Effect of preoperative S-1 combined with regional transcatheter arterial chemoembolization on malignant degree of locally advanced gastric cancer

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ABSTRACT

Objective: To study the effect of preoperative S-1 combined with regional transcatheter arterial chemoembolization on malignant degree of locally advanced gastric cancer. Methods: A total of 134 patients who were diagnosed with advanced gastric cancer in our hospital from May 2012 to December 2014 were selected for study, received surgical resection after chemotherapy, and were divided into intravenous chemotherapy group and combined treatment group according to different chemotherapy regimens. After chemotherapy and before operation, serum tumor marker levels were detected; after operation, recurrence and metastasis-related molecule levels in tumor tissue were detected. Results: After chemotherapy and before operation, serum CEA, CA199, CA72-4, TSGF, ESM-1 and DKK-1 levels of combined treatment group were significantly lower than those of intravenous chemotherapy group; TET1, TET2, LATS1 and RUNX3 levels in tumor tissue of combined treatment group were higher than those of intravenous chemotherapy group while Sipa1, GOLPH3, AEP, MT2-MMP, OPN, Galectin-1, Galectin-3 and Galectin-9 levels were lower than those of intravenous chemotherapy group. Conclusions: Compared with systemic intravenous chemotherapy, preoperative S-1 combined with regional transcatheter arterial chemoembolization can more effectively kill gastric cancer cells and prevent tumor recurrence and metastasis at molecular level.

1. Introduction

Gastric cancer is one of the most common malignant tumors in our country, and is also the malignant tumor of digestive system with highest incidence. In clinical practice, the early diagnostic rate of gastric cancer is low, and the majority of patients have developed into advanced gastric cancer (AGC) at the time of diagnosis. Part of the patients with AGC have serious local invasion, do not have the conditions for surgical removal, and need preoperative chemotherapy to inhibit tumor infiltration and create conditions for surgical resection. S-1 is the commonly used drug of preoperative chemotherapy for gastric carcinoma, but the effect of single agent chemotherapy is not very ideal, and multi-drug combined chemotherapy causes bigger trauma to the body and can affect the implementation of the gastric cancer resection[1,2]. Regional intra-arterial infusion chemotherapy is the intervention method for gastric cancer treatment in recent years, which can form high drug concentration in local gastric cancer and increase the killing effect of drugs on gastric cancer cells[3,4]. In the following research, the effect of preoperative S-1 combined with regional transcatheter arterial chemoembolization on malignant degree of locally advanced gastric cancer was analyzed.
2. Materials and methods

2.1. Treatment methods

A total of 134 patients who were diagnosed with advanced gastric cancer in our hospital from May 2012 to December 2014 were selected for study. All patients were diagnosed with advanced gastric cancer through biopsy, without the indications of surgical resection and received surgical resection after chemotherapy, and those who could not receive surgical resection after chemotherapy were excluded. Patients were divided into intravenous chemotherapy group and combined treatment group according to different chemotherapy regimens. Intravenous chemotherapy group included 72 cases, 44 cases were male and 28 cases were female, and they were (61±7) years old; combined treatment group included 62 cases, 36 cases were male and 26 cases were female, and they were (60±7) years old. Comparison of general information between two groups showed no differences. The research was approved by the hospital ethics committee and got informed consent from all patients.

2.2. Research method

2.2.1. Treatment methods

FOLFOX6 regimen was adopted for chemotherapy, oxaliplatin 100 mg/m², intravenous drip, the 1st day, leucovorin 400 mmg/m², intravenous drip, the 1st day, 5-fluorouracil 2 400 mg/m², intravenous drip, repeating the above regimen every 3 weeks. Treatment method of combined treatment group was as follows: oral administration of S-1 40 mg, 2 times/d, the 1-14 d, and regional intra-arterial infusion chemotherapy was conducted on the 14th day. Seldinger method was adopted for superselective right femoral artery intubation to the supply artery of tumor, then 1/2 of oxaliplatin 100 mg/m² and epirubicin 30 mg/m² were collected respectively and mixed with 5% glucose injection, the mixture was injected into the tumor tissue through the catheter, the remaining 1/2 oxaliplatin and epirubicin were mixed with 10 mL of 4% iodized oil emulsion mixed for tumor embolism, and the above regimen was repeated every 3 weeks.

2.2.2. Evaluation methods of tumor malignancy

Before surgical removal, 5 mL peripheral blood was collected from two groups of patients and centrifuged to get serum. Enzyme-linked immunosorbent assay method was used to determine CEA, CA199, CA72-4, TSGF, ESM-1 and DKK-1 content; after surgical resection, tumor tissue was collected and homogenized to get suspension, and enzyme-linked immunosorbent kit was used to determine TET1, TET2, LATS1 and RUNX3 levels in tumor tissue of combined treatment group were higher than those of intravenous chemotherapy group; Sipa1 and GOLPH3 levels in tumor tissue of combined treatment group were lower than those of intravenous chemotherapy group (Table 2).

2.4 Statistical methods

SPSS 16.0 software package was used for statistical analysis, measurement data of both groups was in terms of mean ± standard deviation and was analyzed by t test, and differences were considered to be statistically significant at a level of P<0.05.

3. Results

3.1. Surgical resection conditions of two groups

Intraoperative exposed operative field and tumor tissue of two groups were shown in Figure 1; tumor tissue from surgical resection was shown in Figure 2.

3.2. Serum tumor malignancy marker molecule levels

Srum CEA, CA199 and CA72-4 levels of combined treatment group were significantly lower than those of intravenous chemotherapy group; serum TSGF, ESM-1 and DKK-1 levels of combined treatment group were significantly lower than those of intravenous chemotherapy group (Table 1).

3.3. Recurrence–related molecule levels in tumor tissue

TET1, TET2, LATS1 and RUNX3 levels in tumor tissue of combined treatment group were higher than those of intravenous chemotherapy group; Sipa1 and GOLPH3 levels in tumor tissue of combined treatment group were lower than those of intravenous chemotherapy group (Table 2).

3.4. Metastasis–related molecule levels in tumor tissue

AEP, MT2-MMP, OPN, Galectin-1, Galectin-3 and Galectin-9 levels in tumor tissue of combined treatment group were significantly lower than those of intravenous chemotherapy group.

4. Discussion

Patients with advanced gastric cancer do not conform to surgery treatment indications, and FOLFOX6 neoadjuvant chemotherapy is mostly adopted in clinical practice to control the disease and create conditions for surgical resection. However, systemic vein chemotherapy is with larger side effect and more postoperative complications, and the overall curative effect is not very satisfactory[5,6]. On the one hand, regional transcatheter arterial chemoembolization can make the chemotherapy drugs locally concentrate, drug concentration in the tumor tissue is 10 times more than systemic chemotherapy, and it can more effectively kill cancer cells while reduce the normal tissue...
Table 1
Comparison of serum tumor marker levels between two groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Traditional tumor markers</th>
<th>New tumor markers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CEA (μg/L)</td>
<td>CA199 (U/mL)</td>
</tr>
<tr>
<td>Combined treatment</td>
<td>10.3±1.2</td>
<td>65.5±7.3</td>
</tr>
<tr>
<td>Intravenous chemotherapy</td>
<td>17.8±2.3</td>
<td>103.4±12.7</td>
</tr>
<tr>
<td>( t )</td>
<td>8.184</td>
<td>7.686</td>
</tr>
<tr>
<td>( P )</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table 2
Comparison of recurrence-related molecule levels in tumor tissue of two groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Proliferation-inhibiting molecules</th>
<th>Proliferation-promoting molecules</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TET1 (μg/L)</td>
<td>TET2 (μg/L)</td>
</tr>
<tr>
<td>Combined treatment</td>
<td>10.3±1.2</td>
<td>65.5±7.3</td>
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<tr>
<td>( P )</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table 3
Comparison of metastasis-related molecule levels in tumor tissue of two groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>AEP (μg/L)</th>
<th>MT2-MMP (μg/L)</th>
<th>OPN (μg/L)</th>
<th>Galectin-1 (ng/L)</th>
<th>Galectin-3 (ng/L)</th>
<th>Galectin-9 (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined treatment</td>
<td>11.3±1.7</td>
<td>8.9±0.9</td>
<td>16.5±2.1</td>
<td>165.5±20.4</td>
<td>242.3±27.6</td>
<td>200.5±24.3</td>
</tr>
<tr>
<td>Intravenous chemotherapy</td>
<td>32.8±3.8</td>
<td>15.5±1.7</td>
<td>30.3±3.6</td>
<td>353.3±41.3</td>
<td>403.5±45.2</td>
<td>478.9±51.6</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>

Figure 1. Intraoperative exposed operative field and tumor tissue of two groups.
Left: intravenous chemotherapy group; Right: combined treatment group.

Figure 2. Tumor tissue from surgical resection.
Left: intravenous chemotherapy group; Right: combined treatment group.
damage[7,8]; on the other hand, mixture of chemotherapy drugs and iodized oil can cause supplying vessel embolism of tumor, which not only result in tumor cell ischemia-hypoxia and necrosis, but also prolongs the retention period of chemotherapy drugs in tumor tissues and strengthens the killing effect of chemotherapy drugs on cancer cells[9].

In recent years, domestic scholars have used regional transcatheater arterial chemoembolization for preoperative treatment of patients with locally advanced gastric cancer, research of Zhang et al[10] suggests that preoperative transcatheter arterial chemoembolization combined with S-1 treatment can improve the surgical resection rate and reduce the incidence of adverse reactions. In the research, preoperative S-1 combined with regional transcatheter arterial chemoembolization approach was also adopted for treatment of locally advanced gastric cancer, and the feasibility of the treatment was analyzed from molecular angle.

Detection of serum tumor marker levels is a common index for clinical evaluation of tumor malignancy and tumor load level, and it is noninvasive and can be used for dynamic disease assessment[11]. CEA, CA199 and CA72-4 are the commonly used indicators for diagnosis of digestive tract tumors and assessment of tumor malignancy, the specificity of the above indicators is relatively poor, but they have good consistency with tumor load level, and as the tumor cells are killed by chemotherapy drugs, their serum levels continuously reduce. TSGF, ESM-1 and DKK-1 are the new tumor markers that are used for gastric cancer diagnosis and evaluation in recent years. TSGF is the cytokine released into the blood circulation along with the growth of tumor and the formation of surrounding new blood vessels, and has specific promoting effect on malignant tumor angiogenesis; ESM-1 is a kind of secretory glycoprotein, is mainly expressed by endothelial cells and released into the blood, and can promote the growth and proliferation of cells; DKK-1 is a member of DKKs family, has inhibiting effect on Wnt/β-catenin pathway and can promote the development of tumor[12,13]. In the research, analysis of serum tumor marker levels of two groups showed that serum CEA, CA199, CA72-4, TSGF, ESM-1 and DKK-1 levels of combined treatment group were significantly lower than those of intravenous chemotherapy group. This meant that S-1 combined with regional transcatheter arterial chemoembolization could promote cell proliferation. In the research, analysis of tumor recurrence-related gene expression in tumor tissue showed that AEP, MT2-MMP, OPN, Galectin-1, Galectin-3 and Galectin-9 levels in tumor metastasis-related molecule content in tumor tissue showed that AEP, MT2-MMP, OPN, Galectin-1, Galectin-3 and Galectin-9 levels in tumor tissue of combined treatment group were significantly lower than those of intravenous chemotherapy group. This meant that that S-1 combined with regional transcatheter arterial chemoembolization could inhibit the expression of invasion and migration-related genes, thus preventing distant metastasis of gastric cancer.

Based on above discussion, it can be concluded that compared with systemic intravenous chemotherapy, preoperative S-1 combined with regional transcatheter arterial chemoembolization can more effectively kill gastric cancer cells and prevent tumor recurrence and metastasis at molecular level.

References


