Effect of preoperative paclitaxel + cisplatin neoadjuvant chemotherapy on the proliferation and invasion of cancer cells in esophageal cancer

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ABSTRACT

Objective: To investigate the effect of preoperative paclitaxel + cisplatin neoadjuvant chemotherapy on the proliferation and invasion of cancer cells in esophageal cancer.

Methods: A total of 106 patients with esophageal cancer who underwent radical operation for esophageal cancer in our hospital between September 2014 and March 2017 were divided into the neoadjuvant chemotherapy group (n=54, receiving preoperative paclitaxel + cisplatin neoadjuvant chemotherapy) and the normal group (n=52, receiving no preoperative neoadjuvant chemotherapy) according to the therapeutic regimen. The differences in the expression of proliferation genes and invasion genes in the postoperative lesion tissue specimens were compared between the two groups.

Results: The proliferation genes MACC1, Nucleostemin, TRAF4 and USP99 mRNA expression in lesion tissue of neoadjuvant chemotherapy group were lower than those in lesion tissue of normal group whereas DECI, PTPN4, KLF4 and LATS1 mRNA expression were higher than those in lesion tissue of normal group; invasion genes EphA2, MACC1, MMP-9, FN2, Snail and SphK1 mRNA expression in lesion tissue of neoadjuvant chemotherapy group were lower than those in lesion tissue of normal group whereas PTEN and RACK1 mRNA expression were higher than those in lesion tissue of normal group.

Conclusion: The paclitaxel + cisplatin neoadjuvant chemotherapy before esophageal cancer surgery can effectively inhibit the proliferation and invasion activity of esophageal cancer cells.

1. Introduction

Esophageal cancer is the gastrointestinal tumor with high clinical malignancy. Surgical radical surgery is the most reliable method for its treatment, but there is the risk of tumor cell residues as well as the recurrence and metastasis of esophageal cancer. The main causes of postoperative recurrence of esophageal cancer are the tumor tissue residues during operation and the small metastases invisible to the naked eye, and given this, many scholars have recommended neoadjuvant chemotherapy before surgery at present. The purpose of neoadjuvant chemotherapy is to kill the invisible metastases and reduce the volume of the tumor before operation so as to facilitate the operation and postoperative chemoradiotherapy.

TP chemotherapy regimen composed of paclitaxel and cisplatin has been used in a variety of malignant tumor diseases before operation, it was used for clinical preoperative treatment of esophageal cancer patients in this study, and these patients were compared with those undergoing conventional radical operation for esophageal cancer in order to clarify the influence of different treatments on esophageal cancer cell malignancy and lay the practice basis for the subsequent selection and implementation of better treatments.

2. Materials and methods

2.1. Case information

A total of 106 patients with esophageal cancer who underwent radical operation for esophageal cancer in our hospital between September 2014 and March 2017 were divided into the neoadjuvant
chemotherapy group (n=54, receiving preoperative paclitaxel + cisplatin neoadjuvant chemotherapy) and the normal group (n=52, receiving no preoperative neoadjuvant chemotherapy) according the therapeutic regimen. There were 28 males and 26 females in the neoadjuvant chemotherapy group, and they were 47-72 years old; there were 27 males and 25 females in the normal group, and they were 45-73 years old. The gender and age distribution of the two groups were not significantly different, and the study plan was approved by the hospital ethics committee.

Inclusion criteria: (1) pathologically diagnosed with primary esophageal cancer; (2) diagnosed and treated for the first time; (3) whose family members signed the informed consent. Exclusion criteria: (1) combined with primary malignant tumor disease in other tissue viscera (2) with history of surgery within 6 months before operation; (3) combined with systemic infectious diseases; (4) combined with severe coagulation insufficiency.

2.2. Preoperative neoadjuvant chemotherapy

Normal group did not receive any treatment before operation, and neoadjuvant chemotherapy group received preoperative paclitaxel + cisplatin neoadjuvant chemotherapy, which was as follows: intravenous drip of paclitaxel, 135 mg·m⁻² on d1; intravenous drip of cisplatin, 75 mg·m⁻² on d1-d3, 21 d as one course of treatment for 3 consecutive courses of chemotherapy. Surgery was performed three weeks after the end of chemotherapy.

2.3. Malignant molecule expression in esophageal cancer lesions

Esophageal cancer lesion tissue was collected from two groups of patients during operation, and fluorescence quantitative PCR method was adopted to detect the expression of proliferation genes MACC1, Nucleostemin, TRAF4, USP39, DEC1, PTPN14, KLF4 and LATS1 as well as invasion genes EphA2, MACC1, MMP-9, PFFN2, Snail, SphK1, PTEN and RACK1.

2.4. Statistical methods

Proliferation-related gene and invasion-related gene expression all belonged to measurement data and were input in SPSS 24.0, and t test was adopted to calculate the P value. The differences were statistically significant if P<0.05.

3. Results

3.1. Proliferation–related genes

Comparison of pro-proliferation genes MACC1, Nucleostemin, TRAF4 and USP39 as well as anti-proliferation genes DEC1, PTPN14, KLF4 and LATS1 mRNA expression in intraoperative lesion tissue between two groups of patients was as follows: MACC1, Nucleostemin, TRAF4 and USP39 mRNA expression in lesion tissue of neoadjuvant chemotherapy group were lower than those in lesion tissue of normal group whereas DEC1, PTPN14, KLF4 and LATS1 mRNA expression were higher than those in lesion tissue of normal group (P<0.05), shown in Table 1 & 2.

3.2. Invasion-related genes

Comparison of pro-invasion genes EphA2, MACC1, MMP-9, PFFN2, Snail and SphK1 as well as anti-invasion genes PTEN and RACK1 mRNA expression in intraoperative lesion tissue

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Table 1.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>MACC1</th>
<th>Nucleostemin</th>
<th>TRAF4</th>
<th>USP39</th>
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<tbody>
<tr>
<td>Normal group</td>
<td>52</td>
<td>94.38±10.17</td>
<td>90.77±10.64</td>
<td>101.26±12.49</td>
<td>84.27±9.13</td>
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<td>Neoadjuvant chemotherapy</td>
<td>54</td>
<td>70.11±7.58</td>
<td>68.29±7.51</td>
<td>74.58±8.21</td>
<td>60.52±6.38</td>
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<tr>
<td>p</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
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</tbody>
</table>

Table 2.

<table>
<thead>
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<th>Groups</th>
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<th>PTPN14</th>
<th>KLF4</th>
<th>LATS1</th>
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<tbody>
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<td>Normal group</td>
<td>52</td>
<td>101.27±13.48</td>
<td>92.49±9.81</td>
<td>95.63±10.28</td>
<td>113.48±14.25</td>
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<tr>
<td>t</td>
<td></td>
<td>14.382</td>
<td>16.291</td>
<td>15.036</td>
<td>9.382</td>
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<tr>
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<td>&lt;0.05</td>
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</tr>
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</table>

Table 3.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>EphA2</th>
<th>MACC1</th>
<th>MMP-9</th>
<th>PEN2</th>
<th>Snail</th>
<th>SphK1</th>
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</thead>
<tbody>
<tr>
<td>Normal group</td>
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<td>80.57±8.62</td>
<td>92.18±10.43</td>
<td>74.29±8.61</td>
<td>100.53±12.49</td>
<td>90.18±9.34</td>
<td>113.26±13.21</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>54</td>
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<td>80.61±8.75</td>
<td>50.38±6.29</td>
<td>73.58±8.12</td>
<td>54.39±6.21</td>
<td>80.46±9.21</td>
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<tr>
<td>p</td>
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<td>&lt;0.05</td>
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<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
between two groups of patients was as follows: EphA2, MACC1, MMP-9, PFN2, Snail and SphK1 mRNA expression in lesion tissue of neoadjuvant chemotherapy group were lower than those in lesion tissue of normal group whereas PTEN and RACK1 mRNA expression were higher than those in lesion tissue of normal group ($P<0.05$), shown in Table 3 & 4.

Table 4.
Comparison of anti-invasion gene expression in lesion tissue between the two groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>PTEN</th>
<th>RACK1</th>
</tr>
</thead>
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<tr>
<td>Normal group</td>
<td>52</td>
<td>74.39±8.35</td>
<td>90.23±9.75</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy group</td>
<td>54</td>
<td>102.18±13.42</td>
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<td>10.274</td>
</tr>
<tr>
<td>$P$</td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
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</table>

4. Discussion

The malignant degree of esophageal cancer is very high, and the current statistical studies show that the recurrence rate of patients with the disease after surgery is high and the 5-year survival rate is low. How to maximize the curative effect of radical operation for esophageal cancer and prolong the patients’ survival time is the focus of current clinical research. Neoadjuvant chemotherapy is the systemic chemotherapy administered before surgical treatment, which aims to kill small metastases and reduce tumor volume in the early stage so as to facilitate the operation and reduce the risk of postoperative recurrence and metastasis[6,7]. This treatment makes some patients with middle-advanced tumors obtain the opportunity of surgery and also actually reduces the postoperative recurrence rate of multiple malignant tumors, such as cervical cancer and colorectal cancer. In this study, TP neoadjuvant chemotherapy was used for esophageal cancer patients, and the effects of the therapeutic regimen on tumor malignancy were explored and elaborated from proliferation gene and invasion gene expression.

MACC1 is a newly discovered proto-oncogene, and studies have found that it is unusually highly expressed in cervical cancer, colon cancer and other malignant tumor tissues, and it activates PI3K/AKT signal pathway to stimulate cancer cell proliferation[8,9]. Nucleostemin exists in stem cells and multiple human tumor tissues, and is not expressed in tissue with normal differentiation and maturation. The expression of Nucleostemin expression in tumor tissues is positively correlated with the proliferation activity of cancer cells[10]. TRAF4 was first found in human breast cancer lymphocytes, it has been confirmed to participate in the occurrence and development of many kinds of malignant tumors, and silencing TRAF4 expression by siRNA technology can effectively inhibit tumor cell proliferation and metastasis[11,12]. USP39 is involved in the spliceosome assembly of human cells, and silencing its expression can significantly inhibit the cloning ability of tumor cells and make cell cycle arrest at G0/G1 phase[13]. DEC1 is a growth gene, and cell research has found that over-expressing DEC1 can significantly inhibit the proliferation and invasion of esophageal cancer ECA109 cells. PTPN14 is involved in multiple processes such as cell proliferation, differentiation, mitosis and malignant transformation, current studies have shown that PTPN14 can inhibit the proliferation of esophageal cancer cells and block the cell cycle, and its specific expression is negatively correlated with tumor cell proliferation activity[14]. KLF4 is a zinc finger transcription factor that is involved in cell cycle regulation, its roles in the malignant tumors are different, for example, it is confirmed to be highly expressed in breast cancer, but its expression abnormally reduces in the esophageal cancer, and it plays a negative regulatory role in the process of esophageal cancer proliferation and invasion. LATS1 is an important molecule that forms the Hippo signaling pathway, and it reduces the proliferation ability of tumor cells by up-regulating the apoptosis gene BAX expression, inducing G1 phase, shortening S phase and other pathways[15,16]. The study results showed that compared with those of normal group, MACC1, Nucleostemin, TRAF4 and USP39 mRNA expression in lesion tissue of neoadjuvant chemotherapy group were lower whereas DEC1, PTPN14, KLF4 and LATS1 mRNA expression were higher, showing that neoadjuvant chemotherapy before radical operation for esophageal cancer can help inhibit the expression of pro-proliferation genes and increase the expression of anti-proliferation genes to help reduce the proliferation activity of esophageal cancer cells.

EphA2 is combined with its ligand to participate in the transduction of multiple intracellular signaling pathways, and it plays an active role in maintaining intercellular adhesion. The expression of EphA2 increases abnormally in the cancerous tissue, and the cancer cells are prone to falling and with enhanced invasion[17]. MACC1 has been found to be abnormally highly expressed in gastric cancer, ovarian cancer, lung cancer and other malignant tumor tissues, and is closely related to the infiltration and metastasis of tumor cells[18,19]. MMP-9 is a member of the matrix metalloproteinase family, which can degrade extracellular matrix, reduce the adhesion between tumor cells and increase cell invasion vitality[20]. The PFN2 is an actin-binding protein, which plays an important role in maintaining normal cell movement, division and differentiation. At present, some studies have shown that the specific reduction of PFN2 expression can significantly inhibit the migration and invasion of esophageal cancer cells. It has been proven that Snail is abnormally highly expressed in various malignant tumor tissues, plays an important role in epithelial mesenchymal transition, and can promote cell carcinogenesis and enhance its invasion activity. SphK1 is a sphingosine metabolism enzyme that is involved in the regulation of cell proliferation and survival. It is found that high expression of SphK1 can stimulate cell growth and become a marker of poor prognosis[21]. PTEN is a typical tumor suppressor gene, which reduces the malignant degree of cancer cells by blocking cell cycle in G1 phase, inhibiting tumor angiogenesis and other mechanisms[22]. RACK1 is a kind of anchor in cytoplasm, it has been confirmed to be involved in
the invasion and metastasis of multiple tumors, and the specific mechanism may be that the RACK1 is combined with the PKC on cytoskeleton, which activates the Wnt signaling pathway[23]. The study results showed that compared with those of normal group, EphA2, MAAC1, MMP-9, PFN2, Snail and SphK1 mRNA expression in lesion tissue of neoadjuvant chemotherapy group were lower whereas PTEN and RACK1 mRNA expression were higher, confirming that paclitaxel + cisplatin neoadjuvant chemotherapy can effectively reduce the invasion activity of esophageal cancer cells and reduce the malignant degree of tumor.

To sum up, it is concluded that preoperative paclitaxel + cisplatin neoadjuvant chemotherapy can effectively reduce the esophageal cancer cell proliferation and invasive vitality in patients with esophageal cancer, it contributes to the realization of expected operative effect, and is worthy of popularization and application in clinical practice in the future.

References


