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Original Article

The Clinical effects and prognosis of postoperative FOLFOX4 chemotherapy on patients with stage II/III colon cancer

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Abstract: Objective: To observe the effects of FOLFOX4 chemotherapy regimen on patients with stage II/III colon cancer postoperatively. Methods: 103 patients with stage II/III colon cancer accepted FOLFOX4 chemotherapy regimen postoperatively from February, 2009 to February, 2012 were selected as observation group. While 102 patients with stage II/III colon cancer in the same period only treated with simple surgical treatment were selected as the control group. All the patients were followed up for 3 years, and the disease-free survival rate, recurrence and metastasis rate, and mortality of two groups were compared. We also analyzed the toxic and side effects of the chemotherapy regimen on patients with stage II/III colon cancer in the observation group. Results: Followed up for 3 years, the median disease-free survival time of the observation group was 19 months, which was significantly higher than 13 months of the control group (P=0.017). In our study, patients in the observation group showed a higher disease-free survival rate, but lower recurrence and metastasis rate and mortality. And the differences were statistically significant (χ^2=9.5114, P=0.009). The DFS of the observation group was significantly affected by the age and the chemotherapy cycle of the patients (P=0.007, 0.001); the age, TNM stage, the first chemotherapy time and the chemotherapy cycle were closely related to the recurrence (P=0.003, 0.011, 0.039 and 0.020); the first chemotherapy time and chemotherapy cycle significantly affected the liver metastasis of the cancer (P<0.001). After the FOLFOX4 chemotherapy, there was few severe toxic and side effects, most of the side effects were comparatively light and tolerable. Conclusion: FOLFOX4 chemotherapy regimen can improve the disease-free survival rate and reduce the recurrence and metastasis rate and mortality of patients with stage II/III colon cancer postoperatively, which has certain clinical value.

Keywords: Stage II/III colon cancer, chemotherapy, prognosis, toxic and side effects

Introduction

In recent years, the incidence of colon cancer is growing in China and has become one of the malignant tumors that seriously affect Chinese residents [1]. Currently, the clinical treatment of colon cancer is still based on surgery. The treatment effect of surgery provided to patients at stage I is often better than those at stage II/III [2]. Due to the highly malignant degree of colon cancer, patients at stage II/III always have high risk of postoperative recurrence and metastasis, short disease-free survival time as well as high mortality [3]. The postoperative disease control is very important since the surgical treatment applied singly cannot satisfy the clinical requirements in the treatment of stage II/III colon cancer. Chemotherapy, as a very significant non-surgical anti-tumor therapy, plays a key role not only in the treatment of those patients could not carry on a surgery due to their physical condition or disease level, but also on the prevention and treatment of cancer recurrence, expansion and metastasis [4]. However, chemotherapy is often associated with different degrees of toxic and side effects; due to the poor physical condition of patients with stage II/III colon cancer, the evaluation of the safety and efficacy of adjuvant chemotherapy is very important; but, a standard adjuvant chemotherapy regimen for them is still not confirmed yet [5]. In clinic, the patients with colon

Table 1. Comparison of the recurrence and metastasis rate and disease-free survival rate of patients in eachgroup (n (%))

Group	No. of patients	Disease-free survival	Recurrence and metastasis	Death
Control group	102	49 (48.04)	35 (34.31)	18 (17.65)
Observation group	103	71 (68.93)	23 (22.33)	9 (8.74)
χ^2 value	9.5114			
P value	0.009			

cancer unsuitable for surgery can be treated with palliative care, and the treatment effect of FOLFOX4 chemotherapy can be obtained. However, as a supplementary treatment for patients with stage II/III colon cancer, the validity and safety of chemotherapy regimen have not been clearly concluded [6]. This study is mainly aimed to discuss FOLFOX4 chemotherapy regimen used as an adjunctive treatment on stage II/III, and its influence on prognosis as well as the evaluation on toxic and side effects. The report is as follows.

Materials and methods

Basic material

103 patients with stage II/III colon cancer accepted FOLFOX4 chemotherapy adjunctive treatment after surgery were selected as observation group to explore the influence of FOLFOX4 adjunctive chemotherapy on the survival and prognosis of stage II/III patients in our hospital from February, 2009 to February, 2012. Among the total 103 cases, there were 53 cases of male and 50 cases of female, aging from 48 to 74, and the median age was 58. According to the TNM stage criteria [7], suggested by Union for International Cancer Control (UICC) in 2009, the patients can be divided into stage II colon cancer of 44 cases and stage III of 59 cases (19 cases of stage IIIA, 20 cases of stage IIIB and 20 cases of stage IIIC). 102 patients with stage II/III colon cancer in the same period only treated with surgery were selected as the control group. Among them, there were 52 cases of male and 50 cases of female, aging from 46 to 77, and the median age was 59. The condition of TNM stage showed 42 cases of stage II colon and 60 cases of stage III (17 cases of stage IIIA, 21 cases of stage IIIB and 22 cases of stage IIIC). The inclusion criteria in this study: the patients were diagnosed stage II/III colon cancer by pathology department; there was no serious complication after surgical treatment; no obvious evidence showed that the patients were not suitable for postoperative adjuvant chemotherapy; the records of medical material were complete. Exclusion criteria: patients had other tumors; patients should not do chemotherapy owing to severely damaged liver and kidney function; the records of medical material were incomplete or the patients unable to follow-up; the patients received postoperative radiotherapy or other chemotherapy; the patients with hematopoietic dysfunction should not do chemotherapy. According to statistical analysis, there was no significant difference (P>0.05) in age, gender or TNM stage of the selected patients, which complied with the principle of sampling survey and can proceed with the research. All the patients involved in this research were informed, and they confirmed to participate in the research voluntarily. This research was approved by the hospital Ethics Committee and all the follow up procedures were implemented strictly according to the regulations of the Ethics Committee.

Chemotherapy regimen

All of the 103 patients in observation group took FOLFOX4 chemotherapy, details as following: the first day: intravenous drip of 85 mg/m^2 oxaliplatin (Shenzhen Haiwang Pharmaceutical Co., Ltd. Zhunzi H20031048) and 200 mg/m^2 calcium folinate (Jiangsu Hengrui Medicine Co., Ltd. Zhunzi H20000584), intravenous injection of 400 mg/m^2 fluorouracil (Shanghai Xudong Haipu Pharmaceutical Co., Ltd. Zhunzi H31020593) and continuously intravenous drip of 600 mg/m^2 fluorouracil for 22 hours; the second day: intravenous injection of 400 mg/m^2 fluorouracil and continuously intravenous drip of 600 mg/m^2 fluorouracil for 22 hours. The patients had a clinical disease evaluation in 3-6 weeks after surgery and then took the first chemotherapy. Examine liver and kidney function every two weeks, and repeat chemotherapy once again if the organ function works well; patients received 8~12 chemotherapy in total.

Table 2. Multivariate analysis on influence factors of postoperative DFS of colon cancer patients in observation group

Variable	B	SE	Wald value	*P* value	OR value	95% Confidence interval
Gender	1.023	0.981	1.087	0.297	2.782	0.407~19.025
Age	1.534	0.567	7.320	0.007	4.637	1.526~14.088
TNM stage	0.568	0.431	1.737	0.188	1.765	0.758~4.107
First chemotherapy time	1.446	1.215	1.416	0.234	4.246	0.392~45.943
Chemotherapy cycle	0.789	0.243	10.542	0.001	2.201	1.367~3.544

Observation indicators and response evaluation

Following up for 3 years (the deadline of follow-up is July 31, 2015 and the interval time is two months), observed and recorded the postoperative disease-free survival time, recurrence and metastasis condition and mortality of all the patients (the period of therapeutic effect evaluation was 3 year, patients took evaluation every 3 months, with the detection method mainly based on imaging examination and the diagnosis confirmed by pathological examination). The disease-free survival time means the time patients died due to all kinds of reasons or tumor metastasis after the surgery. We took multivariate analysis on the DFS time, recurrence and metastasis condition of the patients in observation group, the related indicators included gender, age, TNM stage, first chemotherapy time, chemotherapy cycle and so on. Meanwhile, evaluate the toxic side effects of chemotherapy according to NCI2CTC AE 3.0 criteria [8] suggested by American's National Cancer Institute. Specifically, the toxic and side effects of chemotherapy include: neurotoxicity, alopecia, anemia, constipation, inappetence, nausea and vomiting, oral ulcer and phlebitis etc., which can be categorized as level I, II and III from low to high according to severe degree. There was no quitting in the halfway or losing follow-ups among the groups.

Statistical methods

All the quantitative data involved in this research were summarized and analyzed by SPSS 21.0 software. The age comparison of patients in each group was examined by t test; the comparison of gender, TNM stage and prognosis were examined by χ^2 test; And Logistic analysis was adopted for multivariate analysis. $P<0.05$ means that the difference has statistical significance.

Results

FOLFOX4 adjunctive chemotherapy regimen can improve the prognosis of patients

Following up for 3 years, the median disease-free survival time of the observation group was 19 months, which was significantly higher than that in the control group for 13 months. The disease-free survival rate in the observation group was higher than that in the control group, and the recurrence rate and mortality rate were lower than those in the control group. The differences were statistically significant by χ^2 test ($P=0.009$), which shows FOLFOX4 used as an adjunctive chemotherapy regimen could obviously improve the prognosis of patients, the data are shown in **Table 1**.

Multivariate analysis on influence factors of DFS in observation group

As shown in **Table 2**, age and chemotherapy cycle of patients significantly affected the postoperative disease-free survival time ($P=0.007$, 0.001). The younger age and longer chemotherapy cycle led to longer postoperative disease-free survival time. However, the gender, TNM stage and the first Chemotherapy time did not make great influence on postoperative disease-free survival time.

Multivariate analysis on influence factors of postoperative recurrence in patients with colon cancer in observation group

As shown in **Table 3**, the gender, TNM stage, first chemotherapy time and chemotherapy cycle were closely related to their recurrence ($P=0.003$, 0.011, 0.039, 0.020). The older age and higher TNM stage led to higher recurrence rate. And earlier first chemotherapy time and longer chemotherapy cycle made a lower recurrence rate.

Table 3. Multivariate analysis on postoperative recurrence in patients with colon cancer in observation group

Variable	B	SE	Wald value	*P* value	OR value	95% Confidence interval
Gender	0.447	0.432	1.071	0.301	1.564	0.671~3.646
Age	1.724	0.583	8.745	0.003	5.607	1.788~17.579
TNM stage	1.344	0.531	6.406	0.011	3.834	1.354~10.856
First chemotherapy time	2.034	0.987	4.247	0.039	7.645	1.105~52.906
Chemotherapy cycle	1.257	0.541	5.399	0.020	3.515	1.217~10.149

Table 4. Multivariate analysis on influence factors of postoperative liver metastasis of patients in observation group

Variable	B	SE	Wald value	*P* value	OR value	95% Confidence interval
Gender	0.561	0.433	1.679	0.195	1.752	0.75~4.095
Age	1.739	0.991	3.079	0.079	5.692	0.816~39.7
TNM stage	1.005	0.872	1.328	0.249	2.732	0.495~15.091
First chemotherapy time	1.548	0.234	43.763	0.000	4.702	2.972~7.438
Chemotherapy cycle	1.776	0.327	29.498	0.000	5.906	3.111~11.211

Table 5. Evaluation of toxic and side effects from adjuvant chemotherapy (n (%), n=103)

Toxic and side effects	Toxicity categories		
	I	II	III
Neurotoxicity	48 (46.60)	13 (12.62)	2 (1.94)
Aolpecia	39 (37.86)	18 (17.48)	0 (0.00)
Anemia	12 (11.65)	6 (5.83)	0 (0.00)
Constipation	17 (16.50)	8 (7.77)	0 (0.00)
Inappetence	68 (66.02)	21 (20.39)	8 (7.77)
Nausea and vomiting	57 (55.34)	7 (6.80)	2 (1.94)
Oral ulcer	8 (7.77)	5 (4.85)	2 (1.94)
Phlebitis	15 (14.56)	4 (3.88)	0 (0.00)

Multivariate analysis on influence factors of patients' liver metastasis in observation group

As shown in **Table 4**, the first chemotherapy time and chemotherapy cycle of the patients significantly affected the liver metastasis (P<0.001). The earlier first chemotherapy time and longer chemotherapy cycle led to lower metastasis rate. But other factors were not obviously related to metastasis.

Condition of toxic and side effects from adjuvant chemotherapy of patients in observation group

As shown in **Table 5**, toxic and side effects were evaluated after receiving the FOLFOX4 adjuvant chemotherapy regimen, and the reaction degree of each index was mild. There was less degree III toxicity reaction, and most of them can be tolerated.

Discussion

Colon cancer is a common digestive system tumor in clinic that occurred on colon parts, which is used to occur on the adjacent area of sigmoid colon and rectum. Colon cancer usually has high malignant degree that can severely threat the health and even the life of patients [9]. Colon cancer is very common in western countries, however, in recent years, with the improvement of life standards, changes in diet structure and daily life, and the deterioration of the environment, the prevalence rate of colon cancer in China is still high. Consistent with other digestives system tumors, the main treatment of colon cancer is surgery, which follows the principle of trying to bring a radical cure, avoid the damage of pelvic autonomic nerve, save the patient of urination and defecation function as well as sexual function, etc. The specific surgical type includes right/left hemicolectomy, transverse colectomy, sigmoid colorectomy and colostomy, etc. [10]. The effect of surgery for stage I patients was much better than those of stage II/III. Surgical treatment, as

the main method for the treatment of colon cancer in the present, usually doesn't have an ideal effect and prognosis on stage II/III patients [11]. Short postoperative disease-free survival time and high rate of recurrence and mortality is still at high level in patients with advanced colon cancer. Studies have shown that assisted with suitable chemotherapy postoperatively could effectively improve disease-free survival time of tumor patients, reduce the rate of recurrence and metastasis, and improve prognosis; For example, reported by Morabito A et al. [12], the combination of gemcitabine and cisplatin applied in the postoperative adjuvant chemotherapy of non-small-cell carcinoma achieved a remarkable effect; again reported by Zhang Z et al. [13], Oxaliplatin combined with S-1 and XELOX applied in postoperative auxiliary chemotherapy of gastric cancer can significantly improve the prognosis of patients. However, there is few report on the choice of adjuvant chemotherapy for stage II/III colon cancer patients; the research is still at the exploration phase without uniform standard, and the clinic urgently needs a safe and effective adjuvant chemotherapy with feasibility [14]. FOLFOX4 chemotherapy regimen mainly uses fluorouracil, oxaliplatin and calcium folinate as treatment medicine and fluorouracil are the basic medicine. Fluorouracil is the fluoride of pyrimidine and has similar structure with uracil; through chemical reaction in cells, fluorouracil can transfer into fluorouracil deoxynucleotide and stop the synthesis of thymidylic acid, by which to slow down the replica efficiency of DNA, and further to block the cell cycle and inhibit the tumor cell proliferation [15]. Oxaliplatin is a new type of platinum anticancer drugs, in combination with calcium folinate, it can significantly enhance the fluorouracil antitumor effect [16]. FOLFOX4 regimen is often used as chemotherapy of palliative treatment for patients with colon cancer, and there are many reports revealed that it can be used as a chemotherapy regimen for colon or colorectal cancer, but it also has some side effects [17-20]. As the adjuvant chemotherapy regimen for stage II/III colon cancer patients, the safety and efficacy of FOLFOX4 regimen, as well as the relevant factors affecting the efficacy, are rarely reported.

The results of this study showed that FOLFOX4 can distinctly improve the prognosis of patients with stage II/III colon cancer, improve the disease-free survival rate, and reduce the recurrence rate and mortality. It had certain poisonous side effects, including inappetence, nausea and neurotoxicity and so on, which may be relevant to 5-FU also having certain toxicity on normal cells. But these side effects were all at a light degree and within tolerance. It is less likely to lead to severe poisonous side effects. At the same time, the study analyzed multiple factors influenced on the disease-free survival time, recurrence and metastasis of patients in observation group. It has found that the longer the chemotherapy cycle is, the longer disease-free survival time and lower recurrence and metastasis rate will be. The earlier the chemotherapy time is, the lower recurrence and liver metastasis rate will be. Also, the patient's age has a certain correlation to the recurrence and disease-free survival time. The older the patient's age is, the shorter the disease-free survival time will be. And it is more likely to relapse. This may be related to the poor physical condition and low immunity of older patients, as well as the resistance ability to chemotherapy.

In summary, FOLFOX4 chemotherapy regimen in postoperative treatment of stage II/III colon cancer, can obtain certain curative effect and deserve further investigation.

Disclosure of conflict of interest

None.

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