Effect of systemic vein chemotherapy and internal iliac arterial embolization infusion chemotherapy on angiogenesis and malignant degree of cervical cancer

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ABSTRACT

Objective: To analyze the effect of systemic vein chemotherapy and internal iliac arterial chemoembolization on angiogenesis and malignant degree of cervical cancer.

Methods: A total of 108 cases of patients with middle and advanced cervical cancer were included in the research, and the time range of the research was from February 2014 to December 2015. According to different means of chemotherapy, included patients were divided into observation group 54 cases and control group 54 cases, control group received systemic vein chemotherapy, observation group received internal iliac arterial infusion chemotherapy and embolization treatment, and then differences in the levels of angiogenesis-related indicators, blood flow parameters within tumor, serum illness-related indicators, cervical tumor tissue proliferation-related indicators, etc. were compared between two groups after treatment.

Results: Serum VEGFR-2, HIF-1α, vWF and Lam values of observation group after chemotherapy were lower than those of control group; PI, VI, FI, VFI and Vmax values of observation group after treatment were lower than those of control group while RI value was higher than that of control group; serum SCC-Ag, TK1, HE4, CYFRA21-1, IGF, || and Gal-9 values of observation group after chemotherapy were lower than those of control group; miR-26b, SCD-1, Cyclin D1 and TLR4 protein expression levels in tumor tissue of observation group after treatment were lower than those of control group while miR-99b protein expression level was higher than that of control group.

Conclusions: Internal iliac arterial infusion chemotherapy and embolization can significantly decrease tumor angiogenesis and inhibit tumor cell proliferation, and it is a perfect means of interventional chemotherapy.

1. Introduction

Internal iliac arterial infusion chemotherapy and distal tumor-feeding artery embolization is a newly discovered means of interventional chemotherapy that increases concentration of local chemotherapy and also blocks blood supply arteries of tumor, and it can maximize the killing effect on the tumor and local metastases, and provide good conditions for later surgery[1,2]. Cervical cancer is one of the most common malignant tumors of female reproductive system, is not usually detected in early stage, and is mostly in middle and advanced stage at the time of clinical diagnosis. For middle and advanced cervical cancer patients with local metastasis, preoperative chemotherapy is the currently accepted way, but the choice of specific chemotherapy remains controversial[3]. In the research, the effect of systemic vein chemotherapy and internal iliac arterial chemoembolization on angiogenesis and malignant degree of cervical cancer was mainly analyzed.

2. Materials and methods

2.1. Case selection

A total of 108 cases of patients with middle and advanced cervical cancer were included in the research, and the time range of the research was from February 2014 to December 2015. All included patients were confirmed as cervical cancer by pathology, and the
stage was confirmed. Given that all patients were with different degree of distant metastasis, chemotherapy was the main treatment means of the research, and the included patients were divided into observation group 54 cases and control group 54 cases according to different means of chemotherapy. Control group were 34-69 years old, the average was (53.28±7.71) years, 24 cases were with A stage of tumor, 20 cases were with B stage and 10 cases were with C stage; observation group were 32-68 years old, the average was (52.69±7.45) years, 21 cases were with A stage of tumor, 19 cases were with B stage and 14 cases were with C stage. The research was approved by the hospital ethics committee, patients and families signed informed consent forms, and differences in age, disease severity and other baseline information were not significant between two groups (P>0.05).

2.2. Chemotherapy methods

Control group received systemic vein chemotherapy, specifically as follows: 5-FU 1 000 mg/m², continuous intravenous drip for 96 h, calculating carboplatin amount per unit volume according to the dosage of creatinine clearance rate, continuous intravenous drip for 3 d.

Observation group received internal iliac arterial embolization infusion chemotherapy, specifically as follows: under the monitoring of digital subtraction angiography, Seldinger method was used to enter into the femoral artery, and the catheter was positioned with photoscope and then inserted into the distal iliac artery until the distal superior gluteal arterial branch. Chemotherapy drugs cisplatin 60 mg, bleomycin 45 mg and mitomycin 10 mg were diluted with normal saline and then slowly equally injected into both sides. At last, gelatin sponge particles were mixed in contrast and then slowly injected into the branch with the most obvious blood supply of tumor under the monitoring of photoscope, the sign that artery blood velocity slowed down until completely stagnated indicated that the embolism was successful, the catheter was moved and pressure bandaging was conducted. Patients lay on the back for 12-24 h and received conventional antibiotic treatment for 3-5 d.

2.3. Observation indicators

Two weeks after treatment, 5 mL of fasting peripheral venous blood was drawn from the patients in the morning, let stand at room temperature for 30 min and then centrifuged with high speed for 10 min, and supernatant was obtained and saved under -20 °C for inspection. Enzyme-linked immunosorbent assay was used to detect angiogenesis-related indicators, and immunohistochemical SP method was used to detect serum vascular endothelial growth factor receptor 2 (VEGFR-2), hypoxia-inducible factor-1 α (HIF-1α), von Willebrand factor (vWF) and laminin (Lam).

Color Doppler ultrasound instrument was used to measure blood flow parameters within tumors: resistance index (RI), pulsatility index (PI), vascular index (VI), flow index (FI), vascular flow index (VFI) and peak flow velocity (Vmax).

Table 2

Comparison of blood flow parameter values within tumors between two groups after chemotherapy.

<table>
<thead>
<tr>
<th>Groups</th>
<th>RI</th>
<th>PI</th>
<th>VI</th>
<th>FI</th>
<th>VFI</th>
<th>Vmax (cm/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>0.76±0.07</td>
<td>0.57±0.04</td>
<td>3.17±0.34</td>
<td>32.05±3.19</td>
<td>1.31±0.12</td>
<td>17.23±1.43</td>
</tr>
<tr>
<td>Control</td>
<td>0.45±0.04</td>
<td>1.09±0.12</td>
<td>8.56±0.75</td>
<td>41.67±4.38</td>
<td>4.58±0.43</td>
<td>28.65±2.71</td>
</tr>
<tr>
<td>t</td>
<td>5.283</td>
<td>6.293</td>
<td>7.218</td>
<td>8.493</td>
<td>5.773</td>
<td>8.304</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Serum illness-related indicators were detected: SCC-Ag, thymidine kinase 1 (TK1), human epididymis secretory protein (HE4), CYFRA21-1, IGF-Ⅱ and galectin 9 (Gal-9).

Cervical lesion tissue was obtained, and then western-blot method was used to detect protein expression levels of proliferation-related indicators: miR-26b, miR-99b, stearoyl-coenzyme A desaturase 1 (SCD-1), Cyclin D1 and Toll-like receptor 4 (TLR4).

2.4. Statistical methods

Data obtained in the research was analyzed by SPSS 23.0 software, measurement data was in terms of Mean ± SD, comparison between two groups was by t test, and P<0.05 was set as the standard of statistical significant differences.

3. Results

3.1. Angiogenesis-related indicators

Serum VEGFR-2, HIF-1α, vWF and Lam values of observation group after chemotherapy were lower than those of control group (P<0.05), shown in Table 1.

Table 1

Comparison of angiogenesis-related indicator values between two groups after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>VEGFR-2 (ng/L)</th>
<th>HIF-1α (ng/L)</th>
<th>vWF (μg/mL)</th>
<th>Lam (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>114.82±13.76</td>
<td>9.27±0.86</td>
<td>8.94±0.71</td>
<td>15.94±1.43</td>
</tr>
<tr>
<td>Control</td>
<td>205.67±20.48</td>
<td>24.18±2.27</td>
<td>15.37±1.43</td>
<td>54.31±5.97</td>
</tr>
<tr>
<td>t</td>
<td>11.832</td>
<td>8.394</td>
<td>6.283</td>
<td>9.834</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

3.2. Blood flow parameters within tumors

Results showed that PI, VI, FI, VFI and Vmax values of observation group after treatment were lower than those of control group while RI value was higher than that of control group (P<0.05), shown in Table 2.

3.3. Serum illness-related indicators

Serodetection of above indicators showed that serum SCC-Ag, TK1, HE4, CYFRA21-1, IGF-Ⅱ and Gal-9 values of observation group after chemotherapy were lower than those of control group (P<0.05), shown in Table 3.

3.4. Cervical tumor tissue proliferation-related indicators

Results showed that miR-26b, SCD-1, Cyclin D1 and TLR4 protein expression levels in tumor tissue of observation group after treatment were lower than those of control group while miR-99b protein expression level was higher than that of control group (P<0.05), shown in Table 4.
Table 3

Comparison of serum illness-related indicator values between two groups after chemotherapy.

<table>
<thead>
<tr>
<th>Groups</th>
<th>SCC-Ag (μg/mL)</th>
<th>TK1 (pmol/L)</th>
<th>HE4 (pmol/L)</th>
<th>CYFRA21-1 (ng/mL)</th>
<th>IGF-1 (mg/mL)</th>
<th>Gal-9 (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>0.34±0.03</td>
<td>0.71±0.06</td>
<td>53.27±5.11</td>
<td>2.41±0.23</td>
<td>312.84±35.76</td>
<td>20.16±2.34</td>
</tr>
<tr>
<td>Control</td>
<td>0.79±0.06</td>
<td>1.58±0.13</td>
<td>79.65±7.34</td>
<td>3.27±0.35</td>
<td>437.49±38.27</td>
<td>28.95±2.28</td>
</tr>
<tr>
<td>t</td>
<td>5.374</td>
<td>6.282</td>
<td>8.394</td>
<td>6.382</td>
<td>12.384</td>
<td>7.204</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table 4

Comparison of cervical tumor tissue proliferation-related indicator values between two groups after chemotherapy.

<table>
<thead>
<tr>
<th>Groups</th>
<th>miR-26b</th>
<th>miR-99b</th>
<th>SCD-1</th>
<th>Cyclin D1</th>
<th>TLR4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation</td>
<td>65.38±5.77</td>
<td>127.39±13.27</td>
<td>75.39±7.54</td>
<td>72.84±9.09</td>
<td>53.26±5.48</td>
</tr>
<tr>
<td>Control</td>
<td>94.96±8.52</td>
<td>86.09±8.11</td>
<td>102.68±10.43</td>
<td>115.48±10.83</td>
<td>91.57±8.43</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

4. Discussion

Middle and advanced cervical cancer is mostly accompanied with local or distant metastasis, the effect of direct operation is poor, and chemotherapy is mostly adopted at first. Systemic chemotherapy is the clinical common way that can impact on tumor cells of the whole body and contain their viability. But systemic chemotherapy affects many normal viscera tissue functions, will damage patients’ normal immune function, and is with some limitations of clinical application[4,5]. Internal iliac arterial infusion chemotherapy and embolization is a interventional chemotherapy in recent years that can directly represent the ability of tumor angiogenesis. High-concentration chemotherapy drugs in local internal iliac artery and embolizes distal supply artery of the tumor at the same time, which greatly increases chemotherapy drug exposure concentration of tumor cells, effectively blocks tumor blood supply, and can kill tumor cells and local metastases to the greatest extent. At present, there are few comparative studies about the application effect of traditional systemic chemotherapy and internal iliac arterial infusion chemotherapy and embolization[6]. In this study, patients with middle and advanced cervical cancer were selected as the research subjects, they received systemic chemotherapy as well as internal iliac arterial infusion chemotherapy and embolization respectively, and then the changes in angiogenesis, malignant degree and many other aspects were compared between two groups of patients after the application. VEGFR-2 is mainly distributed in vascular endothelial cell membrane, and is the main factor that regulates tumor angiogenesis. The angiogenesis-promoting effect of VEGF is mainly produced through the combination with VEGFR-2, so the VEGFR-2 levels can directly represent the ability of tumor angiogenesis. High expression of VEGFR-2 is found in almost every kind of malignant tumors, and VEGFR-2 levels are positively correlated with tumor cell invasion and metastasis ability. HIF-1α is involved in the regulation of tumor cell adaptation to hypoxia environment, and promotes tumor angiogenesis so as to further enhance the capacity of tumor cell infiltration and metastasis[7]. VWF is a recognized factor closely associated with angiogenesis, high expression of vWF has been found in the tumor tissue of liver cancer, and vWF is seldom expressed in the non-tumor area, indicating that vWF is directly involved in the formation of tumor blood vessels and can be used as a reliable indicator for judging malignant degree and prognosis of tumor. Lam is a macromolecular non-collagen glycoprotein, is the component of vascular basement membrane and tumor capsule, and is not expressed in the non-tumor area. Lam is one of the typical tumor endothelial markers, and high expression levels of Lam mostly indicate exuberant tumor angiogenesis[8,9]. Above research results showed that serum VEGFR-2, HIF-1α, vWF and Lam values of observation group reduced after chemotherapy, indirectly indicating that interventional chemotherapy could significantly inhibit the formation of blood supply vessels of tumor and tumor activity. Further intuitive detection of blood flow resistance, flow velocity and so on of the supply vessels of tumor showed that PI, VI, FI, VFI and Vmax values of observation group reduced after treatment, further confirming that after interventional chemotherapy, the tumor blood supply decreased, and tumor proliferation, invasion, metastasis and a series of malignant behaviors would be inhibited. SCC-Ag is the currently recognized clinical serum marker of cervical cancer, especially squamous cell carcinoma, and its early high expression is a specific sign of cervical cancer. TK1 is closely associated with cervical cancer, has a great influence on tumor cell proliferation and division, and also has tumor-monitoring value[10]. HE4 belongs to the secretory glycoprotein, and is only expressed in normal testicles, respiratory epithelium and genital tract. Research has confirmed that HE4 is highly expressed in the female reproductive system tumor tissues, is not expressed in the para-carcinoma tissue, and is highly specific. CYFRA21-1 is CK-19 fragment and belongs to the soluble constituent of epithelial cell keratin, and in cases of malignant change of epithelial cells or tumor cell necrosis, CYFRA21-1 is released into the blood and leads to increased serum levels. Cervical squamous epithelium can express CYFRA21-1, and high level of CYFRA21-1 is often a sign of poor prognosis. Abnormal IGF-1 expression can promote abnormal cell proliferation, is one of the discrimination indexes of benign and malignant tumor cells, and can reflect the effect and prognosis of tumor therapy[11]. Gal-9 is a member of galectin protein family, is widely distributed in inside and outside the cells and plays different physiologic roles in different parts. In cervical cancer, Gal-9 expression location changes, mainly manifested as the nucleus and cytoplasm staining. Research has confirmed that Gal-9 is highly expressed in cervical cancer tissue, speculating that it is closely related to the neoplastic transformation of cancer cells, tumor cells...
existence, et al[12]. Above research results showed that serum SCC-Ag, TK1, HE4, CYFRA21-1, IGF-] and Gal-9 values of observation group were lower after treatment, indicating that internal iliac arterial infusion chemotherapy and embolization therapy could effectively contain cervical cancer cell viability and optimize patients’ general condition.

miRNA is the body's most important gene regulation molecule, and is closely related to the biological characteristics of tumor. With the wide application of miRNA chip technology, it has been found that miRNA is abnormally expressed in the occurrence and development of tumor[13]. Studies have shown that miR-26b can inhibit SLC7A11 protein expression and regulate breast cancer cell growth and proliferation. It is also found that miR-26b can adjust the expression of the SCD-1 gene, inhibit SLC7A11 protein expression, and regulate breast cancer cell proliferation. It is also found that miR-26b can adjust the expression of the SCD-1 gene, inhibit SLC7A11 protein expression, and regulate breast cancer cell proliferation.

As for cervical cancer, miR-26b expression is found to be significantly higher in patients with cervical cancer than in normal controls. This indicates that miR-26b may be involved in the progression of cervical cancer. In addition, studies have shown that miR-26b expression is negatively correlated with the proliferation and migration of cervical cancer cells, suggesting that miR-26b may be a potential target for the treatment of cervical cancer.

In summary, miRNA technology has the potential to be applied in the diagnosis and treatment of cervical cancer, and may provide new ideas and methods for the development of cervical cancer treatment in the future.

References