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Prolonged Capecitabine Chemotherapy Following Capecitabine and Oxaliplatin (CAPOX) Regimen Chemotherapy Failed to Improve Survival of Stage III Colorectal Cancer After Radical Resection

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Colorectal cancer (CRC) is considered to be a worldwide health problem because of its increasing incidence and prevalence. Surgery offers an opportunity for cure, but the postoperative recurrence rate is still high despite the advancement of chemotherapy. This study aimed to assess the efficacy and safety of prolonged capecitabine chemotherapy following CAPOX chemotherapy for stage III CRC after radical surgery.

Material/Methods: This study included 212 patients with stage III CRC undergoing open radical surgery from July 2010 to June 2015. Among those patients, 104 patients received prolonged capecitabine chemotherapy (prolonged group) following 8 cycles of CAPOX regimen chemotherapy, while the other 108 patients (control group) received no prolonged chemotherapy. The prolonged chemotherapy consisted of capecitabine (1000 mg/m^2 per day for 2 weeks) and was repeated every 3 weeks for 8 cycles at most. Long-term survival and toxicities were retrospectively compared.

Results: Patient characteristics did not differ between the 2 groups. For all patients, no significant difference was found in the 3-year disease-free survival (DFS) (P=0.7775) or 3-year overall survival (OS) rates between the 2 groups (P=0.5787). The prolonged group had significantly higher frequency of hand-foot syndrome (P=0.0267) and paresthesia (P=0.0164). In further subgroup analyses, no benefit for 3-year DFS or 3-year OS of prolonged capecitabine chemotherapy was found in colon cancer or rectal cancer.

Conclusions: Prolonged capecitabine chemotherapy following CAPOX regimen chemotherapy failed to improve the survival of patients with stage III CRC after radical surgery.

MeSH Keywords: Chemotherapy, Adjuvant • Colorectal Neoplasms • Disease-Free Survival • Survival

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Background

Colorectal cancer (CRC) is considered to be a worldwide health problem because of its increasing incidence and prevalence [1]. More than 1 million people are diagnosed and approximately 600 000 people die from CRC every year [2,3]. Surgery offers an opportunity for cure, but the postoperative recurrence rate is still high despite the administration of postoperative adjuvant chemotherapy [4]. Compared to patients with early stage CRC, the prognosis of those with stage III disease is much worse. Thus, it is necessary to explore innovative adjuvant treatment strategies for stage III CRC.

Prolonged chemotherapy following standard chemotherapy is an innovative treatment modality. Previous studies have shown the survival benefit of prolonged chemotherapy following first-line chemotherapy in unresectable CRC [5,6]. In resected disease, prolonged chemotherapy with tegafur-uracil following fluorouracil/leucovorin plus oxaliplatin (FOLFOX) chemotherapy has also been found to improve overall survival in stage III colon cancer after radical surgery [7]. However, there have been few studies of prolonged chemotherapy with capecitabine following first-line chemotherapy for resected stage III CRC. Therefore, in this study we aimed to assess the efficacy and safety of prolonged chemotherapy with capecitabine following capecitabine and oxaliplatin (CAPOX) chemotherapy for stage III CRC after radical resection.

Material and Methods

Patients

This retrospective study included 212 patients with stage III CRC undergoing open radical surgery from July 2010 to June 2015. The main inclusion criteria were: pathologically verified stage III (any T, N1 or N2, M0) CRC [according to the 7th edition American Joint Committee on Cancer (AJCC) staging system]; no prior chemotherapy; Eastern Cooperative Oncology Group (ECOG) 0-2; disease-free survival (DFS) and overall survival (OS) >6 months; and 18 to 75 years of age.

We conducted the research according to the Declaration of Helsinki and "Good Clinical Practice" guidelines. The Ethics Committee of First People's Hospital affiliated to Huzhou Normal College approved this research (2018-8-15).

Chemotherapy administration

The chemotherapy was initiated within 3 weeks after surgery. All patients received CAPOX regimen chemotherapy consisting of capecitabine (1000 mg/m^2 per day for 14 days) and oxaliplatin (130 mg/m^2 on day 1), which was repeated every 21 days for 8 cycles. After the CAPOX chemotherapy phase, physicians explained the advantages and disadvantages of prolonged chemotherapy to the patients. All patients decided whether to accept prolonged capecitabine chemotherapy at their sole discretion, and informed consent was obtained from all patients.

A total of 104 patients accepted the prolonged capecitabine chemotherapy (prolonged group) consisting of capecitabine (1000 mg/m^2 per day for 14 days). The prolonged chemotherapy was repeated every 21 days for up to 8 cycles. The other 108 patients received observation with no prolonged chemotherapy following 8 cycles of CAPOX regimen chemotherapy (control group).

Chemotherapy toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. In cases of grade 4 neutropenia and/or grade 3 or more severe thrombocytopenia, grade 2 or more severe hand-foot syndrome, or other grade 3 or more severe nonhematologic adverse effects, dose reduction by 25% was applied in the following cycles. The chemotherapy was discontinued in cases of prolonged recovery from adverse reactions (more than 2 weeks), disease progression, or upon patient request.

Assessment and follow-up

Patients were assessed before each session of chemotherapy during treatment, and then they were followed up every month in the first postoperative year, and then every 3 months until the last follow-up or death. The patients who developed recurrence received chemotherapy, palliative therapy, radiofrequency ablation, or surgery.

Statistical analysis

The measurement data are presented as the mean ±SD. The statistical assessments were conducted using the 2-sample *t* test and adjusted with the χ^2 test. The exact χ^2 test was performed if the individual cell size was <5 counts. Chemotherapy toxicities were compared using Ridit analysis. Disease-free survival (DFS) was defined as the interval from the date of surgery to the date of recurrence, death from any cause, or the last follow-up. Overall survival (OS) was defined as the as the interval from the date of surgery to the date of death from any cause or the last follow-up. Survival curves obtained by Kaplan-Meier estimates were tested using the log-rank test. A P value less than 0.05 was considered statistically significant.

Results

Patient characteristics

Patient characteristics, such as gender, age, tumor location, tumor stage, tumor differentiation, tumor size, operating time,

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Table 1. Patient characteristics.

	Control group (n=108)	Prolonged group (n=104)	*P* value
Age (year)	67.5±6.7	66.2±5.8	0.1331
Tumor size (cm)	3.9±1.2	4.1±1.4	0.2648
Operating time (min)	113.8±20.7	118.4±23.5	0.1316
Blood loss during surgery (ml)	233.2±40.3	241.6±42.8	0.1426
Gender			0.9731
Male	75	72	
Female	33	32	
Tumor stage			0.9185
IIIA	32	30	
IIIB	39	38	
IIIC	37	36	
Tumor differentiation			0.9758
Well	18	19	
Moderately	41	37	
Poorly	49	48	
Tumor location			0.9665
Colon	62	60	
Rectum	46	44	
Underlying comorbidity			
Diabetes mellitus	15	13	0.7653
Hypertension	21	24	0.5179
Heart disease	7	10	0.4010

blood loss during surgery and underlying comorbidity did not differ between the 2 groups (Table 1).

Treatment results and chemotherapy toxicities

All patients completed 8 cycles of CAPOX chemotherapy, although 15 patients from the control group and 16 patients from the prolonged group experienced dose reduction.

After CAPOX chemotherapy, 104 patients preferred to receive prolonged chemotherapy. Finally, a total of 86 patients completed 8 cycles of prolonged chemotherapy, of whom 10 patients experienced dose reduction. Prolonged chemotherapy was discontinued in 5 patients due to recurrence and in 5 patients due to refractory grade 3 hand-foot syndrome and grade 3 thrombocytopenia, and these patients received at least 3 cycles of prolonged chemotherapy. All patients were included in the analysis.

The chemotherapy toxicities are listed in Table 2. There was a significantly higher frequency of hand-foot syndrome (P=0.0267) and paresthesia (P=0.0164) in the prolonged group. Most of the toxicities were controlled by symptomatic treatment and dose reduction. No toxicity-related deaths occurred.

Disease-free survival

In the initial 3 postoperative years, recurrence was observed in 32 patients in the control group and 30 patients in the prolonged group. No significant difference was found in the 3-year DFS between the 2 groups (P=0.7775) (Figure 1). The hazard ratio (HR) for recurrence in the prolonged group, as compared with the control group, was 0.9312 [95% confidence interval (CI), 0.5660 to 1.5320]. Sites of recurrence are listed in Table 3.

We further analyzed the efficacy of prolonged capecitabine chemotherapy on the 3-year DFS in colon cancer and rectal cancer subgroups. However, no significant improvement in 3-year DFS was found in colon cancer (P=0.7803; HR for recurrence,

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Table 2. Toxicities.

Event	Control group				Prolonged group				*P* value
	Grade				Grade				
	1	2	3	4	1	2	3	4	
Neutropenia	65	35	6	2	52	43	7	2	0.1587
Thrombocytopenia	67	39	2	0	58	42	4	0	0.3122
Anemia	60	44	4	0	52	48	4	0	0.4380
Nausea/vomiting	65	40	3	0	60	39	5	0	0.6373
Diarrhea	25	19	0	0	29	20	0	0	0.4052
Nephrotoxicity	12	7	0	0	12	8	0	0	0.7448
Hepatic toxicity	9	6	0	0	10	8	0	0	0.4816
Stomatitis	14	13	1	0	15	15	3	0	0.3125
Hand-foot syndrome	32	19	2	–	34	25	6	–	0.0267
Paresthesia	21	16	2	0	29	22	4	0	0.0164

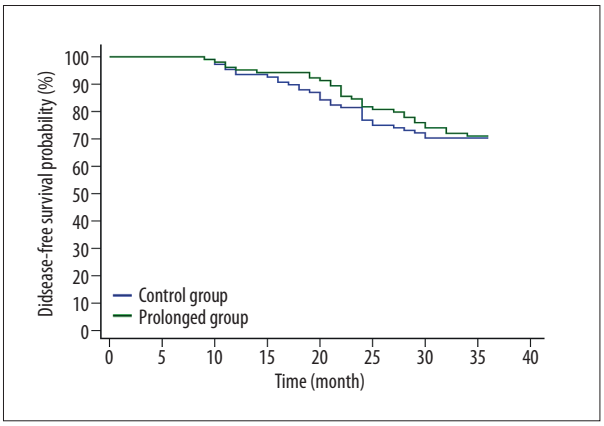

Figure 1. Disease-free survival curves of the 2 groups. In the initial 3 postoperative years, recurrence was observed in 32 patients in the control group and 30 patients in the prolonged group. No significant difference was found in 3-year disease-free survival between the 2 groups (P=0.7775). The hazard ratio for recurrence in the prolonged group, as compared with the control group, was 0.9312 [95% confidence interval (CI), 0.5660 to 1.5320].

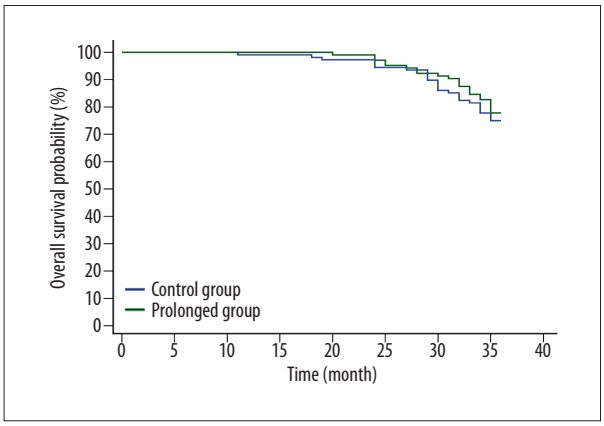

Figure 2. Overall survival curves of the 2 groups. In the initial 3 postoperative years, 27 patients in the control group died and 23 patients in the prolonged group died. No significant difference was found in 3-year overall survival between the 2 groups (P=0.5787, hazard ratio for death, 0.8558; 95% CI, 0.4916 to 1.4898).

Table 3. Sites of recurrence.

	Local	Lung	Brain	Bone	Liver	Dissemination
Sites of first recurrence						
Control group	6	4	2	2	14	4
Prolonged group	6	3	1	4	13	3
Sites of any recurrence						
Control group	8	5	2	3	16	5
Prolonged group	7	3	2	4	15	6

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1.0980; 95% CI, 0.5660 to 2.1302) or rectal cancer (P=0.4533; HR for recurrence, 0.7504; 95% CI, 0.3528 to 1.5963).

Overall survival

In the initial 3 postoperative years, 27 patients in the control group died and 23 patients in the prolonged group died. Of these, 47 patients (25 from the control group and 22 from the prolong group) died of disease progression, 1 patient from the control group died of diabetic complications, and 2 patients (1 from the control group and 1 from the prolong group) died of heart attack. No significant difference was found in 3-year OS between the 2 groups (P=0.5787, HR for death, 0.8558; 95% CI, 0.4916 to 1.4898) (Figure 2).

We further analyzed the efficacy of prolonged capecitabine chemotherapy on the 3-year OS in colon cancer and rectal cancer subgroups. No significant improvement in 3-year OS was found in colon cancer (P=0.8996; HR for death, 1.0501; 95% CI, 0.4867 to 2.2657) or rectal cancer (P=0.3455; HR for death, 0.6811; 95% CI, 0.3059 to 1.5165) subgroups.

Discussion

Radical surgery is the only treatment offering a chance for cure, and postoperative adjuvant chemotherapy is necessary to improve long-term survival for colorectal cancer. In 2004, the superiority of FOLFOX4 over 5-fluorouracil + leucovorin (5-FU + LV) was revealed, and the FOLFOX4 regimen was accepted as first-line adjuvant chemotherapy for advanced CRC [8]. Thereafter, a study comparing the efficacy of CAPOX with modified FOLFOX6 for CRC suggested that the 2 regimens are similar in efficacy and adverse effects [9]. In our study, all 212 patients completed 8 cycles of CAPOX regimen chemotherapy, and only 31 patients experienced dose reduction. This result shows the safety profile of CAPOX chemotherapy for CRC patients.

Approximately 30–40% of CRC patients have stage III disease in China [10,11]. Over 40% of stage III CRC patients develop relapses within 8 years after radical resection, and over 80% of these relapses occur in the initial 3 postoperative years [12]. Therefore, the long-term survival of patients with stage III CRC is much shorter than in those with earlier stages of disease. To provide longer survival for patients with stage III CRC, aggressive treatment strategies are needed.

Prolonged chemotherapy following standard chemotherapy is an innovative treatment modality. The importance of prolonged chemotherapy following first-line chemotherapy has been revealed in several types of solid tumors, especially in lung cancer and gastric cancer [13,14]. For CRC, most previous studies focused on metastatic disease. The OPTIMOX2 study reported that prolonged chemotherapy following 6 cycles of first-line chemotherapy can offer progression-free survival (PFS) and overall survival benefits in patients with metastatic CRC, with minimal additional toxicity [5]. Moreover, prolonged chemotherapy with capecitabine and bevacizumab or capecitabine alone was found to improve the survival of unresectable CRC following first-line chemotherapy [15–17].

Although the survival benefit of prolonged chemotherapy with tegafur-uracil following FOLFOX chemotherapy was proved in resected colon cancer [7], studies of prolonged chemotherapy for resected stage III CRC are still insufficient. In the present retrospective study, 104 of 212 patients received prolonged chemotherapy with capecitabine following 8 cycles of CAPOX regimen chemotherapy after radical surgery. Disappointingly, there was no improvement in 3-year DFS (P=0.7775) or OS (P=0.5787), but a higher frequency of hand-foot syndrome (P=0.0267) and paresthesia (P=0.0164) was observed in the prolonged chemotherapy group. Considering the different characteristics between colon and rectal cancers, we performed survival analyses in colon cancer and rectal cancer subgroup. However, no benefit for DFS or OS of prolonged capecitabine chemotherapy was found in colon cancer or rectal cancer.

Our results show that longer duration of chemotherapy failed to improve survival outcomes but did lead to more toxicities. Similar results were obtained in the recently published SCOT trial, which showed that 3 months of oxaliplatin-containing adjuvant chemotherapy was noninferior to 6 months of the same therapy for patients with high-risk stage II and stage III CRC [18]. Therefore, prolonged chemotherapy may not be an effective or safe option for stage III CRC after surgery.

Colclusions

We assessed the efficacy and safety of prolonged capecitabine chemotherapy following CAPOX chemotherapy for stage III CRC after radical surgery. Our results revealed that prolonged capecitabine chemotherapy following CAPOX regimen chemotherapy failed to improve survival outcomes but did lead to more toxicities. Limitations of our study are that the choice to receive prolonged chemotherapy was mainly made by the patients themselves, and the sample size was small. Therefore, a further prospective randomized control study is warranted.

Conflict of interest

None.

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