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Effect of preoperative neoadjuvant chemotherapy on the expression of malignant molecules in colon cancer tissue and the degree of trauma caused by radical operation

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ABSTRACT

Objective: To study the effect of preoperative neoadjuvant chemotherapy on the expression of malignant molecules in colon cancer tissue and the degree of trauma caused by radical operation. **Methods:** Patients who were diagnosed with colon cancer in Fengrun People′s Hospital between March 2014 and February 2017 were selected and randomly divided into the XELOX group who accepted XELOX neoadjuvant chemotherapy combined with radical operation for colon cancer and the control group who accepted radical operation for colon cancer alone. Surgically removed colon cancer tissue was collected to test the expression of proliferation, apoptosis and invasion genes, and serum was collected to detect the contents of liver and kidney function indicators as well as inflammatory factors. **Results:** Rac1, PLD2, CHD1L, Snail, Vimentin and N-cadherin mRNA expression levels in surgically removed colon cancer lesions of XELOX group were significantly lower than those of control group while MS4A12 and ASPP2 mRNA expression levels were significantly higher than those of control group; serum ALT, AST, β 2-MG, Cys-C, sICAM-1, sVCAM-1, sTM and sE-selectin contents were not significantly different between the two groups of patients 1 day and 3 days after surgery. **Conclusion:** Preoperative neoadjuvant chemotherapy can inhibit the proliferation, apoptosis and invasion gene expression in colon cancer tissues without increasing the trauma of operation.

1. Introduction

Colon cancer is a common malignant tumor of digestive tract in our country, its incidence is increasing, the infected population is getting younger, surgical resection is the preferred way of clinical treatment of colon cancer at present, but it is affected by clinical tumor stage, the surrounding tissue infiltration and other factors, and the treatment effect is not ideal for some patients with surgical resection. Neoadjuvant chemotherapy is the treatment developed in recent years, which adopts preoperative chemotherapy to kill cancer cells, shrink tumors volume and reduce the tumor stage in order to create a more favorable local conditions for radical excision[1,2]. Although the neoadjuvant chemotherapy has exact killing effect on cancer cells, it will also cause damage to normal tissues and organs and affect the body's tolerance to trauma caused by radical surgery, which will increase the surgical trauma and affect postoperative recovery. XELOX scheme is the clinical neoadjuvant chemotherapy regimen widely used at present, and in order to define the application validity and security of the scheme before colon cancer surgery, the effect of preoperative neoadjuvant chemotherapy on the expression of malignant molecules in colon cancer tissue and the degree of trauma caused by radical operation was specifically analyzed in the study.

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2. Research subjects and methods

2.1 Research subjects

Patients who were diagnosed with colon cancer in Fengrun People′s Hospital between March 2014 and February 2017 were

selected, and all patients were diagnosed with colon cancer by pathology biopsy under colonoscopy, conformed to the surgical indications of radical operation for colon cancer and signed informed consent. A total of 114 patients were enrolled and divided into the XELOX group who accepted XELOX neoadjuvant chemotherapy combined with radical operation for colon cancer and the control group who accepted radical operation for colon cancer alone according to random number table, 57 cases in each group. The XELOX group included 33 male patients and 24 female patients that were 46-63 years old; control group included 35 male patients and 22 female patients that were 44-64 years old. There was no statistically significant difference in general information between the two groups (P>0.05).

2.2 Neoadjuvant chemotherapy regimens

Patients received intravenous injection of tropisetron 5 mg 30 min before chemotherapy, then received intravenous drip of oxaliplatin 130 mg/m^2 on the first day of chemotherapy cycle, and orally took capecitabine 1 000 mg/m^2 on the first two weeks of chemotherapy cycle, 2 times/d. 3 weeks was a chemotherapy cycle, oral vitamin B6 was provided during the chemotherapy to reduce adverse reactions, and the liver and kidney function were reviewed and symptomatic treatment was provided. Patients rested for one month after three cycles of continuous chemotherapy, and then received radical operation for colon cancer.

2.3 Detection of malignant molecule expression in colon cancer tissue

After surgical resection, adequate amount of colon cancer tissue was collected, RNA extraction kit and cDNA synthesis kit were used to separate the RNA in tissue and synthesize it into cDNA by reverse transcription, fluorescence quantitative PCR kit was used to amplify Rac1, PLD2, MS4A12, ASPP2, CHD1L, Snail, Vimentin and N-cadherin, and the mRNA expression was calculated.

2.4 Detection of liver and kidney function indexes and inflammatory indexes in serum

1 d and 3 d after operation, 3 mL of peripheral venous blood was collected from two groups of patients and centrifuged to separate serum, automatic biochemical analyzer was used to determine the contents of ALT and AST, and enzyme-linked immunosorbent assay kit was used to detect the contents of β 2-MG, Cys-C, sICAM-1, sVCAM-1, sTM and sE-selectin.

2.5 Statistical methods

SPSS 17.0 software was used for t test of measurement data between two groups and P<0.05 indicated statistical significance in differences in test results.

3. Results

3.1 Proliferation and apoptosis-related gene expression in colon cancer

Analysis of proliferation genes Rac1 and PLD2 as well as apoptosis genes MS4A12 and ASPP2 expression in surgically removed colon cancer lesions between two groups of patients was as follows: Rac1 and PLD2 mRNA expression levels in surgically removed colon cancer lesions of XELOX group were significantly lower than those of control group while MS4A12 and ASPP2 mRNA expression levels were significantly higher than those of control group. Differences in Rac1, PLD2, MS4A12 and ASPP2 mRNA expression in surgically removed colon cancer lesions were statistically significant between two groups of patients (P<0.05).

Table 1.

Comparison of proliferation and apoptosis-related genes in colon cancer lesions between two groups of patients.

Groups	n	Rac1	PLD2	MS4A12	ASPP2
XELOX group	57	0.35±0.06	0.28±0.04	2.76±0.38	2.91±0.42
Control group	57	1.03±0.14	0.98±0.11	0.96±0.13	1.06±0.17
T		19.371	22.552	20.346	17.872
P		<0.05	<0.05	<0.05	<0.05

3.2 Invasion-related gene expression in colon cancer

Analysis of invasion-related genes CHD1L, Snail, Vimentin and N-cadherin expression in surgically removed colon cancer lesions between two groups of patients was as follows: CHD1L, Snail, Vimentin and N-cadherin mRNA expression levels in surgically removed colon cancer lesions of XELOX group were significantly lower than those of control group. Differences in CHD1L, Snail, Vimentin and N-cadherin mRNA expression in surgically removed colon cancer lesions were statistically significant between two groups of patients (P<0.05).

Table 2.

Comparison of invasion-related genes in colon cancer lesions between two groups of patients.

Groups	n	CHD1L	Snail	Vimentin	N-cadherin
XELOX group	57	0.36±0.05	0.29±0.04	0.42±0.07	0.50±0.07
Control group	57	1.03±0.15	0.97±0.12	1.05±0.14	1.07±0.12
T		17.491	25.448	13.247	11.395
P		<0.05	<0.05	<0.05	<0.05

3.3 Postoperative serum indexes

1 d and 3 d after surgery, analysis of serum liver and kidney function indexes ALT (U/L), AST (U/L), β 2-MG (mg/L) and Cys-C

Table 3.

Comparison of postoperative serum liver and kidney function indexes between two groups of patients.

Groups	*n*	Time	ALT	AST	β 2-MG	Cys-C
XELOX group	57	1 d after surgery	46.22±5.56	42.62±5.71	2.98±0.35	1.55±0.20
		3 d after surgery	45.98±6.25	40.98±6.22	3.04±0.37	1.52±0.18
Control group	57	1 d after surgery	46.71±6.88	41.79±5.92	3.07±0.38	1.61±0.22
		3 d after surgery	46.02±6.71	42.15±6.25	3.01±0.32	1.54±0.18

Table 4.

Comparison of postoperative serum inflammatory response indexes between two groups of patients.

Groups	*n*	Time	sICAM-1	sVCAM-1	sTM	sE-selectin
XELOX group	57	1 d after surgery	89.22±10.32	107.78±13.25	52.42±7.74	79.52±9.25
		3 d after surgery	90.21±10.74	109.11±12.89	54.12±6.92	80.11±9.52
Control group	57	1 d after surgery	90.87±11.35	108.52±14.42	53.89±7.11	80.32±9.74
		3 d after surgery	91.28±10.83	108.78±12.52	54.25±6.79	81.02±9.83

(mg/L) as well as inflammatory response indexes sICAM-1 (ng/L), sVCAM-1 (ng/L), sTM (μg/L) and sE-selectin (ng/L) between two groups of patients was as follows: serum ALT, AST, β 2-MG, Cys-C, sICAM-1, sVCAM-1, sTM and sE-selectin contents were not significantly different between the two groups of patients 1 day and 3 days after surgery (P>0.05).

4. Discussion

The radical operation for colon cancer is the first choice for clinical treatment of colon cancer, the peripheral infiltration of the local lesion is more obvious in some patients, and the radical surgical resection is more difficult. Neoadjuvant chemotherapy is the means that has been increasingly used for preoperative treatment of malignant tumors in recent years, and the preoperative chemotherapy can effectively kill cancer cells, reduce the tumor stage and inhibit tumor cells infiltration[3]. XELOX is the neoadjuvant chemotherapy regimen composed of capecitabine and oxaliplatin, XELOX regimen is with smaller toxicity and less adverse reaction than FOLFOX regimen, it can take both efficacy and safety into account when used for preoperative chemotherapy, and it can not only effectively kill the cancer cells, but also reduce the damage to the normal tissue and function[4]. Studies have reported the positive application value of XELOX neoadjuvant chemotherapy before radical operation for colon cancer and its value for improving postoperative disease outcome[5], but there is still no clear report about the effect of the chemotherapy regimen on the malignant biological behavior of cancer cells within colon cancer lesions.

The value of neoadjuvant chemotherapy is to reduce tumor staging and corresponding malignant biological behavior. Malignant proliferation of cancer cells is an important biological behavior of colon cancer cells, and the abnormal expression of multiple proliferation and apoptosis-related genes is involved in the regulation of the biological behavior. Rac1 and PLD2 are the genes associated with cancer cell proliferation. The former is a member of the Rho family and can induce cell proliferation by promoting actin aggregation and increasing the number of new blood vessels[6,7]; the latter is a protein that participates in the regulation of cell cycle, which can antagonize the tumor suppressor gene function and increase the cyclin expression so as to promote cell cycle progression and cell proliferation[8,9]. MS4A12 and ASPP2 are genes related to apoptosis of cancer cells. The former is a member of MS4A family and can hinder cell cycle development and induce cell cycle to arrest[10]; the latter is a member of the ASPP family that activates p53 gene, which can enhance the anti-cancer activity of p53[11]. In the study, analysis of the differences of the proliferation and apoptosis-related gene expression in colon cancer lesions showed that Rac1 and PLD2 mRNA expression levels in surgically removed colon cancer lesions of XELOX group were significantly lower than those of control group while MS4A12 and ASPP2 mRNA expression levels were significantly higher than those of control group. This means that preoperative neoadjuvant chemotherapy can inhibit the cancer cell proliferation and induce cancer cell apoptosis in the lesion.

The cancer cells in colon cancer will invade the surrounding tissue on the basis of malignant proliferation, and the invasion and epithelial mesenchymal transition of the cells are the biological basis of invasive growth. CHD1L is a member of the SFN2 family that promotes cell invasion and can promote cell invasion by regulating the interaction and combination between proteins and DNA[12,13]. Snail is the key transcription factor that regulates the epithelial mesenchymal transition of the cells, which is combined with epithelial phenotype marker gene E-cadherin to inhibit its expression, weaken the epithelial phenotype of cells, reduce intercellular polarity and adhesion, thus result in epithelial phenotype transition to mesenchymal phenotype and enable the cells with strong movement performance to the surrounding tissue[14,15]. In the study, analysis

of the differences in the invasion-related gene expression in colon cancer lesions showed that CHD1L, Snail, Vimentin and N-cadherin mRNA expression levels in surgically removed colon cancer lesions of XELOX group were significantly lower than those of control group. This indicates that preoperative neoadjuvant chemotherapy can inhibit the invasion and epithelial mesenchymal transition of cancer cells in lesions.

Although neoadjuvant chemotherapy before radical operation for colon cancer can effectively kill cancer cells, chemotherapy drugs can also cause the normal tissue damage, weaken the body's ability to tolerate surgical trauma and increase the risk of tissue and viscera function injury after the operation. Liver and kidney are the most common damaged target organs in the process of chemotherapy, perioperative trauma can also increase the risk of liver and kidney function damage, and the changes in ALT, AST, β 2-MG and Cys-C contents can reflect the condition of liver and kidney function. In addition, the operation damage to the body can also cause inflammatory reaction activation, sICAM-1 and sVCAM-1 are the adhesion molecules involved in inflammatory reaction cascade activation, and the sTM and sE-selectin are the cytokines related to the platelet activation and increased blood viscosity caused by inflammation. In the study, analysis of the changes in serum liver and kidney function indexes as well as inflammation index after the operation showed that serum ALT, AST, β 2-MG, Cys-C, sICAM-1, sVCAM-1, sTM and sE-selectin contents were not significantly different between the two groups of patients. It means that compared with radical operation for colon cancer alone, preoperative neoadjuvant chemotherapy will not cause changes in postoperative liver and kidney function as well as inflammation, which indicates that preoperative neoadjuvant chemotherapy will not add tissue trauma caused by radical operation for colon cancer.

Neoadjuvant chemotherapy before radical operation for colon cancer can regulate the proliferation, apoptosis and invasion gene expression in colon cancer tissues, then inhibit cell proliferation and invasion, and induce apoptosis; meanwhile, preoperative neoadjuvant chemotherapy will not increase the trauma of operation.

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