·Colerectal Cancer-related Research·

# Efficacy of FORFIRI regimen on oxaliplatin-based chemotherapy-failed advanced colorectal cancer

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This paper was translated into English from its original publication in Chinese. Translated by: Guangzhou Liheng and Wei Liu

The original Chinese version of this paper is published in: *Ai Zheng* (*Chinese Journal of Cancer*) 28(9);http://www.cjcsysu.cn/cn/article.asp?id=15402)

Submitted: 2008-09-09
Revised: 2009-04-20

[**Abstract**] **Background and Objective**: Irinotecan (CPT-11), oxaliplatin, 5-fluorouracil (5-FU) and capecitabine are main active agents for advanced colorectal cancer. FORFIRI regimen is recommended for the patients who were treated with oxaliplatin plus 5-FU or capecitabine previously. This study was to investigate the efficacy and safety of FORFIRI regimen in treating advanced colorectal cancer failing to prior oxaliplatin-based chemotherapy, and analyze the impacts of clinical factors on the responses. **Methods**: A total of 90 patients with advanced colorectal adenocarcinoma, who had received prior adjuvant FOLFOX6 regimen and progressed within 12 months after the completion of therapy or had no response to prior FOLFOX6/CapeOX regimen as first-line therapy, were treated with FORFIRI regimen. The efficacy and adverse events were observed. **Results**: Of the 81 evaluable patients, two achieved complete remission, 20 achieved partial remission and 34 had stable disease. The overall response rate was 27.2% and disease control rate was 69.1%. The median time to progression was 6.8 months (95% CI, 4.9–8.8 months) and median overall survival time was 18.8 months (95% CI, 17.5–20.2 months). The main adverse events time were nausea, vomiting, neutropenia, alopecia, fatigue, impaired liver function, oral mucositis and diarrhea. Grade Ⅲ adverse events included alopecia in 15 patients (16.7%), vomiting in 10 patients (11.1%), nausea in eight patients (8.9%), neutropenia in five patients (5.6%), impaired liver function in two patients (2.2%) and oral mucositis in two patients (2.2%). **Conclusion**: FOLFIRI regimen is effective and well-tolerated as salvage therapy for advanced colorectal cancer failing to prior FOLFOX6/CapeOX regimen, and thus can be used widely.

**Key words**: colorectal neoplasm, irinotecon, 5-fluorouracil, leucovorin, chemotherapy

Colorectal cancer is the second most common malignant tumor in western countries. The incidence of colorectal cancer in China increases rapidly in recent years and has become the fifth most common tumor. At diagnosis, 20%-30% of colorectal cancers are advanced. The 5-year recurrence or metastasis rate is over 40%. Chemotherapy can improve the quality of life and prolong survival of patients with advanced colorectal cancer. The primary drugs for

chemotherapy include 5-fluorouracil (5-FU), irinotecan (CPT-11), oxaliplatin (LOHP) and capecitabine. FOLFIRI (CPT-11, 5-FU and leucovorin), FOLFOX (LOHP, 5-FU and LV) and CapeOX (LOHP and capecitabine) have been recommended as standard first-line chemotherapy regimens for advanced colorectal cancer.

The 2008 NCCN guideline recommends FOLFIRI regimen for metastatic colorectal cancer patients with disease progression within 12 months after FOLFOX/CapeOX adjuvant chemotherapy or those failed first-line palliative chemotherapy with FOLFOX/CapeOX regimen. 1 However, the study population is relatively small in China. We summarized clinical data of 90 metastatic colorectal cancer patients who failed the LOHP regimen and subsequently underwent FOLFIRI regimen in Cancer Center of Sun Yat-sen University between July 2003 and December 2007. This study was to evaluate the safety and effectiveness of FOLFIRI regimen as the second-line treatment for colorectal cancer.

## Data and Methods

**Clinical data.** A total of 90 patients with metastatic colorectal adenocarcinoma, who had disease progressed within 12 months after the completion of adjuvant chemotherapy with FOLFOX6 regimen or had no response to first-line chemotherapy with FOLFOX6/CapeOX regimen, were recruited from July 2003 to December 2007. All patients had no complications, such as intestinal inflammatory diseases, intestinal obstruction and intestinal dysfunction, as confirmed by histopathology. The ECOG PS (performance status) score was <2. Expected survival time was ≥ 3 months. Routine blood examination, renal and liver functions and electrocardiogram (ECG) were normal.

The patients were aged 23-73 years, with a median of 49. PS scores were 0-1. There were 47 men and 43 women. The common metastatic sites were liver (54 cases), lung (33 cases), lymph nodes (27 cases), pelvic cavity (14 cases), abdominal cavity (14 cases), and ovary (eight cases). Other metastatic sites included bone (three cases), anastomotic recurrence (two cases), soft tissue mass (two cases) and pancreas (one case) and adrenal gland (one case). Twenty-two patients had progressive disease (PD) within 12 months after treated with FOLFOX6 regimen, with a median time to progression (mTTP) of three months (0-11 months). Of the 68 patients who failed the first-line chemotherapy (46 received FOLFOX6 regimen and 22 received CapeOX regimen), 38 had disease progression within three months, and 30 had disease progression three months later. General data of the patients are shown in Table 1.

**Treatment strategy.** All patients received FOLFIRI regimen as follows: intravenous infusion of CPT-11 (180 mg/m$^2$) that dissolved in 250 mL of normal saline for 90 min on day 1; intravenous infusion of LV (400 mg/m$^2$) that dissolved in 250 mL of 5% glucose solution for 2 h on day 1; intravenous bolus injection of 5-FU (500 mg) that added to 40 mL of 5% glucose solution and continuous intravenous infusion of 5-FU (2.4-3.0 g/m$^2$) for 46 h. The regimen was repeated every two weeks. The therapeutic efficacy was evaluated every eight weeks.

Antiemetic drug 5-HT$_3$ antagonist was routinely given before chemotherapy and 0.25 mg atropine was used to prevent acute cholinergic syndrome. If acute diarrhea occurred during chemotherapy, 0.25 mg atropine was injected intramuscularly, and prophylactic administration of 0.5 mg atropine was given before next cycle of chemotherapy. If the patient presented frequent defecation or loose stool, 4 mg loperamide hydrochloride was immediately given orally, followed by 2 mg every two hours till 12 h after symptom relieve.

At the beginning of the second cycle of chemotherapy, doses of CPT-11 and 5-FU were adjusted according to the severity of adverse events in the last cycle. If bone marrow suppression and febrile neutropenia of grade III and above or non-hematologic toxicity (except for the pigmentation) of grade II and above occurred, the doses of CPT-11 and 5-FU were

**Table 1 Responses to FOLFIRI regimen and survival of patients with oxaliplatin-based chemotherapy-failed advanced colorectal cancer**

| Item | Response | | | Survival | | |
|---|---|---|---|---|---|---|
| | Cases | ORR (%) | $P_1$ value | Cases | mOS (months) | $P_2$ value |
| Sex | | | | | | |
| Male | 44 | 36.4 | | 47 | 19.0 | |
| Female | 37 | 16.2 | 0.042 | 43 | 15.2 | 0.766 |
| Serum LDH level | | | | | | |
| Normal | 55 | 36.4 | | 63 | 19.0 | |
| Elevated | 26 | 7.7 | 0.007 | 27 | 18.7 | 0.340 |
| Serum CEA level | | | | | | |
| Normal | 27 | 44.4 | | 34 | 23.6 | |
| Elevated | 54 | 18.5 | 0.013 | 56 | 18.5 | 0.119 |
| Serum CA-199 level | | | | | | |
| Normal | 36 | 38.9 | | 42 | 19.8 | |
| Elevated | 45 | 17.8 | 0.034 | 48 | 18.0 | 0.093 |
| Primary site | | | | | | |
| Colon | 50 | 28.0 | | 56 | 19.0 | |
| Rectum | 31 | 25.8 | 0.807 | 34 | 18.7 | 0.510 |
| Metastases | | | | | | |
| Synchronous | 37 | 21.6 | | 40 | 18.5 | |
| Metachronous | 44 | 31.8 | 0.304 | 50 | 19.0 | 0.042 |
| Number of organs involved | | | | | | |
| 1 | 37 | 29.7 | | 45 | 23.6 | |
| ≥2 | 44 | 25.0 | 0.331 | 45 | 18.0 | 0.229 |
| Liver involvement | | | | | | |
| Yes | 49 | 20.4 | | 54 | 16.1 | |
| No | 32 | 37.5 | 0.091 | 36 | 29.4 | 0.006 |
| Prior treatment | | | | | | |
| FOLFOX6/CapeOX regimen as first-line chemotherapy | 64 | 25.0 | | 68 | 18.7 | |
| FOLFOX6 regimen as adjuvant chemotherapy | 17 | 35.3 | 0.396 | 22 | 23.6 | 0.042 |
| Responses to first-line regimen | | | | | | |
| Time to progression ≤ 3 months | 37 | 24.3 | | 38 | 15.1 | . |
| Time to progression > 3 months | 27 | 25.9 | 0.884 | 30 | 19.0 | 0.112 |

Responses are evaluable in 81 patients. ORR, overall response rate; mOS, median overall survival; LDH, lactate dehydrogenase.

reduced by 15%-20%. The next cycle began only after all adverse events returned to grade 0-I, and treatment-associated diarrhea mitigated.

**Evaluation criteria.** The evaluation criteria were based on RECIST solid tumor criteria: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). CR and PR cases were summed to calculate the overall response rate (ORR); CR, PR and PD cases were summed to calculate the disease-control rate (DCR).

**Follow-up.** The patients were followed up till May 30, 2008. TTP was the duration from the initiation of FORFIRI regimen treatment to PD. The median overall survival (mOS) was the duration from the initiation of FORFIRI regimen treatment to death or the last follow-up. The survival time of the patients lost to follow-up was calculated up to the last follow-up.

**Statistical analysis.** Statistical analyses were performed using SPSS 12.0 software. $X^2$ test was used to analyze factors influencing short-term efficacy. Survival analysis was performed with Kaplan-Meier method. Inter-group differences were tested with log-rank test. A P value of <0.

05 was considered significant.

## Results

**Therapeutic efficacy.** The 90 patients had completed 523 cycles of chemotherapy with a median of 5 (2-12) cycles. PFS and OS could be evaluated for all patients. Nevertheless, nine patients had no evaluable lesions, including seven who had underwent palliative resection on metastatic lesions and two who had underwent radiofrequency ablation on liver metastatic lesions. Of the 81 evaluable patients, two achieved CR, 20 achieved PR, 34 had SD, 25 had PD; the ORR was 27.2% and DCR was 69.1%. Univariate analysis showed that male patients and the patients with normal levels of LDH, CEA and CA199 had higher ORR, while primary site (colon vs. rectum), metastatic time (synchronous metastasis vs. heterochronous metastasis), number of involved organs (1 vs. ≥ 2), liver metastasis, time of first-line chemotherapy failure (within three months after treatment vs. beyond three months after treatment) did not influence the ORR (P>0.05) (Table 1). The ORR of the 17 patients who failed adjuvant chemotherapy was 35.3% and that of the 64 patients failed first-line therapy was 25.0% (P=0.396).

**Follow-up and survival.** Till May 30, 2008, 48 patients died. The mTTP of the 90 patients was 6.8 months [95% confidence interval (CI), 4.9-8.8 months] (Fig. 1). The TTP of the patients who had disease progression within 12 months after adjuvant chemotherapy was 8.7 months (95% CI, 6.7-10.7 months), and TTP of the patients with first-line chemotherapy failure was 6.0 months (95% CI, 4.3-7.7 months). The difference was significant (P=0.029). The mOS of the 90 patients was 18.8 months (95%CI, 17.5-20.2 months) (Fig. 2). The mOS of the patients who failed adjuvant chemotherapy was 18.7 months (95% CI, 13.6-28.8 months), and mOS of the patients with first-line chemotherapy failure was 23.6 months (95% CI, 10.6-36.6 months). The difference was significant (P=0.043).

Univariate analysis showed that mOS was longer in the patients with disease progression within 12 months after adjuvant chemotherapy than in those failed first-line chemotherapy, longer in patients with heterochronous metastasis than in those with synchronous metastasis, and longer in those without liver metastasis than in those with liver metastasis. Sex, age, primary site, number of involved organs, time of first-line chemotherapy failure, LDH, CEA and CA199 levels did not influence the mOS (P>0.05) (Table 1). The mOS of the 14 patients who failed FOLFIRI regimen and

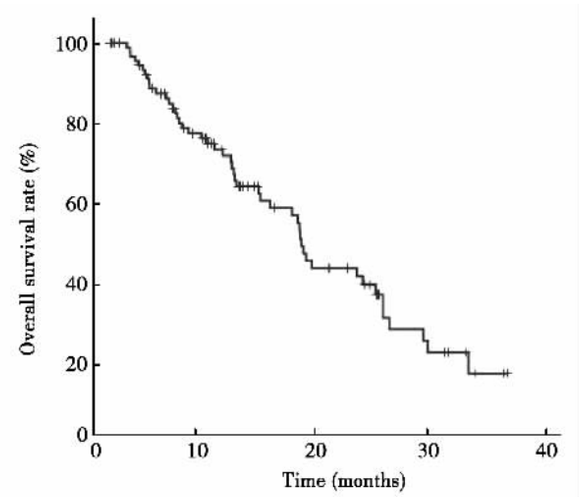


Figure 1 Overall survival curve of 90 patients with advanced colorectal cancer who failed oxaliplatin-based chemotherapy

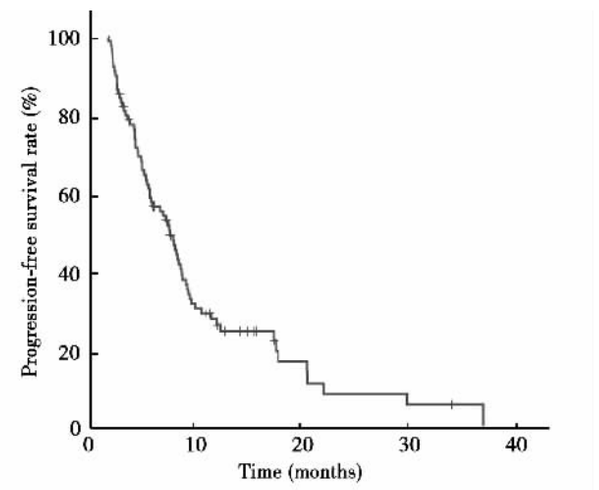


Figure 2 Progression-free survival curve of 90 patients with advanced colorectal cancer who failed oxaliplatin-based chemotherapy

received target drug combined chemotherapy was 26.4 months.

**Adverse events.** Adverse events of all patients could be evaluated (Table 2). Hematological toxicity was mild; only five (5.6%) patients had grade III neutropenia. The common hematological toxicities included alopecia, gastrointestinal reactions, fatigue, liver function impairment, oral mucositis and diarrhea. Fifteen (16.7%) patients had grade III alopecia, eight (8.9%) had grade III anorexia, ten (11.1%) had grade III vomiting, and two had oral mucositis. Two patients with history of hepatitis B showed grade III liver function impairments, which returned to normal after appropriate treatment. Nineteen (21.1%) patients showed grade I-II acute cholinergic syndrome, presenting abdominal pain, diarrhea, lacrimation and salivation, which were resolved after intramuscular injection of 0.25 mg atropine. Eight (8.9%) patients showed grade I-II delayed diarrhea which was immediately resolved after oral intake of loperamide hydrochloride.

**Table 2 Adverse events in 90 patients with advanced colorectal cancer after treatment of FORFIRI regimen**

| Adverse event | Grade Ⅰ [cases (%)] | Grade Ⅱ [cases (%)] | Grade Ⅲ [cases (%)] |
|---|---|---|---|
| Neutropenia | 24(26.7) | 19(21.1) | 5 (5.6) |
| Anemia | 16(17.8) | 3 (3.3) | 0 |
| Thrombocytopenia | 6 (6.7) | 1 (1.1) | 0 |
| Nausea | 44(48.9) | 15(16.7) | 8 (8.9) |
| Vomiting | 17(18.9) | 15(16.7) | 10(11.1) |
| Oral mucositis | 10(11.1) | 7 (7.8) | 2 (2.2) |
| Alopecia | 35(38.9) | 30(23.3) | 15(16.7) |
| Impaired liver function | 14(15.6) | 7 (7.8) | 2 (2.2) |
| Cholinergic syndrome | 18(20.0) | 1 (1.1) | 0 |
| Delayed diarrhea | 6 (6.7) | 2 (2.2) | 0 |
| Fatigue | 44(48.9) | 3 (3.3) | 0 |
| Pigmentation | 14(15.6) | 0 | 0 |

## Discussion

Disease progression is common for patients with metastatic colorectal cancer after first-line chemotherapy, and patients with PS of 0-2 can benefit from second-line chemotherapy. The option of second-line chemotherapy depends on prior treatment, potential feasibility of radical resection and patients constitution. Moreover, the constitution of second-line chemotherapy should be taken in to account, such as the type of drugs, dose, administration route and strategies.

Phase III randomized controlled trials have proved that, for patients with metastatic colorectal cancer who failed 5-FU-based regimens, CPT-11 alone can achieve ORR of 10% -15% and TTP of 4-6 months; as compared with optimal supportive chemotherapy or 5-FU alone regimen, CPT-11 can prolong survival and improve quality of life, therefore, CPT-11 has been approved to treat patients with metastatic colorectal cancer who failed 5-FU-based regimens.[2,3] Imported CPT-11 has completed registered clinical trial in China in 1999, which showed a response rate of 20%.[4] CPT-11 has no cross drug resistance with 5-FU, and can overcome 5-FU-resistance. On investigating optimal doses and strategies of administration, many phase III trials showed that the efficacy and safety of FOLFIRI regimen (CPT-11 plus 5-FU/LV de Gramont) were better than modified IFL regimen (CPT-11 combined intravenous administration of 5-FU and LV, once a week) or CapIRI (capecitabine plus CPT-11).[5,6] Moreover, phase III trials also showed that FOLFIRI and FOLFOX6 regimens had similar efficacy in first-line chemotherapy for metastatic colorectal cancer. These two regimens are therefore recommended as standard first-line treatment of advanced colorectal cancer, and one regimen can be the second-line chemotherapy if the other fails.[7,8]

The treatment of recurrent metastatic colorectal cancer with FOLFIRI as second-line regimen has been reported. However, the sample sizes of the trials in China are small. Our study enrolled 90 patients, with the largest sample size in China up to date. Treating metastatic colorectal cancer patients with FOLFIRI regimen as second-line chemotherapy, the ORR was 12%-38%, DCR was 60%-93%, mTTP was 3-6 months and mOS was 9-12 months.[9-17]

The ORR, DCR and mTTP of our study were 22.6%, 62.7% and 6.8 months, respectively. The TTP of the patients failed first-line chemotherapy was 6.0 months, which was consistent with above mentioned studies. Nevertheless, the mOS in our study was as long as 18.8 months, which was significantly longer than other reports. This difference can be partly explained by the differences of inclusive criteria. We enrolled 22 patients with disease progression within 12 months after adjuvant chemotherapy, and the mOS of these patients was 23.6 months. Moreover, 14 patients received third-line target drug combined chemotherapy, and their mOS reached 26.4 months.

Freyer et al.[18] summarized four phase II clinical trials investigating the efficacy of CPT-11 as second-line chemotherapy on advanced colorectal cancer to find factors that can predict the efficacy of CPT-11. Their results showed that TTP after first-line chemotherapy, the number of involved organs, pretreatment hemoglobin level and the occurrence of diarrhea or bone marrow suppression after first chemotherapy influenced therapeutic effects, while TTP, PS status, liver or lymph node metastasis, age, pretreatment CEA level influenced patients survival. We analyzed the factors that might influence the efficacy and found that male patients with normal LDH, CEA and CA199 levels had higher ORR, while those with adjuvant chemotherapy failure, heterochronous metastasis and without liver metastasis had longer survival. Nonetheless, due to the small simple size of the present study, the efficacy of CPT-11 and factors that may influence the clinical outcomes need further investigations.

In our study, the primary adverse events were nausea, vomiting, neutropenia, alopecia, fatigue, impaired liver function, oral mucositis and diarrhea, most of which were grade I-II and can be resolved with appropriate treatment. Delayed diarrhea, a dose limited adverse reaction, is reported to occur in 20%-30% of the patients in foreign country (grade III/IV). Our results showed that 8.9% patients showed delayed diarrhea and most of them were grade I-II without occurrence of severe diarrhea. It is likely to be associated with the racial differences and the pretreatment education. The incidence of grade III/IV diarrhea reported in China is 2% -15% ,[9-12] which is far lower than foreign countries. CPT-11 is a topoisomerase I inhibitor that transforms to the active form of SN-38 to take effects. UTG1A is the primary metabolic enzyme of SN38, and its functions and gene polymorphism are closely associated with adverse effects of CPT-11 like delayed diarrhea.[19,20] Polymorphism study of UTG1A gene in Chinese population shows that the frequency of the wild type UTG1A1*28 of TA6/6 is relatively higher than Caucasian population, which is likely to be the reason why incidence of delayed diarrhea is significantly lower in China than western countries.[21] Clinical trial that genotyped UGT1A1*28 alleles in patients receiving CPT-11 has been reported, which is conducive to the development of individualized regimen that is highly effective and less toxic.[22]

In recent years, biological target drugs such as cetuximab and bevacizumab have entered into clinical use, and their combination with chemotherapy can further improve the prognosis of patients with advanced colorectal cancer. Nevertheless, due to the expensiveness of the target drugs, cytotoxic drugs are still the main treatments for most Chinese patients. The present study demonstrated that FOLFIRI regimen is effective and well-tolerated salvage chemotherapy for advanced colorectal cancer that progressed after oxaliplatin adjuvant chemotherapy or metastatic colorectal cancer that failed first-line chemotherapy, and can be used widely.

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