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Tegafur gimeracil oter combined with oxaliplatin for advanced colorectal cancer

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Abstract. – OBJECTIVE: To analyze the therapeutic actions of tegafur gimeracil oteracil combined with oxaliplatin for treating patients with advanced colorectal cancer, and its effects on the K-ras gene mutation and the CK20 mRNA.

PATIENTS AND METHODS: Forty-one patients with advanced colorectal cancer from our hospital, from October 2013 to October 2014, were enrolled in this study. After obtaining consent from the hospital Ethics Committee and the patients as well as their relatives, all 41 patients were divided into two groups. The control group, which consisted of 20 cases, were treated with capecitabine combined with oxaliplatin. The study group, which comprised of 21 cases, were treated with tegafur gimeracil oteracil combined with oxaliplatin. Both groups were followed-up after six months to evaluate the treatment outcomes.

RESULTS: The survival rate in the observation group was higher than that in the control group. The progression-free survival time (PFS) in the observation group was longer than that in the control group. The objective response rate (ORR) and disease control rate (DCR) were higher for the observation group. The differences had statistical significance ($p < 0.05$). The proportion of K-ras gene mutation in the observation group was substantially superior to that in the control group. The positive expression rate of CK 20 mRNA in the observation group was significantly lower than that in the control group. The differences had statistical significance ($p < 0.05$). The incidence of adverse reaction in the observation group was lower than that of the control group, and the differences had statistical significance ($p < 0.05$).

CONCLUSIONS: Tegafur/gimeracil/oteracil combined with oxaliplatin therapy had better treatment outcomes than capecitabine combined oxaliplatin for advanced colorectal cancer. This maybe related to K-ras gene mutation and the reduction of CK20 mRNA expression.

Key Words:

Tegafur/gimeracil/oteracil, Oxaliplatin, Colorectal cancer, K-ras gene, Cytokeratin, Progression-free survival.

Introduction

Colorectal cancer is a common malignant tumor of the digestive tract. Its morbidity and mortality rank fourth and second respectively, of all malignant gastrointestinal tract tumors. Colorectal cancer is characterized by an insidious onset, low early diagnostic rate, and poor long-term prognosis[1]. Chemotherapy is the most commonly used therapy to treat advanced metastatic colorectal cancer. Oxaliplatin combined with 5-fluorouracil (5-FU) and calcium folinate regimen (FOLFOX regimen) are the first-line treatments for advanced colorectal cancer. Oxaliplatin combined with capecitabine regimen (XELOX regimen) is convenient and effective and more acceptableed by patients. Its curative effect was equivalent to the FOLFOX regimen, but it leads to a significantly higher occurrence of hand-foot syndrome[2].

The study on the tegafur/gimeracil/oteracil, a type of thymidine phosphorylase (TP) confirmed that tegafur/gimeracil/oteracil (S-1) could be used to treat colorectal cancer with an effectiveness rate of 41%. The efficacy of tegafur/ gimeracil/oteracil combined with oxaliplatin regimen for metastatic colorectal cancer was as good as the EXLOX regimen. Moreover, the occurrence of its complication was much lower[3]. In our study, we further analyzed the clinical effects of tegafur gimeracil oteracil combined with oxaliplatin for treating advanced colorectal cancer. We evaluated whether its mechanism was related to the K-ras gene mutation status and the expression of peripheral blood cell keratin (CK20 mRNA).

Patients and Methods

General Materials

A total of 41 patients diagnosed with advanced colorectal cancer in our hospital from October

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2013 to October 2014, were enrolled in this study. All patients were confirmed with stage IV adenocarcinoma by pathological diagnosis.

The inclusion criteria was as follows: (1) Patients aged ≥ 18 years old and < 75 years old; (2) Patients confirmed with stage IV colorectal cancer; (3) Patients that have not yet accepted surgery, radiotherapy and chemotherapy; (4) Patients whose ECOG PS scores were between 0-2 points, with measurable focus and estimated survival ≥ 3 months.

The exclusion criteria was as follows: (1) Patients with complications caused by other gastrointestinal tumors. (2) Patients with a history of digestive tract surgery. (3) Patients allergic to chemotherapy and those who could hardly complete the prescribed treatment course. (4) Patients with poor compliance and those who refused to participate in the study.

After obtaining consent from our hospital Ethics Committee and the patients, all 41 patients were divided into two groups. The control group, which consisted of 20 cases were treated with capecitabine combined with oxaliplatin. The observation group, comprised of 21 cases,were treated with tegafur gimeracil oteracil combined with oxaliplatin. In the control group, there were 12 male and 8 female cases. They were aged from 38-74 years old, with an average age of (57.5 ± 12.3) years old. Thirteen cases were confirmed with colon cancer, 8 cases of rectal cancer; 14 cases with hepatic metastases, 2 cases with pulmonary metastasis and three cases with abdominal lymph metastasis. In the observation group, there were 13 male and 8 female cases. They were aged from 35-73 years old, with an average age of (56.4 ± 13.4) years old. Fourteen cases were confirmed with colon cancer, 7 cases of rectal cancer; 15 cases with hepatic metastases, 2 cases with pulmonary metastasis and 4 cases with abdominal lymph metastasis.The difference between the gender, age, tumor and metastasis site between the two groups had no statistical significance ($p > 0.05$).

Treatment Method

Both groups were given expectant treatments, such as nutrition support, analgesia, gastric mucosa prevention, and bowels relaxation. They were monitored for blood routine, hepatic and renal function, electrolyte and coagulation. Patients in the control group were treated with capecitabine combined with oxaliplatin regimen. The details of the treatment were as follows: 2500 mg/m^{2}capecitabine (Shanghai Roche), 100 mg/m^{2}oxaliplatin (Jiangsu Lian Yungang Henrui Pharmaceutical Co., Ltd.), intravenous injection on the first day; oral administration after breakfast and supper from day 1-14, then withdraw the drugs for 7 days after continuous administration for 14 days. The cycle consisted of 21 days, and the treatment outcomes were assessed every two cycles. We continued with chemotherapy on the patients with an active treatment progression and changed for another regimen in patients without progression.

Patients in the observation group were treated with a regimen of tegafur/gimeracil/oter combined with oxaliplatin. Specifics of the treatment were as follows: the initial dose of tegafur/gimeracil/oter (Lunan Pharmaceutical Group, Shandong New Area Pharmaceutical Co., Ltd) was confirmed according to the body surface area. Initial dose: body surface area < 1.25 m^2, tegafur/gimeracil/oter 40 mg/time, 2 times/day; body surface area between 1.25-1.5 m^2, tegafur/gimeracil/oter 50 mg/time, 2 times/day; body surface area > 1.5 m^2, tegafur/gimeracil/oter 60 mg/time, 2 times/day. The dose of oxaliplatin was the same for both groups. Patients with hematological toxicity were given treatment for increasing leukopoiesis, thrombopoiesis and erythropoiesis. Stop the treatment of chemotherapy drugs temporarily in the case of IV hematological toxicity. After toxicity levels are reduced, continue using the drugs. But the suspended doses of drugs are not supplemented and each patient shall be treated for at least two cycles.

Evaluation Criteria

After two weeks of chemotherapy, reexamine their breast and abdominal by enhanced CT scan and evaluate the treatment outcomes by comparing the sum of tumor's maximum diameter ≥10 mm and the baseline. PD: the sum of maximum diameter enlarged at least 20% or new focus occurred; PR: the size of tumor reduced by at least 20%; SD: the sum of maximum diameter reduced not as much as PR and increased not as much as PD. PFS: the period from random grouping to the first time the disease had shown progress or death. RECIST standard was applied to evaluate the treatment effects. Treatment outcomes were divided into complete remission (CR), partial remission (PR), stable disease (SD), progressive disease (PD), objective response rate

(ORR) = (CR+PR)/(CR+PR+SD+PD) × 100 ; disease control rate (DCR) = (CR+PR+SD)/(CR+PR+SD+PD) × 100 . The adverse response was subject to the acute and sub-acute adverse response of the WHO anti carcinogen. After 6-month follow-up, the treatment outcomes will be evaluated.

To analyze the K-ras mutation and the expression rate of the peripheral blood cell keratin between the two groups, we performed a tissue biopsy under endoscopy, using direct sequencing to detect the status of K-ras gene. Detection of the CK20 mRNA was performed as follows: collect venous blood, and then centrifuge, use PRISM 7000 real-time quantitative polymerase chain reaction machine (American ABI Corporation), RNA extraction kit (QIAGEN Corporation, Hilden, Germany), CK20 mRNA fluorescence quantitative PCR kit (Tiangen Biotech Co., Ltd, Beijing, China), and oligo DT method to reverse and transcribe the mRNA into the cDNA. All of the primer sequences were synthesized by TAKARA Clontech (Otsu, Shiga, Japan).

Statistical Analysis

All data were analyzed by SPSS 20.0 statistical software (SPSS Inc., Chicago, IL, USA). Quantitative data was presented by means ± standard deviation; *t*-test was applied to make comparisons between the groups; case or percentage was used to present enumeration data; χ^2-test was used to make comparison between groups, and $p < 0.05$ was considered with statistical significance.

Results

Comparison of Survival Rate, PFS, ORR and DCR Between the Two Groups

The survival rate in observation group was significantly higher than that in the control group. The PFS in the observation group was longer than that in the control group. The ORR and DCR in the observation group were higher than those in the control group. Differences had statistical significance ($p < 0.05$) (Table I).

Comparison of K-ras Mutation Rate, CK20 mRNA Positive Rate and Level Between the Two Groups

The K-ras mutation rate in the observation group was higher than that in the control group and the positive rate and level of CK20 mRNA in the observation group were lower than those in the control group. The difference had statistical significance ($p < 0.05$) (Table II).

Comparison of the Incidence of Adverse Reactions Between the Two Groups

Most patients had adverse reactions in the third chemotherapy cycle. The prevalence of adverse reactions in the observation group was lower than that in the control group and difference had statistical significance ($p < 0.05$) (Table III).

Discussion

The NCCN Diagnostic and Treatment Standard has recommended using FOLFO, FOLFIRI, CapeOx ± tuximab or CapeOx ± bevacizumab regimen as the first-line therapeutic regimens. The CapeOx regimen involved oral administration of capecitabine. Capecitabine was an oral fluorouracil carbamate agent that could be degraded into 5-FU[4] through thymidine phosphorylase. Tegafur gimeracil oter was also a kind of fluorouracil drugs, which was composed of a certain proportion of tegafur, gimeracil and oterical. Tegafur's toxicity was only 1/5 of the fluorouracil, but its chemotherapeutic index was 2-3 times of the fluorouracil. Gimeracil was an active 5-FU degrading enzyme inhibitor, which could extend the action time of 5-FU. Oterical could inhibit the orotate phosphoribosyltransferase inside

Table I. Comparisons on survival rate, PFS, ORR and DCR between the two groups of patients [case (%)].

Group	Case	Survival rate	PFS(d)	CR	PR	SD	PD	ORR	DCR
Control group	20	6 (30.00)	85.6 ± 13.7	4	5	2	9	9 (45.00)	11 (55.00)
Observation group	21	13 (61.90)	134.7 ± 25.4	8	8	2	3	16 (76.19)	18 (85.71)
χ^2		4.193	5.627					4.188	4.668
p		0.041	0.029					0.041	0.031

Table II. Comparison on K-ras mutation rate, CK20 mRNA positive rate and level between the two groups of patients.

Group	Case	K-ras gene mutation rate	CK20 mRNA positive rate	Relative level
Control group	20	7 (35.00)	8 (40.00)	0.46 ± 0.06
Observation group	21	14 (66.67)	15 (71.43)	0.27 ± 0.03
t (χ^2)		4.111	4.108	5.127
p		0.043	0.043	0.024

the intestinal mucosal cells and block the phosphorylation of 5-FU, thus protecting intestinal mucosa[5].

Japan Center for Study conducted a retrospective analysis on the application of oxaliplatin combined with capecitabine as first-line treatment for advanced colon cancer. They found out that the ORR was 45% and the median time to progression was 10.5[6]. Bokemeyer et al[7] conducted a randomized control trial of 340 cases of stage III colorectal cancer and obtained the following results. The ORR with tegafur gimeracil ote combined with oxaliplatin regimen (168 cases) was 48% and the median time to progression was 8.9 months, The ORR with oxaliplatin combined with capecitabine (172 cases) was 35% and median time to progression was 6.4 months. The differences in the ORR, DCR, and median time to progression had no statistical significance. But the ORR and DCR in both groups showed an increasing trend, and also the median time to progression revealed a prolonging trend. Differences on adverse reaction, such as hematological toxicity, gastrointestinal reaction and liver and kidney dysfunction, between the two groups had no statistical significance. The results indicate that the efficacy of tegafur gimeracil ote combined with oxaliplatin regimen was as good as oxaliplatin combined with capecitabine regimen. Tegafur gimeracil ote combined with oxaliplatin regimen could be used as a new adjuvant therapy. The results of this study have shown that the survival rate of the observation group was significantly higher than that of the control group. Also, progression-free survival in the observation group was significantly longer than that in the control group, and that the ORR as well as DCR in theobservation group was higher than those in the control group. All of these differences had statistical significance. Moreover, the occurrence of adverse response in observation group was lower than that in the control group, and the difference had statistical significance.

It is confirmed that the K-ras gene mutation plays a significant role in the occurrence and development of colorectal cancers[8]. Recently, Brodowicz et al[9,10] did a study on the colorectal cancers in different K-ras gene state and found that the chemotherapy regimens, which included oxaliplatin, had better treatment outcomes. Current reports show that K-ras gene mutation rate in the primary lesion of colorectal cancer was 30%-50%. The 12 and 13 codon mutation rate was over 95%, and that the 12 codon mutation rate was higher than the 13 codon mutation rate[11,12]. CK20 was a newly discovered polypeptide with tissue specificity confined only to the gastrointestinal epithelium. It had prominent expression in almost all of the colorectal cancers[13-15]. Studies[16-18] have shown that colorectal cancer patients with a high expression of CK20 were more prone to metastases. CK20 is a predictive target for colorectal cancer metastases. Our study discusses the clinical effects of tegafur gimeracil oteracil combined with oxaliplatin for advanced colorectal cancer, and further analyzes its impact on K-ras

Table III. Comparisons on the occurrence of adverse reactions between the two groups of patients [Case (%)].

Group	Case	Bone marrow transplantation	Gastrointestinal reaction	Liver and kidney injury	Hand foot syndrome	Incidence of adverse reaction
Control group	20	1 (5.00)	3 (15.00)	2 (10.00)	1 (5.00)	7 (35.00)
Observation group	21	0	1 (4.76)	1 (4.76)	0	2 (9.52)
χ^2					3.881	
p					0.049	

gene mutation status and the expression of CK20 mRNA. The results of our study demonstrate that the proportion of K-ras gene mutation in the observation group was higher than that in the control group. The positive expression rate of CK 20 mRNA in observation group was lower than that in the control group. The differences had statistical significance ($p < 0.05$).

Conclusions

Tegafur gimeracil ote combined with oxaliplatin regimen had better treatment outcomes than capecitabine combined with oxaliplatin for advanced colorectal cancer. It might be related to K-ras gene mutation and the reduction of the CK20 mRNA expression. Since the number of cases in our study was small, and the observation time was short, the results of our study might have some objective and subjective deviations. However, we conclude that tegafur gimeracil ote combined oxaliplatin regimen was a favorable choice for advanced colorectal cancer patients. Moreover, the financial burden of this regimen was much less. The clinical efficacy of tegafur gimeracil ote combined with oxaliplatin regimen still awaits the results of further large-scale prospective tests. We expect that the combination therapy with targeted drugs against colorectal cancers could have better outcomes.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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