Effect of Aidi injection-assisted intravenous chemotherapy on serum tumor markers and peripheral blood immune molecules in patients with colon cancer

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ABSTRACT

Objective: To discuss the effect of Aidi injection-assisted intravenous chemotherapy on serum tumor markers and peripheral blood immune molecules in patients with colon cancer.

Methods: 92 patients with colon cancer who were hospitalized in Deyang People’s Hospital in Sichuan Province between October 2013 and October 2016 were collected and divided into the control group (n=50) who received intravenous chemotherapy alone and the observation group (n=42) who received Aidi injection-assisted intravenous chemotherapy after the therapies were reviewed. The differences in serum tumor markers and peripheral blood immune molecule contents before and after treatment were compared between two groups of patients.

Results: Before treatment, differences in serum tumor marker levels and peripheral blood immune molecule levels were not statistically significant between two groups of patients. After treatment, serum tumor markers CEA, CA199, CA50, PTN and CCSA-2 levels of observation group were lower than those of control group, peripheral blood Th1/Th2 cytokines IL-2 and IFN-\textgamma levels were higher than those of control group while IL-4 and IL-10 levels were lower than those of control group, and peripheral blood Th17 cytokines IL-17A and IL-22 levels were lower than those of control group.

Conclusion: Aidi injection-assisted intravenous chemotherapy can effectively reduce the serum tumor marker contents and optimize the immune molecule levels in patients with colon cancer.

1. Introduction

Colon cancer is the most common clinical malignant intestinal tumor, the main clinical manifestations include stool property change, intestinal bleeding and so on, and intravenous chemotherapy is the most common treatment for patients who were in advanced stage or cannot tolerate surgery trauma\cite{1,2}. FOLFOX4 chemotherapy is the intravenous chemotherapy regimen with the most mature clinical application, it has achieved certain efficacy in controlling the disease in colon cancer patients, but some scholars have also pointed out that the role of FOLFOX4 chemotherapy alone is limited in inhibiting the progress of tumor, and recommend to join other mechanisms of drugs to expand the curative effect\cite{3,4}. Aidi injection is the traditional Chinese medicine preparation made from blister beetle, ginseng, astragalus root, etc.it has been successfully applied in the treatment of lung cancer, gynecologic malignant tumor and so on\cite{5}, but there is not much research on its curative effect in the colon cancer at present. In the study, Aidi injection was added to the comprehensive treatment of patients with colon cancer, and its clinical application value was explored from the serum tumor markers, peripheral blood immune molecules and other aspects so as to lay the foundation for subsequent clinical practice, now reported as follows.
2. Information and methods

2.1 General information

92 cases of patients with colon cancer who were hospitalized in Deyang People’s Hospital in Sichuan Province between October 2013 and October 2016 were collected as the research subjects, and the patients signed the informed consent themselves. The therapies were reviewed, and according to the different therapies they received, the patients were divided into the control group who received intravenous chemotherapy alone and the observation group who received Aidi injection-assisted intravenous chemotherapy. The control group included 50 cases, including 26 men and 24 women that were 38-79 years; the observation group included 42 cases, including 22 men and 20 women that were 40-76 years old. The gender and age distribution of the two groups were not statistically significant (P>0.05), and the hospital ethics committee approved the study.

2.2 Therapy

Control group received FOLFOX4 intravenous chemotherapy alone, specifically as follows: oxaliplatin (from Chengdu Changqing Pharmaceutical Co., Ltd., approved by H20020648 before March 2015, and from Hainan Jinrui Pharmaceutical Co., Ltd., approved by H20143023 after that) 85 mg/m², by intravenous drip, on d1; calcium leucovorin (from Shandong Laxuin Pharmaceutical Co., Ltd., approved by H20054302 before March 2015, and from Shanxi Pude Pharmaceutical Co., Ltd., approved by H14022464 after that) 200 mg/m², by intravenous drip, on d1; 5-fluorouracil (Tianjin Kingyork Amino Acid Co., Ltd., approved by H12020959) 400 mg/ m², by intravenous drip, on d1, then continuous pumping at 600 mg/ m², on d1-d2, 14 d as one cycle, for continuous 4 cycles of treatment. Observation group of patients, based on FOLFOX4 intravenous chemotherapy, received Aidi injection for auxiliary treatment, specifically as follows: Aidi injection (Guizhou Yibai Pharmaceutical Co., LTD., model Aeroset) was used to determine the interleukin-2 (IL-2), interferon γ (IFN-γ), interleukin-4 (IL-4) and interleukin-10 (IL-10), and the levels of Th17 cytokines were determined, including interleukin-17A (IL-17A) and interleukin-22 (IL-22).

2.3 Serum tumor markers

Before and after treatment, 2-3 mL of cubital venous blood was extracted from two groups of patients at the same point in time, anti-coagulated with heparin and then centrifuged at 3 500 r/min for 10-15 min, the upper serum was collected, and the ELISA kit instructions were followed to detect the levels of tumor markers, including carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199), carbohydrate antigen 50 (CA50), pleiotrophin (PTN) and colon cancer-specific antigen-2 (CCSA-2). The ELISA kit was purchased from the United States Abcam Company, and article number was MSK-109, LAK-637, AJS-184, MDJ-672 and LKS-493 respectively.

2.4 Peripheral blood immune molecules

Before and after treatment, cubital venous blood was obtained from two groups of patients in the same way and anti-coagulated, and automatic blood biochemical analyzer (Abbott laboratories pharmaceutical co., LTD., model Aeroset) was used to determine interleukin-17A (IL-17A) and interleukin-22 (IL-22).

2.5 Statistical methods

Obtained data were counted by specially-assigned person, and statistical software was SPSS 21.0. Serum and peripheral blood detection data were in terms of mean ± standard deviation, and comparison was by t test. Statistics P<0.05 was the standard of statistical significance in differences.

3. Results

3.1 Changes in serum tumor markers before and after treatment

Before and after treatment, comparison of serum tumor markers CEA (mg/L), CA199 (kU/L), CA50 (IU/mL), PTN (μg/L) and CCSA-2 (μg/L) levels between two groups of patients was as follows: before treatment, differences in serum CEA, CA199, CA50, PTN and CCSA-2 levels were not statistically significant between two groups of patients (P>0.05); after treatment, serum CEA, CA199, CA50, PTN and CCSA-2 levels of both groups were lower than those before treatment, and serum CEA, CA199, CA50, PTN and CCSA-2 levels of observation group were lower than those of control group (P<0.05), shown in Table 1.

Table 1.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>CEA</th>
<th>CA199</th>
<th>CA50</th>
<th>PTN</th>
<th>CCSA-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>50</td>
<td>Before treatment</td>
<td>14.32±1.79</td>
<td>35.27±4.88</td>
<td>62.83±7.11</td>
<td>173.28±20.17</td>
<td>20.73±2.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>7.15±0.84</td>
<td>20.06±2.88</td>
<td>37.66±4.52</td>
<td>99.63±10.24</td>
<td>12.63±1.72</td>
</tr>
<tr>
<td>Observation group</td>
<td>42</td>
<td>Before treatment</td>
<td>14.51±1.86</td>
<td>34.98±4.76</td>
<td>62.79±7.05</td>
<td>174.66±21.05</td>
<td>20.84±2.91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>7.15±0.84</td>
<td>20.06±2.88</td>
<td>37.66±4.52</td>
<td>99.63±10.24</td>
<td>12.63±1.72</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12.74±1.89</td>
<td>15.88±2.12</td>
<td>74.36±9.37</td>
<td>7.03±0.85</td>
<td></td>
</tr>
</tbody>
</table>

Note: compared with same group before treatment, *P<0.05; compared with control group after treatment, #P<0.05.
Changes in peripheral blood Th1/Th2 cytokine levels before and after treatment.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>IL-2</th>
<th>IFN-γ</th>
<th>IL-4</th>
<th>IL-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>50</td>
<td>Before treatment</td>
<td>5.48±0.71</td>
<td>20.38±2.95</td>
<td>16.83±2.09</td>
<td>94.37±10.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>6.71±0.75</td>
<td>32.61±4.85</td>
<td>11.52±1.74</td>
<td>75.06±8.21</td>
</tr>
<tr>
<td>Observation group</td>
<td>42</td>
<td>Before treatment</td>
<td>5.46±0.68</td>
<td>20.51±2.85</td>
<td>17.79±2.11</td>
<td>95.44±11.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>11.09±1.85*</td>
<td>48.93±5.62*</td>
<td>5.08±0.74*</td>
<td>36.92±4.51*</td>
</tr>
</tbody>
</table>

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

3.2 Changes in peripheral blood Th1/Th2 cytokines before and after treatment

Before and after treatment, comparison of peripheral blood Th1/Th2 cytokines IL-2 (ng/L), IFN-γ (μg/L), IL-4 (ng/L) and IL-10 (μg/L) levels between two groups of patients was as follows: before treatment, peripheral blood Th1/Th2 cytokine levels were not significantly different between two groups of patients (P>0.05); after treatment, peripheral blood IL-2 and IFN-γ levels of both groups were higher than those before treatment while IL-4 and IL-10 levels were lower than those before treatment, and peripheral blood IL-2 and IFN-γ levels of observation group were higher than those of control group while IL-4 and IL-10 levels were lower than those of control group (P<0.05), shown in Table 2.

3.3 Th17 cytokines

Before and after treatment, comparison of peripheral blood Th17 cytokines IL-17A and IL-22 levels between two groups of patients was as follows: before treatment, peripheral blood Th17 cytokine levels were not significantly different between two groups of patients (P>0.05); after treatment, peripheral blood IL-17A and IL-22 levels of both groups were lower than those before treatment, and peripheral blood IL-17A and IL-22 levels of observation group were lower than those of control group (P<0.05), shown in Table 3.

Table 3.

Changes in peripheral blood Th17 cytokine levels before and after treatment (pg/mL).

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Time</th>
<th>IL-17A</th>
<th>IL-22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>50</td>
<td>Before treatment</td>
<td>3.71±0.45</td>
<td>39.47±4.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>2.62±0.33*</td>
<td>21.63±2.95*</td>
</tr>
<tr>
<td>Observation group</td>
<td>42</td>
<td>Before treatment</td>
<td>3.68±0.39</td>
<td>39.61±4.75</td>
</tr>
<tr>
<td></td>
<td></td>
<td>After treatment</td>
<td>1.47±0.18*</td>
<td>10.72±1.38*</td>
</tr>
</tbody>
</table>

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

4. Discussion

Colon cancer is common in clinical practice, radical surgery is the best treatment for early-middle patients, and advanced patients have lost surgical opportunity, so the intravenous chemotherapy is the most common way to prolong the survival time. FOLFOX4 chemotherapy is the intravenous chemotherapy commonly studied at present, the role in extending the survival time of patients with advanced colon cancer has been proven, but some scholars think that FOLFOX4 intravenous chemotherapy alone cannot ascend 2-year and 5-year survival rate, in other words, the effect of pure FOLFOX4 chemotherapy treatment of advanced colon cancer is limited. Combined traditional Chinese and western medicine therapy is the new way to treat patients with advanced tumor, Aidi injection is the Chinese patent medicine that is currently recommended for colon cancer treatment, blister beetle in the prescription breaks blood and eliminates syndrome as well as attacks toxin and removes sore, ginseng can supplement qi and stem desertion, astragalus tonifies qi and strengthens exterior, acahanthopanax tonifies deficiency and support the weak, and all drugs work together to supplement qi and strengthens exterior as well as disperse stasis and dissipate binds[6,7].

In the study, Aidi injection was added on the basis of intravenous chemotherapy as auxiliary treatment in order to clarify the role of combined Chinese and western medicine treatment in expanding the clinical benefit of colon cancer patients.

Serum tumor markers are the most commonly used indicators to macro reflect the disease severity in patients with malignant tumor, and evaluate the treatment efficacy, and there are many serum tumor markers abnormally expressed in colon cancer patients[8,9]. CEA, CA199 and CA50 belong to the broad-spectrum tumor markers, which are highly expressed in the serum of multiple malignancies, including colorectal cancer, ovarian cancer and cervical cancer[10]. PTN is highly expressed in the embryo tissue, the level drops rapidly after birth, and many studies have shown that highly expressed PTN is closely related to the proliferation and invasion of tumor cells, and can promote tumor angiogenesis and suppress tumor cell apoptosis[11]. CCSA-2 belongs to colorectal cancer-specific antigen, its diagnostic specificity and sensitivity to colorectal cancer are both high, they are the newly discovered colorectal cancer tumor markers, and their high expression mostly indicates poor outcome.

In the study, serum levels of above tumor markers were compared between two groups of patients, and it was found that compared with control group, the observation group of patients were with lower serum CEA, CA199, CA50, PTN and CCSA-2 levels after treatment, confirming that the adjuvant Aidi injection therapy can macroscopically improve the curative effect of the overall therapy.

Th1 and Th2 cells are the T lymphocyte subsets with different functions, the expression of the two are in dynamic equilibrium in the physiological state, and their expression imbalance in the case of...
malignant tumor is directly involved in the progress of tumor[12,13]. Previous studies have shown that patients with colon cancer are in Th2 cytokine-dominant state, which is one of the most important mechanisms for immune escape of tumor cells. Th1 cells mainly secrete IL-2 and IFN-γ, Th2 cells mainly secrete IL-4 and IL-10, peripheral blood Th1/Th2 cytokine expression in two groups of patients were detected in the study, and it was found that compared with those before treatment, peripheral blood Th1 cytokine levels increased while Th2 cytokine levels decreased in both groups after treatment; further compared with control group, the observation group were with higher peripheral blood Th1 cytokine levels and lower Th2 cytokine levels after treatment, confirming that the Aidi injection-assisted intravenous chemotherapy can effectively reverse the imbalance of Th1/Th2 cytokines in patients with colon cancer, and reduce the Th2 cytokine hyperfunction and the resulting immune escape of tumor cells.

The role of Th17 cells in tumor immunity has received more and more attention, and previous studies have shown that peripheral blood Th17 cell levels in patients with malignant tumor are higher than those in normal subjects, and their levels are highly consistent with tumor stage[14,15]. Activated Th17 cells mainly secreted IL-17A, IL-22 and other cytokines, which are highly expressed in patients with colon cancer, and participate in the inflammation and immune state changes in local tumor[16,17]. It was found in the study that peripheral blood IL-17A and IL-22 levels in both groups after treatment were lower than those before treatment, and peripheral blood IL-17A and IL-22 levels of observation group were lower than those of control group after treatment, which indicates that Aidi injection-assisted intravenous chemotherapy can effectively inhibit the immune function of Th17 cells, and help to optimize the tumor immune state and curb its progress.

To sum up, it can be concluded as follows: Aidi injection-assisted intravenous chemotherapy can effectively reduce the serum tumor marker contents and optimize immune molecule levels in patients with colon cancer, and it is worth popularization and application in clinical practice in the future.

References