Effect of nutritional support + intravenous chemotherapy on anti-tumor immunity and cancer cell proliferation in patients with colon cancer complicated by incomplete intestinal obstruction

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ABSTRACT

Objective: To study the effect of nutritional support + intravenous chemotherapy on anti-tumor immunity and cancer cell proliferation in patients with colon cancer complicated by incomplete intestinal obstruction. Methods: Patients with colon cancer complicated by incomplete intestinal obstruction who were treated in Midi Branch, Pangang Group General Hospital between March 2015 and October 2017 were selected and randomly divided into the nutrition group who accepted nutritional support + FOLFOX4 intravenous chemotherapy and the control group who accepted FOLFOX4 intravenous chemotherapy alone, and they underwent surgery after two cycles of chemotherapy. The contents of immune cells in peripheral blood and the contents of immune cytokines in serum were determined before chemotherapy and two cycles after chemotherapy; the expression levels of proliferation genes in colon cancer lesions were determined after surgical resection. Results: Compared with those of same group before chemotherapy, peripheral blood Treg, Th9, Th17 and Th22 contents as well as serum IL-4, IL-9, IL-10, TGF-β1, IL-17 and IL-22 contents of nutrition group were decreased significantly after chemotherapy whereas peripheral blood Treg, Th9, Th17 and Th22 contents as well as serum IL-4, IL-9, IL-10, TGF-β1, IL-17 and IL-22 contents of control group did not change significantly after chemotherapy, and compared with those after chemotherapy between groups, peripheral blood Treg, Th9, Th17 and Th22 contents as well as serum IL-4, IL-9, IL-10, TGF-β1, IL-17 and IL-22 contents of nutrition group were significantly lower than those of control group, and CyclinD1, Bcl-2, USP22, VEGF and N-cadherin mRNA expression were not different from those of control group. Conclusion: Nutritional support + intravenous chemotherapy can improve the anti-tumor immune response without affecting the proliferation of cancer cells in the lesion of patients with colon cancer complicated by incomplete intestinal obstruction.

1. Introduction

Colon cancer is one of the most common digestive tract malignancies in China, its occurrence is closely related to genetic factors, dietary factors and so on, and its incidence has been rising in recent years. In clinical practice, part of the patients with colon cancer are first manifested as the intestinal obstruction, the colon cancer patients combined with complete intestinal obstruction should receive emergency surgery, and colon cancer patients combined with incomplete intestinal obstruction may consider limited operation[1-2]. In the course of colon cancer, the high metabolism of tumor lesions can cause various nutrients in the body to be constantly consumed and the body to be in a state of malnutrition; after the occurrence of incomplete intestinal obstruction, the nutritional risk of emergency surgery is greater, and the necessary preoperative adjuvant therapy should be performed before limited operation. Neoadjuvant chemotherapy is a common preoperative adjuvant therapy for patients with malignant tumor,
which kills cancer cells to create favorable conditions for radical resection of the lesions[3]; preoperative nutrition support can target the malnutrition state to supplement nutrients and reduce the nutritional risk of surgery[4]. In the following studies, we specifically analyzed the effects of nutritional support + intravenous chemotherapy on anti-tumor immunity and cancer cell proliferation in patients with colon cancer complicated by incomplete intestinal obstruction.

2. General information and research methods

2.1 General case information

Patients with colon cancer complicated by incomplete intestinal obstruction who were treated in Midi Branch, Pangang Group General Hospital between March 2015 and October 2017 were chosen. All patients were diagnosed with incomplete intestinal obstruction by abdominal erect pain film and got better after conservative treatment, they were diagnosed with colon cancer by colonoscopic pathological biopsy and had no significant distant metastases, and they intended to receive radical operation for colon cancer. A total of 62 patients were enrolled and divided into two groups by random number table, each with 31 cases. There were 18 males and 13 females in the nutrition group, and they were 42-62 years old; there were 17 males and 14 females in the control group, and they were 41-60 years old. There was no significant difference in the general data between the two groups (P>0.05).

2.2 Research methods

2.2.1 Nutritional support and chemotherapy methods

Both groups of patients received FOLFOX4 chemotherapy after admission, and the method was as follows: intravenous drip of oxaliplatin 85 mg/m² on day 1, intravenous drip of leucovorin calcium 200 mg/m² on day 1-2 and intravenous drip of 5-fluourouracil-400 mg/m² on day 1-2, 14 days as one cycle of chemotherapy, for a total of 2 times of chemotherapy as well as stomach protection, liver protection, vomiting stopping, hematopoiesis promoting and other routine symptomatic and supportive treatments during chemotherapy. On the basis of the above treatment, nutrition group received nutritional support, which was as follows: total parenteral nutrition with the calorie of 25 kcal/kg/d and the fat emulsion and glucose energy ratio of 2:3 was provided at first, then gradually changed to parenteral nutrition combined with enteral nutrition, and finally changed to total enteral nutrition support until the operation was started.

2.2.2 Detection of indexes in peripheral blood and serum

6-8 mL of cubital venous blood was collected before chemotherapy and two cycles after chemotherapy, 5-6 mL cubital venous blood was taken and centrifuged to separate serum, and then the Elisa kit instructions were followed for experiments and determination of IL-4, IL-9, IL-10, TGF-β1, IL-17 and IL-22 contents; the rest of the cubital venous blood was taken and anti-coagulated with EDTA to incubate fluorescence antibody, and the contents of Treg, Th9, Th17 and Th22 were determined on the flow cytometer.

2.2.3 Detection of gene expression in colon cancer lesions

After surgical resection, right amount of colon cancer lesions was collected from the two groups of patients, the kit was used to extract the RNA from the tissue, and the RNA was used as template to synthesize cDNA; cDNA was taken to configure PCR reaction system, the amplification was done on the PCR apparatus, and the CyclinD1, Bcl-2, USP22, VEGF and N-cadherin mRNA expression were detected.

2.3 Statistical methods

Software SPSS 20.0 was used to input the data, the differences in measurement data between the two groups were analyzed by t test and P<0.05 indicated statistical significance in the differences.

3. Results

3.1 Peripheral blood immune cell contents

Before chemotherapy and 2 cycles after chemotherapy, analysis of peripheral blood immune cells Treg, Th9, Th17 and Th22 contents between the two groups of patients was as follows: compared with those of same group before chemotherapy, peripheral blood Treg, Th9, Th17 and Th22 contents of nutrition group were significantly decreased after chemotherapy (P<0.05) whereas peripheral blood Treg, Th9, Th17 and Th22 contents of control group did not change significantly after chemotherapy (P>0.05); compared with those after chemotherapy between groups, peripheral blood Treg, Th9, Th17 and Th22 contents of nutrition group were significantly lower than those of control group (P<0.05).

| Table 1. |
| Changes of peripheral blood immune cells in the two groups of patients. |  |
| Groups          | n | Time             | Treg     | Th9     | Th17     | Th22     |
|Nutrition group  | 31 | Before chemotherapy | 9.12±1.03 | 1.33±0.16 | 4.86±0.62 | 3.47±0.52 |
|                 | 31 | After chemotherapy | 5.42±0.78* | 0.79±0.11* | 2.72±0.35* | 1.77±0.24* |
|Control group    | 31 | Before chemotherapy | 9.19±0.95 | 1.31±0.14 | 4.91±0.58 | 3.51±0.45 |
|                 | 31 | After chemotherapy | 9.08±1.03 | 1.28±0.16 | 4.78±0.51 | 3.42±0.41 |

* comparison between before and after chemotherapy within group, P<0.05; * comparison between groups after chemotherapy, P<0.05.
3.2 Serum immune cytokine contents

Before chemotherapy and 2 cycles after chemotherapy, analysis of serum immune cytokines IL-4 (pg/mL), IL-9 (pg/mL), IL-10 (pg/mL), TGF-β1 (ng/mL), IL-17 (pg/mL) and IL-22 (pg/mL) between the two groups of patients was as follows: compared with those of the same group before chemotherapy, serum IL-4, IL-9, IL-10, TGF-β1, IL-17 and IL-22 contents of nutrition group were significantly decreased after chemotherapy (P<0.05) whereas serum IL-4, IL-9, IL-10, TGF-β1, IL-17 and IL-22 contents of control group did not change significantly after chemotherapy (P>0.05); compared with those after chemotherapy between groups, serum IL-4, IL-9, IL-10, TGF-β1, IL-17 and IL-22 contents of nutrition group were significantly lower than those of control group (P<0.05).

3.3 Proliferation gene expression in colon cancer lesions

After surgical resection, analysis of proliferation genes CyclinD1, Bcl-2, USP22, VEGF and N-cadherin expression in colon cancer lesions between the two groups of patients was as follows: CyclinD1, Bcl-2, USP22, VEGF and N-cadherin mRNA expression in colon cancer lesions of nutrition group were not significantly different from those of control group, and the differences in CyclinD1, Bcl-2, USP22, VEGF and N-cadherin expression in colon cancer lesions were not statistically significant between the two groups of patients (P>0.05).

4. Discussion

Incomplete intestinal obstruction is the first manifestation for some patients with colon cancer. When colon cancer progresses to incomplete intestinal obstruction, the tumor lesion is large, locally infiltrates to different levels and is difficult to be removed by radical resection, and using preoperative neoadjuvant chemotherapy to kill cancer cells can increase the chances of radical resection of lesions[5]. Therefore, under the premise of effective conservative treatment of intestinal obstruction, it is clinically recommended that neoadjuvant chemotherapy should be conducted before the surgery of colon cancer combined with incomplete intestinal obstruction and emergency operation should be replaced by limited operation[6,7]. But in the process of colon cancer lesion growth, the metabolism is active and will consume the nutrients in the body and lead to undernutrition, and the effects of incomplete intestinal obstruction on eating will further aggravate malnutrition, so the nutritional risk of elective surgery is high[8]. In the study, in view of the perioperative nutritional risk of patients with colon cancer complicated by incomplete intestinal obstruction, nutrition support was provided during intravenous chemotherapy in order to supplement nutrients and improve nutritional status through parenteral and enteral nutritional support. Immune hypofunction is an important manifestation of malnutrition in patients with malignant tumor, the differentiation of a variety of immune cells is abnormal, and Treg, Th9, Th17, Th22 and other immunosuppressive cells are excessively differentiated and increased in contents, which can inhibit the scavenging effects of specific immune response and nonspecific immune response on tumor cells and promote the development of tumor[9,11]. Analysis of the changes of above immunosuppressive cell contents in peripheral blood before and after chemotherapy showed that compared with those before chemotherapy, peripheral blood Treg, Th9, Th17 and Th22 contents of nutrition group decreased significantly whereas peripheral blood Treg, Th9, Th17 and Th22 contents of control group did not change significantly after chemotherapy. This means that the immune response is without obvious improvement after patients with colon cancer complicated by incomplete intestinal obstruction accepted intravenous chemotherapy alone while the immune response has been significantly improved after they accepted nutritional support + intravenous chemotherapy, which indicates that nutrition support + intravenous chemotherapy can enhance antitumor immune response and improve nutritional status.

In the occurrence and development of malignant tumors, immune cells such as Treg, Th9, Th17 and Th22 exert corresponding biological effects by secreting different cytokines. Treg cells take Foxp3 as surface molecules and secrete the T cell subsets of IL-4, TGF-β1 and other cytokines, which on the one hand, can suppress the differentiation of a variety of immunoactive cells through intercellular direct action and exert immunosuppressive effect, and on the other hand, suppress the antitumor immune response through the biological activity of IL-4 and TGF-β1[12]. Th9 is the newly discovered T cell subset, which is activated under the induction of IL-4 and TGF-β1, and massively secreted cytokines such as IL-9 and IL-10; IL-9 and IL-10 have negative immune regulation activity, which can inhibit the release of multiple immunoactive factors. IL-17 and IL-22 are the cytokines secreted by Th17 and
Th22 cells respectively, and both of them promote tumor cell proliferation and invasion in the course of tumor, and can speed up the progress of tumor[13,14]. In the study, in order to further clarify the effect of nutrition support on nutritional status of patients with colon cancer complicated by incomplete intestinal obstruction, the changes of above immune cytokine contents in serum before and after chemotherapy were analyzed, and the results showed that compared with those before chemotherapy, serum IL-4, IL-9, IL-10, TGF-β1, IL-17 and IL-22 contents of nutrition group decreased significantly whereas serum IL-4, IL-9, IL-10, TGF-β1, IL-17 and IL-22 contents of control group did not change significantly after chemotherapy. This indicates that nutritional support + intravenous chemotherapy can improve the immune response and nutritional status of patients with colon cancer complicated by incomplete intestinal obstruction.

The purpose of preoperative neoadjuvant chemotherapy for colon cancer combined with incomplete intestinal obstruction is to kill cancer cells and shrink tumor volume so as to create favorable conditions for radical resection of tumor lesions. The growth of cancer cells in colon cancer is related to the high expression of CyclinD1, Bcl-2, USP22, VEGF, N-cadherin and other proliferation genes. CyclinD1 is the positive regulation molecule of cell cycle, which forms complexes with corresponding kinases CDK4 and CDK6 to accelerate the cells to cross through the cell cycle checkpoint, and is conducive to the acceleration of cell cycle and the enhancement of cell proliferation activity[15]; the Bcl-2 regulates cell proliferation through anti-apoptotic way, and can block mitochondrial cytochrome C from entering into cytoplasm on the mitochondrial membrane, and then impede the apoptosis mediated by cytochrome C release[16]; USP22 is an auxiliary molecule of Myc gene family to regulate transcription, which can enhance the pro-proliferation effect mediated by N-myc and C-myc; VEGF is a growth factor that specifically acts on endothelial cells, and can promote the proliferation of cancer cells by promoting the endothelial cell growth and tumor angiogenesis in tumor lesions[17]; N-cadherin is the marker of mesenchymal cells, and its high expression can enhance the movement performance of cells to promote the invasive growth of cancer cells[18]. In the study, comparison of the differences in above proliferation gene expression in colon cancer lesions between the two groups of patients showed that CyclinD1, Bcl-2, USP22, VEGF and N-cadherin mRNA expression in colon cancer lesions of nutrition group were not significantly different from those of control group. This indicates that the nutritional support on the basis of intravenous chemotherapy will not affect the expression of proliferation genes in tumor lesions in patients with colon cancer complicated by incomplete intestinal obstruction.

Above all, it can be concluded that nutrition support + intravenous chemotherapy can improve the nutritional status and antitumor immune responses in patients with colon cancer complicated by incomplete intestinal obstruction without affecting the proliferation of cells within the tumor lesion.

References