growth factor (VEGF) was detected by enzyme-linked immunosorbent assay, hypoxia-inducible factor (HIF-1α), insulin-like growth factor (IGF-1), insulin-like growth factor receptor-7 (IGFBP-7), high mobility group protein AT-hook2 (HMGA2) and high migration Rate family protein B1 (HMGB1).

2.4 Statistical methods

The data were analyzed by SPSS 19.0 statistical software. The measurement data were expressed by mean ± standard deviation (Mean ± SD). The two groups were compared by independent sample t test. When $P<0.05$, the difference was considered statistically significant.

3. Results

3.1 Comparison of cancer treatment effects between the two groups of patients

Before treatment, there was no significant difference in CYFRA21-1, CEA and CA50 between the two groups ($P>0.05$). After treatment, the levels of CYFRA21-1, CEA and CA50 in the two groups were significantly lower than those before treatment ($P<0.05$). Patients in the observation group were CYFRA21-1 [(2.04±0.21) ng/mL], CEA [(10.07±2.59) ng/mL], and CA50 [(16.44±3.93) U/mL] levels compared with the control group [(3.52±0.31) The decrease of ng/mL, (18.17±3.80) ng/mL, (22.52±3.49) U/mL] was more obvious ($P<0.05$), as shown in Table 1.

Table 1. Comparison of cancer treatment effects between the two groups.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>CYFRA21-1 (ng/mL) Before treatment</th>
<th>After treatment</th>
<th>CEA (ng/mL) Before treatment</th>
<th>After treatment</th>
<th>CA50 (U/mL) Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>50</td>
<td>5.21±0.26</td>
<td>2.04±0.21$^*$</td>
<td>24.50±4.06</td>
<td>10.07±2.59$^*$</td>
<td>27.58±5.01</td>
<td>16.44±3.93$^*$</td>
</tr>
<tr>
<td>Control group</td>
<td>50</td>
<td>5.18±0.33</td>
<td>3.52±0.31$^*$</td>
<td>22.80±6.50</td>
<td>18.17±3.80$^*$</td>
<td>28.03±3.93</td>
<td>22.52±3.49$^*$</td>
</tr>
</tbody>
</table>

Note: $^*$: Compared with before treatment, $P<0.05$; $^+$: Compared with the control group after treatment, $P<0.05$. 
Comparison of tumor cell proliferation factor levels between two groups.

Table 3.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>VEGF (pg/mL) Before treatment</th>
<th>VEGF (pg/mL) After treatment</th>
<th>HIF-1 α (ng/L) Before treatment</th>
<th>HIF-1 α (ng/L) After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>50</td>
<td>509.18±155.96</td>
<td>353.79±110.33</td>
<td>64.28±7.76</td>
<td>37.53±2.69</td>
</tr>
<tr>
<td>Control group</td>
<td>50</td>
<td>517.48±134.00</td>
<td>436.23±134.00</td>
<td>64.45±9.30</td>
<td>49.44±3.62</td>
</tr>
</tbody>
</table>

Note: *: Compared with before treatment, P<0.05; #: Compared with the control group after treatment, P<0.05.

Comparison of tumor cell migration factor levels between two groups.

Table 4.

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>HMGA2 Before treatment</th>
<th>HMGA2 After treatment</th>
<th>HMGB1 Before treatment</th>
<th>HMGB1 After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>50</td>
<td>1.49±0.17</td>
<td>0.89±0.13</td>
<td>1.81±0.21</td>
<td>1.02±0.22</td>
</tr>
<tr>
<td>Control group</td>
<td>50</td>
<td>1.50±0.13</td>
<td>1.17±0.12</td>
<td>1.81±0.21</td>
<td>1.44±0.21</td>
</tr>
</tbody>
</table>

Note: #: Compared with before treatment, P<0.05; Compared with the control group after treatment, P<0.05.

3.2 Levels of angiogenic factors in two groups

Before treatment, there was no significant difference in the levels of angiogenic factors (including vascular endothelial growth factor and HIF-1α) between the two groups (P>0.05); after treatment, the levels of angiogenic factors in the two groups were significantly lower than those before treatment (P<0.05), and the levels of angiogenic factors in the observation group [vascular endothelial growth factor was (353.79 ± 110.33) pg/mL, HIF-1α was (37.53 ± 2.69) ng/L] was significantly lower than that of the control group [vascular endothelial growth factor was (436.23 ± 134.00) pg/mL, HIF-1α was (37.53 ± 2.69) ng/L].

3.3 Levels of tumor cell proliferation factor in two groups

Before treatment, there was no significant difference in tumor cell proliferation factors (including IGF-1 and IGFBP-7) between the two groups (P>0.05). After treatment, the levels of IGF-1 in the two groups were significantly lower than those before treatment (P<0.05). The level of IGFBP-7 was significantly higher than before treatment (P<0.05), and compared with the control group [IGF-1 was (154.24±39.21) ng/mL, IGFBP-7 was (34.35±10.15) ng/L]. The level of IGF-1 in the observation group [(111.72±33.70) ng/mL] decreased more significantly (P<0.05), and the level of IGFBP-7 [(38.71±8.47) ng/L] increased more significantly (P<0.05), see Table 3.

3.4 Levels of tumor cell migration factor in two groups

Before treatment, there was no significant difference in tumor cell migration factors (including HMGA2 and HMGB1) between the two groups (P>0.05). After treatment, the tumor cell migration factor levels in the two groups were significantly lower than those before treatment (P<0.05). The tumor cell migration factor level in the observation group [HMGA2 was (0.89±0.13) ng/mL, HMGB1 was (1.02±0.22) ng/mL] compared with the control group [HMGA2 was (1.17±0.12) ng/mL, HMGB1 was (1.44±0.21) ng/mL]. The decrease was more obvious (P<0.05), see Table 4.

4. Discussion

The incidence of NSCLC patients is mainly male, with low specificity in the early stage of the disease, short median survival, and low 1-year survival rate[5]. Often, patients are diagnosed at mid-to-late stage, prone to metastasis, surgical treatment is poor, often treated with chemotherapy, but the effect is not satisfactory. The main treatment regimen for patients with advanced NSCLC is gemcitabine, paclitaxel and other drugs combined with cisplatin. Although there is a certain effect, the survival benefit of patients is limited[13]. In recent years, anti-angiogenesis has become an important way to treat tumor invasion and metastasis. Studies have shown that anti-angiogenic drugs can significantly inhibit neovascularization around the tumor, and synergistic effects with other chemotherapy drugs[14]. Endostar is an endostatin that inhibits vascular endothelial cell proliferation and inhibits tumor cell growth. The main mechanism of action is to interfere with vascular endothelial growth factor to affect its conduction pathway, weaken proteolytic activity, and cause endothelial cell apoptosis. It can prevent the formation of new blood vessels, interfere with the nutritional channels of tumor cells, enhance the sensitivity of chemotherapy drugs, and control the proliferation or migration of tumor cells by interfering with endothelial cell migration[15,16].
study concluded that endostar can improve the safety of NSCLC patients, promote drug concentration on local cells, and have good therapeutic effects in both primary and secondary lesions[9].

In the occurrence and development of malignant tumors, there are many levels of serologically relevant indicators that will change accordingly. The degree of change is closely related to the degree of malignancy of the tumor. These indicators are called “tumor markers”, among which CYFRA21-1, CEA and CA50 are both tumor markers. CYFRA21-1 is mainly present in the epithelial cytoplasm of lung tumors. When malignant tumor cells are necrotic, they are released into peripheral blood, and their high levels reflect the presence of malignant tumors[17]; CEA is mainly found in embryonic tissues and is a human embryo. An antigen-specific acid glycoprotein whose high level of expression can reflect the embryonic tissues and is a human embryo. An antigen-specific acid glycoprotein whose high level of expression can reflect the degree of malignancy and efficacy of the tumor. Therefore, detecting the level of relevant angiogenesis markers can reflect the degree of malignancy and efficacy of the tumor. It is found that VEGF and HIF-1α play an important role in the process of tumor neovascularization. The combination of VEGF and downstream factor HIF-1α can enhance the hypoxia tolerance of tumor cells, accelerate the proliferation of vascular endothelial cells and increase vascular permeability. To provide a material basis for the proliferation and metastasis of tumor cells[19,20]. VEGF is the first hypoxia induced proangiogenic factor, and its expression level is closely related to the malignant degree, metastasis and prognosis of non-small cell lung cancer[14]. Studies have shown that the higher the expression level, the higher the malignancy of non-small cell lung cancer, the worse the prognosis[1]. HIF-1α can directly participate in the angiogenesis process around hypoxic tissue, affecting the expression levels of other factors[22], plays a key role in tumor growth, and is associated with tumor prognosis[14]. The study found that the levels of VEGF and HIF-1α in the observation group were significantly lower than those in the control group (P<0.05), suggesting that the use of Endostar in the treatment of non-small cell carcinoma patients has significant anticancer effect.

The proliferation and migration of tumor cells are dependent on the regeneration of internal blood vessels and the supply of oxygen and nutrients. The promotion of angiogenesis and inhibitory factors play an important role in the regulation of tumor angiogenesis[10]. Therefore, detecting the level of relevant angiogenesis markers can reflect the degree of malignancy and efficacy of the tumor. In conclusion, Endor therapy can improve the therapeutic effect of cancer and is one of the most widely used multifunctional cell proliferation regulator that promotes cell differentiation, proliferation and individual growth and development. IGFBP is a receptor of IGF-1, in which IGFBP-7 is a secreted protein, which can protect IGF-1 from the degradation of related proteolytic enzymes, and is negatively correlated with the occurrence of lung cancer, and is involved in regulating cell proliferation, tumor angiogenesis and Tumor invasion[9]. Abnormal expression of both plays an important role in tumor progression. The study found that the level of IGF-1 in the observation group was significantly lower than that in the control group (P<0.05), while the level of IGFBP-7 was significantly increased, suggesting that Endor therapy can inhibit the proliferation of tumor cells.

HMGA2 and HMGB1 are members of the high mobility protein family. HMGA2 normally exists mainly in immature interstitial tissues[23]. The expression level of HMGA2 increases when cells become cancerous. HMGB1 is a proinflammatory factor, which can maintain nucleic acid structure and regulate gene transcription. Studies have shown that HMGB1 is highly expressed in hepatocellular carcinoma, colorectal cancer and other cancers. Both of them are highly expressed in lung cancer and are closely related to the development and invasion and metastasis of cancer cells. Neovascularization is the main pathological basis. Therefore, inhibition of neovascularization may affect the expression of both and play a role in inhibiting the development and migration of cancer[26]. The results showed that the levels of HMGA2 and HMGB1 in the observation group were significantly lower than those in the control group (P<0.05), suggesting that Endor therapy can inhibit the development and migration of cancer cells.

In conclusion, Endor therapy can improve the therapeutic effect of patients with non-small cell cancer, inhibit angiogenesis and proliferation and migration of tumor cells, which is worthy of clinical application.

Reference


