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ORIGINAL ARTICLE

Phase II study of FOLFIRI regimen in patients with advanced colorectal cancer refractory to fluoropyrimidine and oxaliplatin

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Abstract
Purpose To evaluate the efficacy and safety of FOLFIRI regimen in patients with advanced colorectal cancer refractory to fluoropyrimidine and oxaliplatin.
Methods The FOLFIRI regimen consisted of intravenous infusion of irinotecan 180 mg/m^2 on day 1 plus leucovorin (LV) 400 mg/m^2 on day 1 plus 5-fluorouracil (5-FU) 400 mg/m^2 bolus on day 1 plus 46-hour intravenous infusion of 5-FU 2,400 mg/m^2, every 2 weeks as one cycle. The main selection criterion for this study was the advanced colorectal cancer refractory to fluoropyrimidine and oxaliplatin.
Results Of the 57 evaluable patients for efficacy, 4 (7.5%) had a partial response, 36 (67.9%) had stable disease, and 13 (24.5%) had progressive disease. Median progression-free survival was 4.8 months (95% CI 3.9–5.7 months), and median overall survival was 7.8 months (95% CI 13.1–16.5 months). Safety analysis was based on the data of 57 evaluable patients. The most frequently observed grade 3 or 4 toxicities were neutropenia 16 (27.8%), nausea/vomiting 7 (12.3%), and diarrhea 1 (1.8%).
Conclusion FOLFIRI regimen is effective and well tolerated in patients with advanced colorectal cancer refractory to fluoropyrimidine and oxaliplatin in Chinese population.

Keywords FOLFIRI · Metastatic colorectal cancer · Irinotecan · Second-line chemotherapy

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Introduction

Colorectal cancer is the second leading cause of mortality in western countries [1]. In China, the incidence of colorectal cancer is on the rise recently and has been ranked in the malignant at the sixth [2]. Approximately half of all patients with colorectal cancer develop to metastatic disease. First-line therapy of advanced colorectal cancer has moved from 5-fluorouracil (5-FU) with leucovorin (LV) or oral fluoropyrimidines to combination of fluoropyrimidines with oxaliplatin or irinotecan [3–6], alongside the introduction of bevacizumab [7]. The FOLFOX4 regimen has become established as a standard first-line therapy for advanced disease after de Gramont et al. and N9741 studies, which demonstrated superiority over LV/5-FU and LV/5-FU bolus and irinotecan (IFL), respectively [3, 5]. OPTIMOX1 has shown that stopping oxaliplatin after six cycles followed by simplified LV/5-FU2 (LV 200 mg/m^2 day 1, 5-FU bolus 400 mg/m2 day 1 followed by a 46 h 5-FU continuous infusion 2,400 mg/m^2) alone achieved the same efficacy results, progression-free survival (PFS), and overall survival (OS), Furthermore, discontinuing oxaliplatin after the sixth cycle greatly reduced the risk of grade 3–4 toxicities. Irinotecan, a camptothecin analogue, has definite activity against advanced metastatic colorectal cancer both in chemotherapy-naive and after 5-FU failure [4, 6, 8, 9]. However, few data are available about second-line irinotecan-based chemotherapy in patients previously treated with front-line FOLFOX in Chinese population. In a phase III trial, single-agent irinotecan therapy of advanced colorectal cancer achieved 4.4% response rate with 2.6 months PFS after oxaliplatin-based first-line chemotherapy [11], this study showed irinotecan-based chemotherapy of advanced colorectal cancer after oxaliplatin-based first-line chemotherapy was reasonable.

To evaluate the efficacy and safety of FOLFIRI regimen in patients with advanced colorectal cancer refractory to fluoropyrimidine and oxaliplatin in Chinese population, a Phase II trial study was designed to assess the impact of combined irinotecan with to LV/5-FU2 biweekly schedule (FOLFIRI). The primary objective of our study was to determine the objective response rate and safety to the FOLFIRI regimen. Our secondary objective was to determine progression-free survival and overall survival.

Patients and methods

Eligibility criteria

The eligibility criteria were adenocarcinoma of the colon or rectum; unresectable metastases; at least 1 bidimensionally measurable lesion of $\geq$2 cm; adequate bone marrow, liver, and renal function; Eastern Cooperative Oncology Group performance status of 0–2; and the scope of age $\geq$18 and $\leq$75. The main selection criterion for this study was the advanced CRC refractory to fluoropyrimidine and oxaliplatin. Patients with central nervous system metastases, second malignancies, or disease confined to previous radiation fields were excluded. Written informed consent was required, and the study was approved by the ethics committees of our center.

Chemotherapy

FOLFIRI consisted of LV 400 mg/m^2 on day 1 as a 2-hour infusion followed by bolus 5-FU 400 mg/m^2 on day 1 and a 46-hour infusion of 5-FU 2,400 mg/m^2, irinotecan 180 mg/m^2 on day 1 only, given as a 2-hour infusion in 250 ml of dextrose 5%, every 2 weeks as one cycle. When LV and oxaliplatin were given concurrently via a Y-connector, both drugs were administered in 5% dextrose. Routine antiemetic prophylaxis with a 5-hydroxytryptamine-3 receptor antagonist was used for FOLFIRI. The disposable and electronic pumps were used in all inpatients. Treatment would be continued until disease progression or unacceptable toxicity occurred or until patients themselves determine to discontinue treatment. Patients were assessed before starting each 2-week cycle using the National Cancer Institute Common Toxicity Criteria (NCI-CTC 2.0). Chemotherapy was delayed until recovery if neutrophils decreased to less than 1.5×10^9/L or platelets decreased to less than 100×10^9/L or for significant persisting on hematologic toxicity. The irinotecan dose was reduced after National Cancer Institute Common Toxicity Criteria Grade $\geq$3 diarrhea, stomatitis, or dermatitis.

Study parameters physical examinations and blood counts were performed every cycle. Hepatic and renal function tests, carcinoembryonic antigen (CEA), and computed tomography (CT) scans or magnetic resonance imaging (MRI) of measurable lesions were assessed at baseline and repeated every four 2-week cycles. WHO criteria were used to assess tumor response. Complete response was defined as the complete disappearance of all clinically assessable disease for at least 4 weeks, and partial response was defined as a decrease of at least 50% of the sum of the products of the diameters of measurable lesions for at least 4 weeks. CT or MRI scans were obtained 4 weeks later to confirm a response. Stable disease was defined as a decrease of less than 50% or an increase of less than 25% of measurable lesions, and progressive disease was defined as an increase of at least 25% of measurable lesions or the appearance of new malignant lesions. All CT and MRI scans were subjected to external review by at least 2 radiologists who were blinded to the patients' treatment to confirm responses and the date of progression. Progression-free survival was measured from the date of commencing protocol treatment to the date of first progression or death from any cause without progression. Overall survival was measured from the date of commencing protocol treatment to the date of death from any cause. Post study second-line chemotherapy was allowed at the discretion of the investigators and prospectively monitored for exploratory survival analysis.

Statistical considerations

Confidence intervals (CI) (95%; 95%CI) for the response rates were estimated using the exact probabilities of the binomial distribution. The Kaplan–Meier method was used to calculate PFS and OS. Statistical analyses were performed using SPSS 11.5 for Windows procedures.

Dose intensity was defined as the actual dose intensity relative to the protocol dose intensity.

Result

Patient characteristics

A total of 57 patients were registered from our center between September 2003 and September 2008. Of all, 57 patients received $\geq$1 dose of irinotecan and were analyzed for treatment and safety results. Pretreatment characteristics of these patients are listed in Table 1. While the median age was 52 (range 20–75), 28% were aged 60 or older, 8.8% were above 70; 100% were Chinese. Four of the 57 registered patients were deemed ineligible to be analyzed for efficacy; 4 patients had received 1 cycle of FOLFIRI with insufficient measurable disease, the remaining 53 eligible patients were analyzed for efficacy and 57 for toxicity. At the close-out date of September 7, 2008, the median

Table 1 Baseline patient's characteristics

	No.	%
No. included	57	
Median age (years)	52 (20–75)	
Male/female	33/24	58/42
Primary tumor		
Colon	35	61.4
Rectum	22	38.6
Site of metastases		
Liver	30	52.6
Lung	21	36.8
Peritoneal carcinomatosis	5	8.7
Other	18	31.6
No. of involved sites		
One	32	56.1
Two (liver and other)	18	31.6
>Two	7	12.3
ECOG performance status		
0	14	24.6
1	42	73.7
2	1	1.7
CEA		
Within normal range	21	36.8
Increased	36	63.2
Prior adjuvant therapy for colorectal cancer		
No	12	21.1
Yes	45	78.9

potential follow-up time from the commencement of treatment was 10.4 months (range 1.5–30 months).

Treatment given

In total, 269 cycles were given, with a range of 1–12 cycles and a median of 6 biweekly cycles per patient. Out of 57 patients, all received more than 1 cycle of therapy. Of these, 53 patients received more than 2 cycles of therapy, 31 patients ≥4 cycles, 9 patients ≥8 cycles, and 5 patients ≥12 cycles. Although the protocol specified 14 days between cycles, 28 patients (49.1%) received all their treatment cycles within ±2 days of the protocol 14-day period. In total, 65 cycles (24.2%) in 25 patients were delayed more than 2 days. Of these, 48 cycles (17.8%) were delayed for toxicity reasons.

Efficacy

Of the 53 eligible patients, the best response to treatment was assessed as a partial response (PR) in 4 patients (7.5%), for an overall objective response rate was 7.5% (4/53), for a stable disease (SD) was 67.9% (36/53), and for an progressive disease (PD) was 24.5% (13/53).

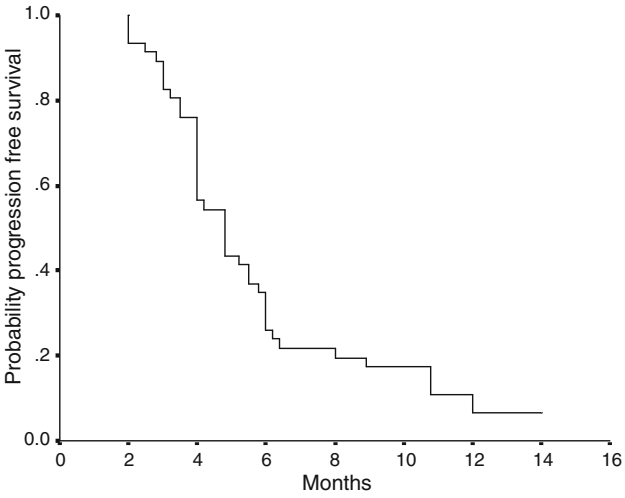

Fig. 1 Kaplan-Meier curve for progression free survival

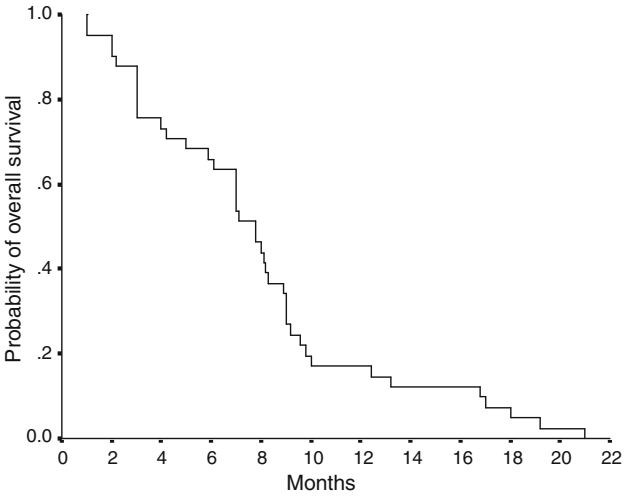

Fig. 2 Kaplan-Meier curve for overall survival

By the close-out date, 3 patients (5.2%) were alive without progression and 54 patients (94.8%) had progressed. The median PFS was 4.8 months (95% CI 3.9–5.7 months) with an estimated proportion of patients surviving without progression of 6.52% at 1 year (Fig. 1). As at the close-out date, 12 (21%) patients were still alive, and 45 (79%) patients had died. The median OS was 7.8 months (95% CI 13.1–16.5 months) (Fig. 2).

Dose intensity and toxicity

The median relative dose intensity of irinotecan was 93.5%, 99% of LV, 100% of bolus 5-FU (omitted for hematological or gastrointestinal toxicity), and 98% of 5-FU infusion. At the study close-out date, of the 57 patients who received

Table 2 Hematological and nonhematological toxicities (by patient)

	NCI-CTC grade (n = 57)					
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 3–4 (%)	Grade 1–4 (%)
Leukocytopenia	7 (12.3)	7 (12.3)	7 (12.3)	1 (1.7)	8 (14)	22 (38.6)
Neutropenia	5 (8.7)	2 (3.5)	9 (15.7)	7 (12.3)	16 (27.8)	23 (40)
Febrile neutropenia	0	0	0	1 (1.8)	1 (1.8)	1 (1.8)
Anemia	2 (3.5)	3 (5.2)	0	0	0	5 (8.7)
Thrombocytopenia	1 (1.7)	2 (3.5)	0	0	0	3 (5.2)
Nausea	15 (26.3)	35 (61.4)	7 (12.3)	0	7 (12.3)	57 (100)
Vomiting	15 (26.3)	35 (61.4)	7 (12.3)	0	7 (12.3)	57 (100)
Diarrhea	8 (14.0)	5 (8.7)	1 (1.8)	0	1 (1.8)	14 (24.6)
Constipation	3 (5.3)	1 (1.8)	0	0	0	4 (7.1)
Increased AST	3 (5.3)	0	0	0	0	3 (5.3)
Increased creatinine	0	0	0	0	0	0
Alopecia	10 (17.5)	4 (7)	1 (1.8)	0	1 (1.8)	15 (26.3)
Neurological toxicity	6 (10.5)	5 (8.8)	0	0	0	11 (19.3)
Mucositis	1 (1.8)	3 (5.3)	2 (3.5)	0	2 (3.5)	6 (10.6)
Fatigue	10 (17.5)	16 (28.1)	0	0	0	26 (45.6)

Table 3 Hematological and nonhematological toxicities (by cycle)

	NCI-CTC grade (n = 269)					
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 3–4 (%)	Grade 1–4 (%)
Leukocytopenia	33 (12.2)	28 (10.4)	9 (3.3)	2 (0.7)	11 (4.0)	72 (26.6)
Neutropenia	13 (4.8)	30 (11.1)	24 (8.9)	11 (4)	35 (12.9)	78 (28.9)
Febrile neutropenia	0	0	0	2 (0.7)	2 (0.7)	2 (0.7)
Anemia	6 (2.2)	10 (3.7)	0	0	0	16 (5.9)
Thrombocytopenia	1 (0.37)	2 (0.7)	0	0	0	3 (1.07)
Nausea	70 (26.0)	165 (61.3)	34 (12.6)	0	34 (12.6)	269 (100)
Vomiting	70 (26.0)	165 (61.3)	34 (12.6)	0	34 (12.6)	269 (100)
Diarrhea	21 (7.8)	5 (1.9)	1 (0.3)	0	1 (0.3)	27 (10.0)
Constipation	17 (6.3)	2 (0.7)	0	0	0	19 (7.0)
Increased AST	10 (3.7)	0	0	0	0	10 (3.7)
Increased creatinine	0	0	0	0	0	0
Alopecia	25 (9.3)	10 (3.7)	1 (0.3)	0	1 (0.3)	36 (13.3)
Neurological toxicity	24 (8.9)	7 (2.6)	0	0	0	31 (11.5)
Mucositis	6 (2.2)	10 (3.7)	0	0	0	16 (5.9)
Fatigue	30 (11.1)	28 (10.4)	0	0	0	58 (21.5)

≥1 treatment cycle, 5 patients (8.8% had completed more than 12 treatment cycles and 52 patients (91.2%) had discontinued treatment. In all, 14 patients (24.6%) discontinued due to disease progression or death, 25 (43.9%) due to toxicity: 1 (1.8%) diarrhea, 16 (27.8%) hematological toxicity, 8 (14%) due to other toxicity, 9 (15.8%) due to a decision of the patient, and 4 (7.0%) due to other reasons. Grades 1, 2, 3, and 4 acute toxicities were listed in Tables 2 and 3. The most common reported toxicity was neutropenia. Grade 3–4 neutropenia occurred in 16 (27.8%) patients; however, only 1 patient (1.8%) experienced febrile neutropenia. There were no deaths due to toxicity. Diarrhea Grade 3–4 was observed in only one patient (1.8%).

Discussion

Selecting an appropriate second-line regimen depends on several factors, including the first-line regimen, the degree

of response to first-line therapy, toxicity concerns, and the performance status of the patient. Single agent 5-FU given as an intravenous bolus injection produces a response rate of approximately 10%. Two strategies have been pursued to improve on this prolonged infusion schedules and biochemical modulation. Leucovorin (LV) modulation was the standard of care [12]. Prolonged infusions of 5-FU have been shown in a meta-analysis to have a higher response rate and longer duration of response compared with bolus schedules [13]. Two drugs, irinotecan and oxaliplatin, have demonstrated survival improvement, when given either alone or in combination with LV and 5-FU, in first- or second-line therapy [3–6, 8, 9]. Second-line studies have also shown an impact on survival. The two randomized second-line studies have shown that irinotecan as a single agent increased survival compared with best supportive care or LV plus 5-FU infusion, the benefit on survival ranged between 1.5 and 3 months [8, 9]. Phase III study investigated two sequences: FOLFIRI followed by FOLFOX6 and FOLFOX6 followed by FOLFIRI. Results have shown that both sequences are similar and achieve an impressive survival [10]. The FOLFIRI regimen has been recently reported to offer superior activity to two other irinotecan-based regimens (mIFL and CapeIRI) [14]. Moreover, Patients older than 70 years of age who were selected for inclusion in phase III trials derived similar benefits as younger patients from irinotecan-containing chemotherapy, and the risk of toxicity was similar [15]. In China, oxaliplatin entered Chinese health Insurance earlier than irinotecan more than 2 years, thus, oxaliplatin-based regimes were usually used as first-line chemotherapy in colorectal cancer of Chinese population. Therefore, when patients were refractory to fluoropyrimidine and oxaliplatin, irinotecan-based regimes served as second-line chemotherapy was reasonable in China.

In present study, the toxicity of the FOLFIRI regimen in oxaliplatin-pretreated patients in Chinese population, the most frequently observed grade 3 or 4 toxicities were neutropenia (27.8%), including 1.8% of febrile neutropenia, nausea/vomiting (12.3%), but very rare in diarrhea (1.8%). In Tournigand et al. study [10], the toxicity of the second-line FOLFIRI regimen, the most frequently observed grade 3 or 4 toxicities were neutropenia (21%) and diarrhea (8%). The toxicity of the FOLFIRI regimen in oxaliplatin-pretreated patients, reported in the phase II trial [16], was mostly neutropenia (grade 3/4 neutropenia was experienced 37% of the patients, including 5% of febrile neutropenia) and diarrhea (grade 3/4 in 23% of the patients). Of note, irinotecan doses were shrunk from 100 mg/m^2 days 1 and 3–80 mg/m2 days 1 and 3 in 30% of patients included in the phase II trial because of hematological toxicity [16]. But in the current study, the median relative dose intensity of irinotecan was 93.5%, 99% of LV, 100% of bolus 5-FU (omitted for hematological or gastrointestinal toxicity), and 98% of 5-FU infusion. Obviously, the dose of this study is adequate. Therefore, FOLFIRI regime in Chinese population exhibits less irinotecan-related diarrhea, this result was supported by a study from China. In wanget al study [17], a significant correlation was found between polymorphisms of UGT1A gene and irinotecan toxicity in Chinese patients with colorectal cancer. Pharmacodynamics studies showed a significant relationship between the percentage in diarrhea and the biliary index. These results should be confirmed by other studies [18].

The PFS reported in our study with FOLFIRI (4.8 months) appeared similar to previously reported in the phase II trial (4.7 months) [16]. In Tournigand et al. [10] study, which has compared FOLFIRI with FOLFOX in first-line treatment, with cross-over in second line, the PFS achieved by second-line FOLFIRI in oxaliplatin-pretreated patients was 2.5 months, and the response rate was 4%. In the same second-line setting, the EPIC study reported that PFS achieved by irinotecan as single agent and combined with cetuximab was 2.6 and 4.0 months, respectively [11]. The response rate was 4.2% for irinotecan and 16.4% when combined with cetuximab. In the current study, second-line FOLFIRI regimen was also associated with a long PFS (4.8 months), and the response rate was 7.5% in oxaliplatin-pretreated patients. Of note, a 4.2-month PFS was initially reported after 5-FU failure with a suboptimal irinotecan-based second line [9].

As reported here, FOLFIRI regimen indicated superior activity to two another irinotecan-based regimens (mIFL and CapeIRI) [14], and weekly CPT-11 followed by 5-FU/LV at relapse/progression did not demonstrate any advantage of median TTP and OS compared with 5-FU/LV [6]; therefore, the optimization of the cytotoxic regimens is critical, as the use of targeted therapies (bevacizumab, cetuximab) uniformly enhances the cytotoxic antitumor effect: the BICC-C study has demonstrated that FOLFIRI remains superior to mIFL even when bevacizumab was added to these two regimens [14, 19].

In conclusion, the results of the present trial emphasize the activity of FOLFIRI in the metastatic colorectal cancer of Chinese population refractory to fluoropyrimidine and oxaliplatin. We therefore believe that FOLFIRI with bevacizumab or with cetuximab regimens should be superior to irinotecan-based regimens. Finally, our pilot study results may provide support to initiate a randomized phase III trial comparing the irinotecan-based regimens combined with an appropriate targeted therapy in Chinese population.

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