A phase II study of modified FOLFOX as first-line chemotherapy in advanced small bowel adenocarcinoma

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This study aimed at assessing the efficacy and safety of biweekly oxaliplatin in combination with continuous infusional 5-fluorouracil and leucovorin (modified FOLFOX regimen) in patients with advanced small bowel adenocarcinoma (SBA). Thirty-three eligible patients with previously untreated SBA received 85 mg/m^2 of oxaliplatin intravenously over a 2-h period on day 1, together with 400 mg/m^2 of leucovorin over 2 h, followed by a 46-h infusion of 5-FU 2600 mg/m^2 every 2 weeks. All patients were evaluable for efficacy and toxicity. A median of nine cycles (range 3–18) was administered. The objective response rate was 48.5% [95% confidence interval (95% CI): 31–67%], with one complete response, 15 partial responses, 12 stable diseases, and five progressions. The median time to progression was 7.8 months (95% CI: 6.0–9.6) and the median overall survival was 15.2 months (95% CI: 11.0–19.4). Toxicity was fairly mild. Grade 3 toxicities included neutropenia (12.1%), thrombocytopenia (3.0%), nausea (6.1%), vomiting (3.0%), diarrhea (3.0%), peripheral neuropathy (9.1%), and fatigue (3.0%), and grade 4 toxicities occurred in none of the patients. The modified FOLFOX regimen is highly active and well tolerated as first-line chemotherapy for advanced SBA patients. ***Anti-Cancer Drugs*** **23:561–566 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Small bowel adenocarcinoma (SBA) is a rare malignancy, accounting for less than *2%* of all gastrointestinal tumors [1]. SBA is the second most common histologic subtype of malignant small bowel tumors, constituting 37% of cases, slightly less common than neuroendocrine tumors [2,3]. Approximately 2500 new patient cases of SBA were estimated in the US in 2008 [4]. Symptoms of SBA are frequently nonspecific, and the majority of patients present with advanced disease. The prognosis for patients with advanced SBA is poor: according to the National Cancer Data Base, the 5-year overall survival (OS) rates for patients with stage III or stage IV SBA are 35 and 4%, respectively [5].

Because of the rarity of SBA, limited data exist on the role of chemotherapy in advanced disease. Several retrospective studies have indicated that chemotherapy prolonged OS in patients with advanced SBA [6–10], but there is no standard frontline regimen due to a lack of randomized trials. Most available studies are small, retrospective, or included old chemotherapy regimens, which reported overall response rates of 6–37.5%, median OS 8–18.6 months [6,8,11–13]. Recently, a retrospective single-center study suggested that chemotherapy with 5-fluorouracil (5-FU) and a platinum agent in metastatic SBA patients led to a higher response rate (46 vs. 16%; $P = 0.01$) and progression-free survival (PFS) (8.7 vs. 3.9 months; $P \leq 0.01$) compared with other chemotherapy regimens [14]. Another retrospective multicenter study indicated that LV5FU2 plus oxaliplatin (FOLFOX) was superior to LV5FU2-cisplatin in terms of PFS (6.9 vs. 4.8 months; $P = 0.02$) and OS (17.8 vs. 9.3 months; $P = 0.04$) [15].

In our previously published studies, we modified the FOLFOX4 regimen by omitting bolus 5-FU and increasing the dose of infusional 5-FU to 2600 mg/m^2, and found it to be highly active and more tolerable in the patients with advanced colorectal or gastric cancer [16,17]. Therefore, we designed this phase II study to investigate the efficacy and tolerability of a modified FOLFOX regimen in the patients with advanced SBA.

Patients and methods

Eligibility

Patients with advanced SBA who had histologically confirmed and measurable target lesions were enrolled in the study. Patients with ampullary cancer were excluded. The patients were required to have radiographically measurable disease. Other eligibility criteria were as follows: Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, a life expectancy greater than 3 months, age at least 18 years, adequate bone marrow function (absolute neutrophil count $\geq 1.5 \times 10^9$/l, platelet count $\geq 75 \times 10^9$/l,

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hemoglobin ≥ 90 g/l), adequate renal and hepatic function (serum creatinine $\leq 1.5 \times$ upper normal limit, hepatic enzymes $\leq 2 \times$ upper normal limit, bilirubin $\leq 1.5 \times$ upper normal limit), a normal cardiac function, absence of a second primary tumor other than nonmelanoma skin cancer or in-situ cervical carcinoma, no central nervous system involvement, and no concurrent uncontrolled medical illness. Previous adjuvant chemotherapy, if given, must have been completed at least 6 months before inclusion. Patients who received earlier adjuvant treatment with oxaliplatin were not eligible. The protocol was approved by the Ethics Committee and was carried out according to the principles of the Declaration of Helsinki and good clinical practice guidelines, and all patients gave their written informed consent to participate in the trial.

Treatment schedules

Modified FOLFOX consisted of 400 mg/m^2 of leucovorin (LV) as a 2 h infusion, followed by a 46 h infusion of 5-FU 2600 mg/m^2, and oxaliplatin 85 mg/m^2 on day 1 given as a 2 h infusion. When LV and oxaliplatin were given concurrently through a Y-connector, both drugs were administered in 5% dextrose. Cycles were repeated every 2 weeks. Routine antiemetic prophylaxis with a 5-hydroxytryptamine-3 receptor antagonist was used for modified FOLFOX. The disposable and electronic pumps were used in all inpatients. Chemotherapy could be delayed for up to 2 weeks if the absolute neutrophil count decreased to less than 1.5×10^9/l or the platelet count decreased to less than 75×10^9/l or for significant persisting nonhematologic toxicity. Any patient who required more than 2 weeks for recovery from adverse reactions was removed from the study. The 5-FU dose was reduced after NCI-CTC 2.0 Criteria grade ≥ 3 diarrhea, stomatitis occurred. The oxaliplatin dose was reduced by 25% in the event of grade 3 or 4 thrombocytopenia, grade 4 neutropenia, or any other severe ($\geq$ grade 3) organ toxicity, and for paresthesia with pain or functional impairment greater than 7 days, or paresthesia with pain persistent between cycles. For paresthesia with functional impairment persistent between cycles, oxaliplatin was discontinued. Chemotherapy was continued until disease progression, unacceptable toxicity, patient's refusal, or physician's decision.

Evaluation criteria

Physical examinations, biochemical profile, and electrocardiogram were performed every cycle. Complete blood counts were tested every week. Tumor markers, and computed tomography scans or MRIs of measurable lesions were assessed at baseline and repeated every three cycles of treatment. Responses were assessed by at least two observers, and were confirmed by an expert independent radiologist. Tumor assessment was performed for every three cycles of chemotherapy, or earlier when indicated clinically. Responses were to be confirmed by subsequent CT scans 4 weeks after the initial response documentation. The Response Evaluation Criteria in Solid Tumors (version 1.0) were used to evaluate clinical response [18]. Assessment of time to progression (TTP) was carried out by measuring the time interval from the beginning of treatment until the first documentation of progression. OS was determined by measuring the time interval from the beginning of the treatment to the date of death or last contact. Toxicity was assessed in each treatment cycle of therapy using the National Cancer Institute Common Toxicity Criteria (version 2.0).

Statistical consideration

The primary endpoint of this study was to estimate the overall response rate and safety of the regimen. The secondary end points were TTP and OS. The Simon minimax two-stage design was used to determine the sample size [19]. Interim analysis was carried out when the first 18 assessable patients had been recruited. If more than four responses were observed, 15 additional patients were to be recruited; otherwise, the study was to be terminated. If more than 10 responses were observed in the 33 patients, the regimen was considered sufficiently active with a significance level of 5% and a power of 80% to be submitted for further evaluation. TTP and OS were analyzed according to the Kaplan–Meier method. The log-rank test was used to compare survival between groups. Multivariate analyses were performed using the Cox proportional hazards test. Statistical computations were performed using SPSS (version 10.0; SPSS Inc., Chicago, Illinois, USA).

Results

Patients characteristics

From March 2007 to February 2011, 33 patients with a metastatic or advanced SBA were enrolled in this trial from three centers. In all, 33 patients received three or more treatment cycles, and were eligible to be analyzed for efficacy and toxicity. The pretreatment characteristics of the patients are listed in Table 1. Of the three patients who had received adjuvant chemotherapy, two received the cisplatin/5-FU regimen and one received 5-FU/LV. At the closing date of 10 May 2011, the median follow-up time from the commencement of treatment was 16.5 months (range 3–45 months).

Efficacy

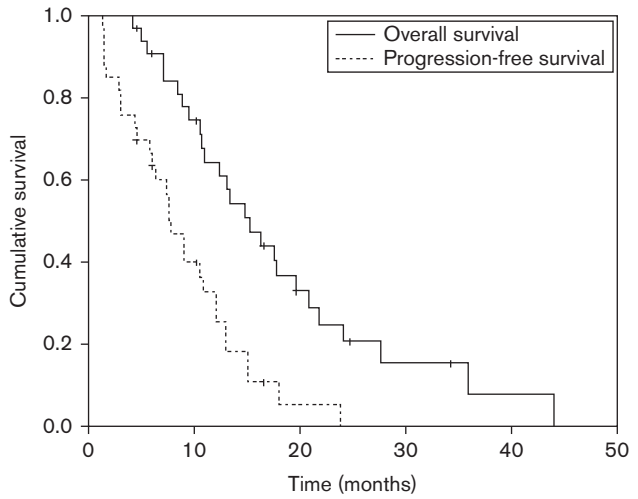
Among the 33 assessable patients, we observed one (3.0%) complete response and 15 (45.5%) partial responses, yielding an overall response rate of 48.5% [95% confidence interval (CI): 31–67%]. Twelve (36.4%) patients had stable disease and five (15.1%) had progressive disease. The median TTP was 7.8 months (95% CI: 6.0–9.6 months) and the median OS was 15.2 months (95% CI: 11.0–19.4 months) (Fig. 1). The OS rate was 61.0% (95% CI: 44–78%) at 1 year and 20.6% (5–36%) at 2 years. Twenty-six patients had died at the time of the present evaluation. A total of 20 patients (60.6%) received second-line chemotherapies: 14 irinotecan based

Table 1 Baseline patient characteristics ($n=33$)

	No.	%
No. included	33	
Median age (years)	57 (32–76)	
Males/females	23/10	69.7/30.3
ECOG performance status		
0	7	21.2
1	19	57.6
2	7	21.2
Disease status		
Locally advanced	4	12.1
Metastatic	29	87.9
Histology		
Well to moderately differentiated	13	39.4
Poorly differentiated	20	60.6
Primary tumor site		
Duodenum	26	78.8
Jejunum + ileum	7	21.2
Sites of metastases		
Liver	16	48.9
Lung	4	12.1
Peritoneum	9	27.3
Distant lymph nodes	11	33.3
Other	3	9.1
Prior adjuvant chemotherapy		
None	30	90.9
Yes	3	9.1

ECOG, Eastern Cooperative Oncology Group.

Fig. 1



Kaplan–Meier plots of progression-free survival and overall survival for all patients.

and six gemcitabine based. Most of them have been treated with irinotecan-based chemotherapy, because this regimen is usually proposed as the second-line treatment after failure of first-line platinum-based chemotherapy in patients with advanced SBA, as suggested by the largest study in this setting published by Zaanan *et al.* [20].

Prognostic factors that may potentially influence PFS and OS were investigated. Parameters studied included performance status, histologic grade, and primary tumor site. Upon univariate analysis of these 33 patients (Table 2), low histologic grade (well to moderately differentiated) and good performance status (0–1) were significantly associated with longer PFS and OS, respectively. But upon multivariate analysis (Table 2), only good performance status (0–1) was an independent predictor of better PFS ($P = 0.01$) and OS ($P = 0.001$). Although the response rate was slightly higher in patients with tumors in the jejunum and ileum than with the duodenum (57.1 vs. 46.2%), the primary tumor site was not found to be correlated with PFS or OS.

Toxicity

In total, 305 chemotherapy cycles were administered, with a median of nine cycles per patient (range 3–18). Eleven patients (33%) received at least 12 treatment cycles. The planned dose intensity was 42.5 mg/m^2/week for oxaliplatin, 200 mg/m^2/week for LV, and 1300 mg/m^2/week for 5-FU. The relative dose intensities of each drug were 94, 100, and 97%, respectively. Although the protocol specified 14 days between cycles, 260 out of 305 treatment cycles (85.2%) were administered without delay. Thirty-two cycles (10.5%) were delayed for less than 7 days and 13 cycles (4.3%) for more than 7 days. Of these, 35 cycles (11.5%) were delayed for toxicity reasons.

The frequencies of hematological and nonhematological toxicities are shown in Table 3. Grades 3–4 neutropenia occurred in four patients (12.1%), and none of the patients experienced febrile neutropenia. Grades 1–2 anemia and thrombocytopenia developed in 51.5 and 30.3% of the patients, respectively, and one patient experienced grade 3 thrombocytopenia. None of the patients required platelet transfusion and two patients received packed red blood cell transfusion. The most common nonhematological toxicities included nausea, vomiting, diarrhea, neurotoxicity, and fatigue. Grade 1–2 vomiting, diarrhea, neurotoxicity, and fatigue were reported in 36.4, 27.3, 54.5, and 48.5% of the patients, respectively, and grade 3 in 3.0, 3.0, 9.1, and 3.0% of the patients, respectively. Grade 4 toxicities occurred in none of the patients. No serious hepatic or renal function impairment was reported and no toxic deaths occurred during the study.

Discussion

Because of the rarity of SBA, no randomized phase III trials have been conducted to evaluate the role of chemotherapy and no standard chemotherapy regimen has been established in advanced SBA. Patients with advanced SBA are often treated with the same chemotherapy regimens as patients with advanced colorectal or gastric cancers. Therefore, in retrospective studies with SBA patients, the most commonly used regimens were 5-FU or 5-FU-based schedules (Table 4). Among them, combination chemotherapy of 5-FU and a platinum agent was considered more effective compared with other regimens [14], and FOLFOX seemed to be the most effective platinum-based chemotherapy regimen [15]. However, because of the potential bias for both selection and

Table 2 Univariate and multivariate analysis of factors associated with survival

		Univariate		Multivariate	
Outcome/factors	No.	Time (months; 95% CI)	*P*	Relative risk (95% CI)	*P*
Progression-free survival					
ECOG performance status			0.005	3.94 (1.39–11.22)	0.01
0–1	26	9.0 (4.8–13.2)			
2	7	4.5 (0.4–8.6)			
Histology			0.027	2.30 (0.93–5.69)	0.072
Well to moderately differentiated	13	10.8 (4.9–16.7)			
Poorly differentiated	20	6.0 (3.6–8.4)			
Primary tumor site			0.10		
Duodenum	26	7.3 (4.8–9.8)			
Jejunum + ileum	7	13.0 (7.0–19.0)			
Overall survival					
ECOG performance status			0.0003	6.36 (2.07–19.61)	0.001
0–1	26	17.7 (12.7–22.7)			
2	7	10.5 (4.5–16.5)			
Histology			0.032	2.18 (0.94–5.05)	0.068
Well to moderately differentiated	13	19.6 (14.3–24.9)			
Poorly differentiated	20	13.1 (9.1–17.1)			
Primary tumor site			0.171		
Duodenum	26	14.8 (10.3–19.3)			
Jejunum + ileum	7	17.7 (8.5–26.9)			

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group.

Table 3 Most common treatment-related toxicities according to National Cancer Institute Toxicity Criteria ($n = 33$)

	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Neutropenia	8 (24.2)	7 (21.2)	4 (12.1)	0
Febrile neutropenia	0	0	0	0
Anemia	12 (36.4)	5 (15.2)	0	0
Thrombocytopenia	7 (21.2)	3 (9.1)	1 (3.0)	0
Nausea	11 (33.3)	6 (18.2)	2 (6.1)	0
Vomiting	8 (24.2)	4 (12.1)	1 (3.0)	0
Diarrhea	7 (21.2)	2 (6.1)	1 (3.0)	0
Stomotitis	8 (24.2)	2 (6.1)	0	0
ALT/AST elevation	6 (18.2)	3 (9.1)	0	0
Creatinine elevation	1 (3.0)	0	0	0
Peripheral neuropathy	12 (36.4)	6 (18.2)	3 (9.1)	0
Fatigue	9 (27.3)	7 (21.2)	1 (3.0)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

interpretation in retrospective studies, prospective trials are still needed to confirm the activity of chemotherapy in advanced SBA.

In this phase II study, we evaluated the efficacy and safety of a modified FOLFOX regimen in advanced SBA. This is the first prospective report of this schedule in advanced SBA so far and it has shown promising results. The overall response rate in 33 evaluable patients was 48.5%, the median TTP was 7.8 months, and the median OS was 15.2 months. The efficacy results in this trial compare favorably with those retrospective reports (Table 4). Our findings also compare well with two retrospective studies that evaluated treatment with 5-FU and a platinum agent, in which the response rates were 21–41%, the median PFS were 8–8.7 months, and the median OS were 14–14.8 months [12,14]. In addition, the efficacy of our modified FOLFOX was similar to that of FOLFOX in a retrospective multicenter study [15]. In that study, 93 patients with advanced SBA received one of four chemotherapy regimens: LV5FU2, FOLFOX, FOLFIRI, or LV5FU2-cisplatin. The median PFS with the above treatments were 7.7, 6.9, 6.0, and 4.8 months, respectively, whereas the median OS were 13.5, 17.8, 10.6, and 9.3 months, respectively. Multivariate analysis indicated that FOLFOX was a significant predictor of better PFS ($P \leq 0.001$) and OS ($P = 0.02$).

So far, to the best of our knowledge, only two prospective, phase II studies have assessed chemotherapy as first-line treatment in advanced SBA patients [13,21]. The first study, conducted by the ECOG [13], evaluated the combination of 5-FU, doxorubicin, and mitomycin (FAM) in 38 patients with either advanced SBA or ampullary adenocarcinoma. This regimen demonstrated a response rate of 18%, a median TTP of 5 months, and a median OS of 8 months. The efficacy results in our study were obviously superior to the data in the ECOG study. Another phase II study [21] assessed capecitabine plus oxaliplatin (CAPOX) in the patients with advanced SBA or ampullary adenocarcinoma. The response rate was 50%, the median TTP was 11.3 months, and the median OS was 20.4 months. Both TTP and OS with CAPOX were slightly better than that reported in our study, respectively. One possible reason for this is that more patients in our study had a performance status of 2 (21.2 vs. 3%), which has been demonstrated to be an independent factor predictive of worse PFS and OS in former studies [8,15] and this study. Also, published data indicated that poorly differentiated pathology grade was another independent predictor of worse OS [8], which occurred in 60.6% of the patients in our study and in 43% of the patients in the CAPOX cohort. In addition, up to 78.8% of patients in our study had duodenal tumors, which was considered by some authors as a poor prognostic factor compared with tumors in the jejunum or the ileum [2,5]. Despite the minor differences in survival data between our study and the CAPOX study, both trials have demonstrated the

Table 4 Efficacy of selected studies in advanced small bowel adenocarcinoma

References	Study type	Number of patients	Chemotherapy	RR (%)	OS (months)	TTP (months)
Xiong *et al.* (this study)	Phase II	33	Modified FOLFOX	48.5	15.2	7.8
Zaanan *et al.* [15]	Retrospective	93	LV5FU2-based regimens	26.5	15.1	6.6 (PFS)
Overman *et al.* [21]	Phase II	30	CAPOX	50	20.4	11.3
Overman *et al.* [14]	Retrospective	80	Various agents	25	13	4.6 (PFS)
Fishman *et al.* [8]	Retrospective	44	Various agents	29.5	18.6	NR
Gibson *et al.* [13]	Phase II	38	FAM	18	8	5
Locher *et al.* [12]	Retrospective	20	5-FU and a platinum agent	21	14	8 (PFS)
Czaykowski *et al.* [6]	Retrospective	16	5-FU-based regimens	6	15.6	NR
Crawley *et al.* [11]	Retrospective	8	ECF or 5-FU	37.5	13	7.8 (PFS)

5-FU, 5-fluorouracil; CAPOX, capecitabine, oxaliplatin; ECF, epirubicin, cisplatin, and 5-FU; FAM, 5-FU, doxorubicin, and mitomycin; FOLFOX, oxaliplatin, leucovorin, and 5-FU; LV5FU2, leucovorin, 5-FU; NR, not reported; OS, overall survival; PFS, progression-free survival; RR, response rate; SBA, small bowel adenocarcinoma; TTP, time to progression.

survival benefit of oxaliplatin and fluoropyrimidine combination as first-line chemotherapy in advanced SBA.

An interesting finding is that SBA in the duodenum was more predominant (78.8%) in this study than in the Western series (38–59%) [2,5,7,14,15]. For instance, in the largest study of small bowel cancers conducted by Bilimoria *et al.* [2], only 55.7% of SBA patients had tumors in the duodenum. However, data from the Korean studies also suggested that SBA occurred more in the duodenum in Asian patients (74–82%) [9,22,23]. The reason for this phenomenon still remains unclear, although a hypothesis was presented that the duodenum is at a much higher risk of exposure to potential gastric carcinogens that pass down the stomach in gastric cancer-prevalent areas such as Asia [9]. In the study by Bilimoria *et al.* [2], patients with duodenal adenocarcinoma were found to have a poorer prognosis compared with those with jejunal tumors. Another large study also indicated that SBA patients with tumors in the duodenum had a worse outcome than those who had tumors in the jejunum or the ileum [5]. Explanations for this may be as follows [7]: first, more patients with duodenal tumors did not receive any cancer-directed surgery; second, patients with duodenal tumors require more complex or extended surgeries, which is associated with a higher mortality rate. In our study, however, no significant differences were detected in PFS and OS according to the tumor site. To explain this, two factors may be considered: a small sample size in this study and all patients enrolled with advanced stages. As far as patients with advanced SBA are concerned, available data showed no correlation between the survival outcome and the primary tumor sites [8,14,15].

It should be noted that an important aspect with our modified FOLFOX is that we excluded bolus 5-FU and increased the dose of infusional 5-FU to 2600 mg/m^2 in order to reduce hematological toxicity. The trial conducted by De Gramont *et al.* [24] showed that the infusion-based 5-FU/LV regimen was better tolerated than the bolus-based program developed at the Mayo Clinic, with a substantially lower frequency of neutropenia and diarrhea. In the N9741 study [25], the infusional 5-FU in FOLFOX was associated with significantly less febrile neutropenia and less risk of early death than its delivery by a bolus. A recent meta-analysis also indicated that regimens containing 5-FU as a bolus exhibit a higher rate of toxic deaths than schedules using a continuous infusion of 5-FU [26]. In this study, our modified FOLFOX regimen was fairly tolerable. There were no grade 4 adverse events and treatment-related deaths. Grade 3 neutropenia occurred in only four (12.1%) patients. By contrast, up to 42–43% of advanced colorectal cancer patients developed grade 3/4 neutropenia when treated with a bolus 5-FU-retained FOLFOX4 regimen [27,28]. In our study, grade 3 non-hematological toxicities included peripheral neuropathy (9.1%), nausea (6.1%), vomiting (3.0%), diarrhea (3.0%), and fatigue (3.0%). As sensory peripheral neuropathy is closely associated with the cumulative dose of oxaliplatin, the oxaliplatin dosage adopted here remains 85 mg/m^2. In the GERCOR V308 study [29], however, the FOLFOX6 regimen with oxaliplatin at 100 mg/m^2 was delivered for a median of 12 cycles; up to 34% of patients developed grade 3 neurotoxicity.

In conclusion, the modified FOLFOX regimen is highly active, fairly tolerable as first-line chemotherapy for patients with SBA, and deserves to be studied further. Given the good tolerability of this schedule, targeted agents (e.g. cetuximab, bevacizumab) are also expected to be incorporated to optimize the efficacy.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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