Cancer Chemother Pharmacol (2016) 78:949–958
DOI 10.1007/s00280-016-3147-y

ORIGINAL ARTICLE

A dose-finding study for oxaliplatin, irinotecan, and S-1 (OIS) in patients with metastatic or recurrent gastrointestinal cancer

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Received: 9 May 2016 / Accepted: 24 August 2016 / Published online: 15 September 2016

Abstract
Purposes To determine the maximum tolerated dose (MTD), recommended dose (RD), and activity of combined oxaliplatin, irinotecan, and S-1 chemotherapy for metastatic or recurrent gastrointestinal (GI) cancer.
Methods Oxaliplatin and irinotecan were administered intravenously on day 1, and S-1 was administered orally on days 1–7, every 2 weeks. This phase I study used the following dose levels for oxaliplatin/irinotecan/S-1: level 1, 85/120/60 mg/m^2; level 2, 85/120/80 mg/m^2; level 3, 85/120/100 mg/m^2; level 4, 85/150/100 mg/m^2; and level 5, 85/180/100 mg/m^2. Treatment was repeated for a maximum of 12 cycles, until disease progression, or until unacceptable toxicity.
Results Twenty-four patients were enrolled between October 2012 and February 2014 (median age 59 years). During the first cycle, one of the six patients in levels 1, 3, and 4 developed a dose-limiting toxicity (grade 3 febrile neutropenia), and none of the three patients in level 5 developed a dose-limiting toxicity. As the planned maximum dose did not reach the MTD, the level 5 dose was defined as the RD. Twenty-one patients were evaluated for response, which included 2 cases of complete response and 8 cases of partial response, with an overall response rate of 47.6 %.
Conclusions The combination of oxaliplatin, irinotecan, and S-1 provided an acceptable toxicity profile and modest clinical benefits in patients with advanced GI cancer. The RD was 85 mg/m^2 of oxaliplatin, 180 mg/m^2 of irinotecan, and 100 mg/m^2 of S-1 every 2 weeks.

Keywords Gastrointestinal cancer · Oxaliplatin · Irinotecan · S-1 · Maximum tolerated dose

Introduction

In recent years, the treatment options for patients with advanced gastrointestinal (GI) cancer have considerably increased. Although 5-fluorouracil (5-FU) remains a cornerstone for the management of these patients, several novel drugs provide appreciable activities in these diseases. For example, when combined with 5-FU, oxaliplatin or irinotecan provides considerable antitumor activity in patients with GI cancer. However, oxaliplatin, irinotecan, and 5-FU have different mechanisms of actions and do not share major toxicity profiles. As they have a synergistic effect, many recent clinical trials have evaluated the efficacy of the triplet combination of oxaliplatin, irinotecan, and 5-FU (FOLFOXIRI), which provides significant survival benefits with favorable toxicity profiles [1–7].

S-1 and capecitabine are oral fluoropyrimidines, and several phase III trials have demonstrated that these agents have activities, efficacies, and safety profiles that are similar to those of 5-FU in patients with GI cancer [8–11]. Furthermore, phase I and II studies have evaluated the safety

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and activity of the biweekly triplet combination of capecitabine, oxaliplatin, and irinotecan (XELOXIRI) in patients with untreated metastatic colorectal cancer, and their results suggest that the triplet combination is feasible and active in these patients [12–15]. Moreover, the triplet combination of oxaliplatin, irinotecan, and S-1 (TIROX) has been evaluated in three phase II trials, which have demonstrated that this combination was feasible, effective, and well tolerated [16–18]. However, because the treatment was repeated every 3 weeks (unlike the biweekly cycle in previous trials), the dose intensities of oxaliplatin and irinotecan were reduced in the TIROX regimen. Thus, based on the available clinical data, the biweekly triplet combination of S-1, oxaliplatin, and irinotecan (OIS) is an interesting alternative that may facilitate simpler and more convenient treatment delivery. Therefore, the present study aimed to determine the feasibility of the OIS combination, identify the maximum tolerated dose (MTD) and recommended dose (RD) for the individual agents, and evaluate the preliminarily antitumor activity in patients with untreated advanced GI cancer.

Methods

Patient eligibility

Patients were eligible for this study if they fulfilled all of the following criteria: (1) histologically confirmed unresectable or metastatic GI or biliary tract adenocarcinoma; (2) age of ≥18 years; (3) Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; (4) at least one measurable lesion, as defined using version 1.1 of the Response Evaluation Criteria In Solid Tumors (RECIST) [19]; (5) prior adjuvant chemotherapy without oxaliplatin, irinotecan, and S-1 that had been completed >4 weeks before enrollment; (6) adequate hematological, renal, and hepatic functions, as defined using an absolute neutrophil count (ANC) of $\geq 1.5 \times 10^9$/L, a platelet count of $\geq 100 \times 10^9$/L, serum creatinine levels of ≤1.4 mg/dL, serum total bilirubin of ≤twofold above the upper limit of normal (ULN), or aspartate aminotransferase and alanine aminotransferase levels of ≤2.5-fold above the ULN (or ≤fivefold above the ULN in the presence of hepatic metastasis); and (7) willing to provide informed consent to participate in this study.

The exclusion criteria were: (1) a history of chemotherapy, with the exception of adjuvant chemotherapy; (2) contraindication for any drug in the OIS regimen; (3) serious GI bleeding or obvious bowel obstruction; (4) central nervous system metastasis; (5) other previous or concurrent malignancies within the last 5 years, with the exception of cured basal cell carcinoma of the skin or carcinoma in situ of the uterine cervix; (6) pregnant or lactating; (7) sexually active and the partner being unwilling to practice contraception during the study; and (8) other clinically significant comorbid conditions, such as active infection or severe cardiopulmonary dysfunction. The study's protocol was approved by the institutional review board of Hallym University Sacred Heart Hospital, Anyang, South Korea (protocol number: HMC-HO-GI-1203).

Treatment and study design

To determine the MTD and RD, the doses of oxaliplatin, irinotecan, and S-1 were increased through five levels if dose-limiting toxicities (DLTs) were not identified. The dose escalation scheme for each drug (oxaliplatin/irinotecan/S-1) was: level 1, 85/120/60 mg/m^2; level 2, 85/120/80 mg/m^2; level 3, 85/120/100 mg/m^2; level 4, 85/150/100 mg/m^2; and level 5, 85/180/100 mg/m^2. Oxaliplatin and irinotecan were administered intravenously on day 1, and S-1 was administered orally on days 1–7, every 2 weeks. Dose escalation was continued until more than one-third of the patients in a given dose level exhibited a DLT during the first cycle of treatment. At least 3 patients were enrolled in each level. Before escalating to the next level, all 3 patients were required to receive at least one treatment cycle. If at least 2 patients had a DLT, the corresponding dose level was to be defined as the MTD. If none of the 3 patients had a DLT, the dose was to be escalated to the next level and the process continued. If 1 of the 3 patients treated had a DLT, 3 additional patients were to be treated at the corresponding dose level. If none of these 3 additional patients had a DLT, the dose level was to be escalated to the next dose level, and the process would continue; otherwise, the current dose level would be defined as the MTD. The RD for a subsequent phase II study was to be defined as one level below the MTD. Intra-patient dose escalation was not permitted. Treatment was repeated every 2 weeks to a maximum of 12 cycles and was continued in the absence of disease progression, unacceptable toxicity, or the patient's refusal to continue treatment.

Dose-limiting toxicities

DLTs were defined as any of the following events during the first cycle of treatment: (1) any grade 4 neutropenia that lasted for ≥7 days or grade 3/4 febrile neutropenia; (2) any grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding; (3) any grade 3/4 non-hematological toxicity, with the exception of alopecia; and (4) any grade 3/4 nausea or vomiting that could not be reduced to grade 1 with antiemetic support. Toxicity was evaluated every week during the first cycle and then every 2 weeks for the duration of treatment. All adverse events were evaluated according to version 4.0 of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

Dose modification and dose intensity

In cases with apparent adverse events during the previous cycle of treatment, dose modifications were applied for the subsequent cycle according to the grade of the toxicities. The degree of the modification depended on the frequency of grade 3/4 hematological or non-hematological toxicities, with reductions of 25, 50 %, or permanent interruption. In cases with an ANC of $<1.5 \times 10^9$/L or a platelet count of $<75 \times 10^9$/L on day 1 of a cycle, treatment was delayed by 1 week for a maximum of 2 weeks, until recovery to an ANC of $\geq 1.5 \times 10^9$/L and a platelet count of $\geq 75 \times 10^9$/L. Once the dose of any drug had been reduced, it was not increased at a later time. The dose of oxaliplatin was reduced by 25 % of the initial dose for related grade 2 peripheral neuropathy and interrupted for grade 3 neuropathy or the second occurrence of the same grade 2 neuropathy.

To evaluate the exact administered dose, we calculated the relative dose intensity (RDI) as the ratio of the actually administered dose per time unit (mg/m^2/week) to that of the originally planned regimen [20].

Adverse events and response evaluation

A physical examination with vital signs, complete blood cell count with differentials, and blood chemistry tests were performed weekly for the first cycle, and then every 2 weeks within 3 days prior to treatment in each subsequent cycle. Response to treatment according to RECIST version 1.1 was evaluated every 3 cycles. Progression-free survival (PFS) was defined as the interval from the date of treatment initiation to the first date of documented disease progression or death due to any cause. Overall survival (OS) was defined as the interval from the date of treatment initiation to the date of death.

Statistical analysis

The primary purpose of this study was to determine the MTD and RD for the OIS combination, and the secondary aim was to assess this regimen's efficacy. Descriptive statistics were used to summarize the patients' characteristics, tumor responses, and safety events. The Kaplan–Meier method was used to estimate the median PFS and OS.

Results

Patient characteristics

Twenty-four patients were enrolled between October 2012 and February 2014 at Hallym University Sacred Heart Hospital. All patients were evaluated for safety events, and 21 patients were assessed for treatment response. The patients' characteristics are described in Table 1.

Dose-limiting toxicities during the first cycle and toxicities during all cycles

All patients who received at least one dose of OIS were considered evaluable for toxicities. The major toxicities that occurred during the first cycle at each dose level are summarized in Table 2. At dose level 1, 1 of the 3 initial patients developed grade 3 febrile neutropenia. Therefore, 3 additional patients were enrolled to confirm tolerability, and none of the additional patients exhibited a DLT. At dose level 2, none of the 3 initial patients exhibited a DLT. At dose levels 3 and 4, we observed grade 3 febrile neutropenia in 1 of the 3 patients in each level; therefore, 3 additional patients were treated in these dose levels, although no additional DLTs were observed. The final 3

Table 1 Patient characteristics ($n = 24$)

Characteristic	Number of patients (%)
Sex	
Male	14 (58.3)
Female	10 (41.7)
Age, years	
Median	59
Range	34–78
ECOG PS*	
0	9 (37.5)
1	13 (54.2)
2	2 (8.3)
Primary cancer	
Stomach	7 (29.2)
Colorectal	7 (29.2)
Biliary tract	9 (37.5)
Duodenum	1 (4.2)
Metastatic sites	
Lymph nodes	20 (83.3)
Peritoneum	10 (41.7)
Liver	10 (41.7)
Lung	8 (33.3)
Bone	2 (8.3)
Ureter	2 (8.3)
Colon	1 (4.2)
Gall bladder	1 (4.2)
Number of metastatic organs	
1	5 (20.8)
2	9 (37.5)
≥3	10 (41.7)

* *ECOG PS* Eastern Cooperative Oncology Group performance status

Table 2 Toxicities that were observed per patients at the various doses of oxaliplatin, irinotecan, and S-1 during the first treatment cycle

Dose level	Level 1				Level 2				Level 3				Level 4				Level 5			
	($n = 6$)				($n = 3$)				($n = 6$)				($n = 6$)				($n = 3$)			
Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Leukopenia	1	0	0	0	0	0	0	0	1	0	1	0	1	0	1	0	0	1	0	0
Neutropenia	0	0	1	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0
Anemia	3	2	0	0	2	0	0	0	2	3	0	0	4	1	1	0	2	1	0	0
Thrombocytopenia	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
Anorexia	2	1	1	0	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0
Nausea	2	0	1	0	1	1	0	0	1	0	0	0	0	2	0	0	0	0	0	0
Abdominal discomfort	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Diarrhea	1	0	0	0	0	0	0	0	1	1	0	0	1	1	0	0	1	0	0	0
Mucositis	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Fatigue	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Peripheral neuropathy	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Toxicity grading was performed according to version 4.0 of the National Cancer Institutes' Common Terminology Criteria for Adverse Events

Table 3 Dose-limiting toxicities during the first treatment cycle

	Level 1 ($n = 6$)	Level 2 ($n = 3$)	Level 3 ($n = 6$)	Level 4 ($n = 6$)	Level 5 ($n = 3$)
Febrile neutropenia	1	0	1	1	0

patients were enrolled at dose level 5, although they did not exhibit any DLTs during the first cycle. Therefore, as the maximum dose level in this study did not cause any DLTs, we concluded that the RD for the OIS regimen was dose level 5 (85 mg/m^2 of oxaliplatin, 180 mg/m^2 of irinotecan, and 100 mg/m^2 of S-1). The DLTs that we observed in this study are shown in Table 3. No grade 3/4 non-hematological DLTs were observed during the first cycle of treatment at all dose levels. The toxicities that we observed throughout the entire course of treatment are listed in Table 4. Neutropenia was a common toxicity, although only 33.3 % of patients developed grade 3/4 neutropenia and only 12.5 % of patients developed febrile neutropenia. The non-hematological toxicities were generally mild (grade 1/2) and manageable, and the most common non-hematological toxicities were peripheral sensory neuropathy, nausea, anorexia, abdominal discomfort, diarrhea, and fatigue.

Table 4 Toxicities that were observed per cycle and per patient during the entire course of treatment

Grade	Toxicity grade per cycle (178 evaluable cycles)					Toxicity grade per patient (24 evaluable patients)				
	1	2	3	4	3/4 (%)	1	2	3	4	3/4 (%)
Leukopenia	46	9	5	0	2.8	16	10	3	0	12.5
Neutropenia*	5	28	15	2	9.6	5	14	8	0	33.3
Anemia	107	41	2	0	1.1	22	14	1	0	4.2
Thrombocytopenia	25	9	0	0	0	12	5	1	0	4.2
Anorexia	6	8	1	0	0.6	4	6	1	0	4.2
Nausea	14	14	3	0	1.7	11	9	2	0	8.3
Abdominal discomfort	12	3	0	0	0	8	1	0	0	0
Diarrhea	6	7	0	0	0	6	7	0	0	0
Stomatitis	1	2	0	0	0	1	1	0	0	0
Fatigue	6	3	0	0	0	5	2	0	0	0
Peripheral neuropathy	32	9	0	0	0	12	5	0	0	0

Toxicity grading was performed according to version 4.0 of the National Cancer Institutes' Common Terminology Criteria for Adverse Events

* Febrile neutropenia, 6/178 cycles (3.4 %); 3/24 patients (12.5 %)

Table 5 Responses according to dose level

Dose level	Overall response			
	CR	PR	SD	PD
1 ($n = 6$)	1	1	4	0
2 ($n = 3$)*	0	1	0	1
3 ($n = 6$)$^{+}$	1	2	2	0
4 ($n = 6$)	0	3	3	0
5 ($n = 3$)*	0	1	1	0
Total ($n = 24$)	2	8	10	1

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

* Two patients were lost to follow-up

$^{+}$ One patient withdrew their consent; 21 patients were evaluated for treatment response

Table 6 Response according to the primary tumor

Primary tumor	Overall response			
	CR	PR	SD	PD
Stomach ($n = 7$)	1	3	3	0
Colorectal ($n = 7$)*$^{+}$	1	1	3	0
Biliary tract ($n = 9$)	0	4	4	1
Duodenum ($n = 1$)*	0	0	0	0
Total ($n = 24$)	2	8	10	1

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

* Two patients were lost to follow-up

$^{+}$ One patient withdrew their consent; 21 patients were evaluated for treatment response

Efficacy

A total of 178 chemotherapy cycles were administered to 24 patients, with a median of 7.5 cycles (range, 3–12 cycles) per patient; 21 patients were evaluated for treatment response. Two patients were lost to follow-up, and 1 patient withdrew their consent prior to the response evaluation. The tumor responses at each dose level are presented in Table 5. The response rates at dose levels 1–5 were 33.3, 50.0, 60.0, 50.0, and 50.0 %, respectively. Among the 21 evaluable patients, 2 patients achieved complete response and 8 patients achieved partial response. The overall response rate (ORR) was 47.6 % [95 % confidence interval (CI), 28.3–67.6 %], and the disease control rate was 95.2 % (95 % CI, 77.3–99.2 %). The median time to response among the 10 patients who exhibited a tumor response was 1.5 months (95 % CI, 1.3–1.6 months), and the median duration of the response was 4.6 months (95 % CI, 4.5–4.7 months). The response rates according to the primary tumor type were 57.1 % for gastric cancer (GC), 40.0 % for colorectal cancer (CRC), and 44.4 % for biliary tract cancer (BTC) (Table 6).

Among the 21 evaluable patients, the median PFS and OS were 6.2 months (95 % CI, 5.7–6.6 months) and 11.0 months (95 % CI, 9.7–12.4 months), respectively, with a median follow-up of 9.8 months (range, 0.6–20.1 months) (Fig. 1). Waterfall plots for the best response and spider plots for tumor shrinkage over time are presented according to the specific tumor types in Figs. 2 and 3, respectively. We also performed univariate analyses to identify factors that might predict response, although we did not observe any consistent and statistically significant results, based on the small and heterogeneous patient population (Table 7).

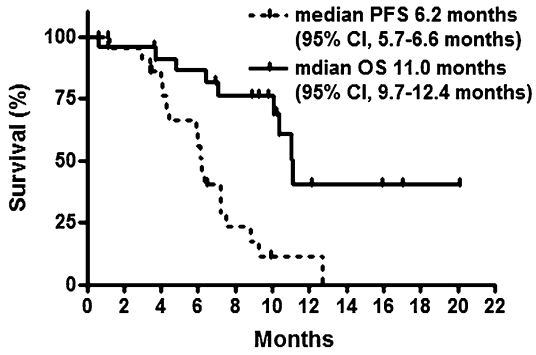

Fig. 1 Progression-free and overall survival

Dose intensity

The mean RDIs of oxaliplatin, irinotecan, and S-1 were 78.9, 81.4, and 80.1 %, respectively. The trends in the drugs' mean RDIs are presented in Fig. 4. During the 178 cycles, the chemotherapy dose was reduced in 49 cycles (27.5 %) due to grade 3/4 neutropenia (45 cycles) or grade 3 thrombocytopenia (4 cycles). Sixty cycles (33.7 %) were delayed due to grade 2 neutropenia (23 cycles), grade 3 neutropenia (12 cycles), grade 3 febrile neutropenia (5 cycles), grade 2 thrombocytopenia (6 cycles), grade 3 thrombocytopenia (1 cycle), grade 3 nausea (2 cycles), grade 2 diarrhea (3 cycles), postoperative bowel adhesion (1 cycle), and upper respiratory tract infection (1 cycle).

Discussion

In this phase I study, we identified the RDs for oxaliplatin (85 mg/m^2 on day 1), irinotecan (180 mg/m^2 on day 1), and S-1 (100 mg/m^2 on days 1–7) when they are administered

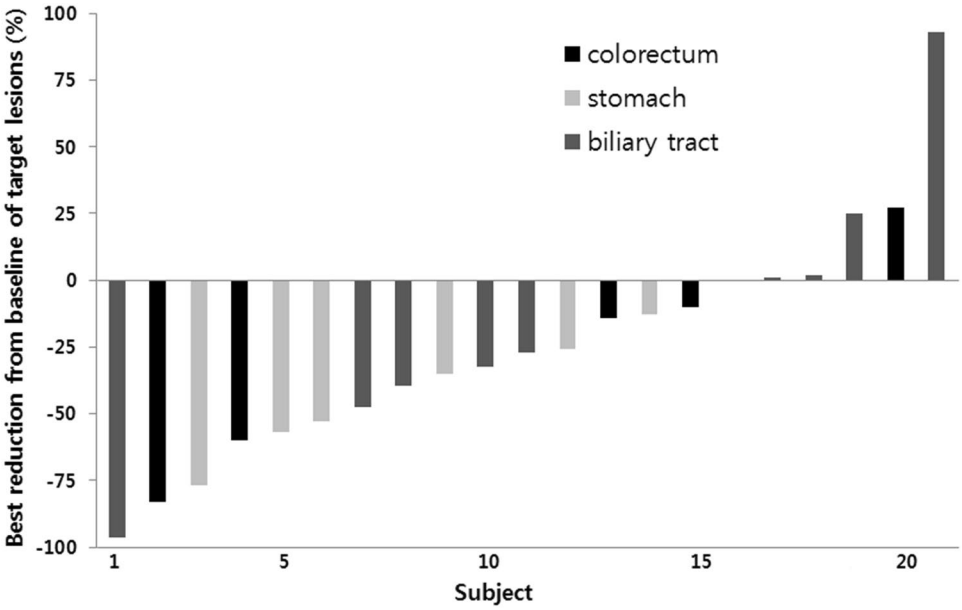

Fig. 2 Best response to treatment for each patient

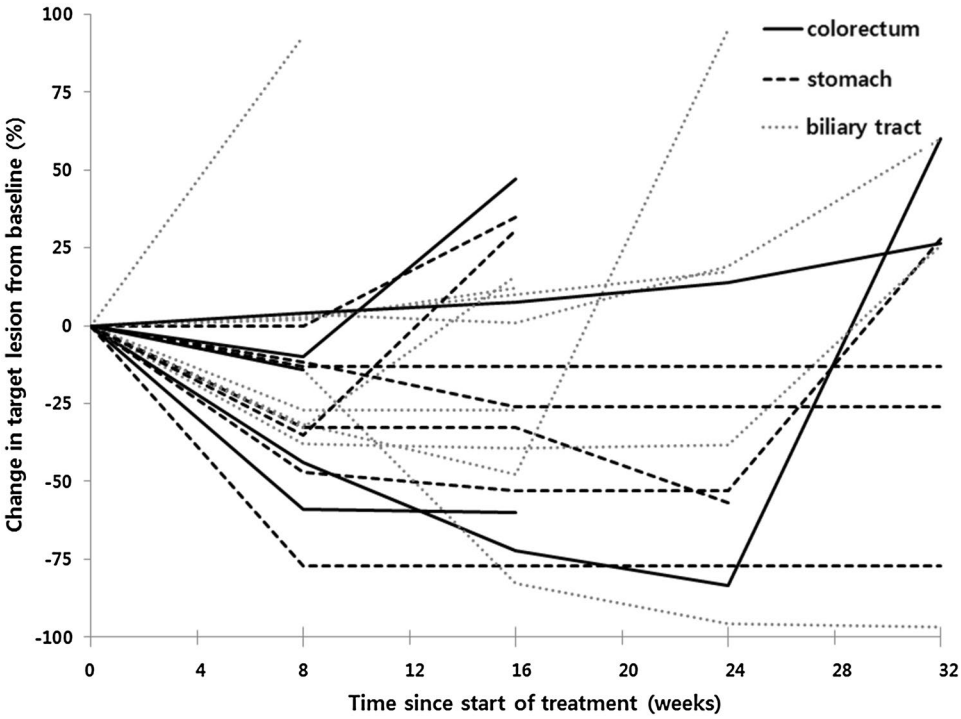

Fig. 3 Tumor changes after treatment for each patient

as a triplet chemotherapy regimen every 2 weeks. These doses are currently being examined in a follow-up phase II study. Grade 3 febrile neutropenia was the only DLT that was observed in the present study (3 of 24 patients, 12.5 %), and none of the 3 patients who were treated at the maximum planned dose level experienced a DLT. Our dose range was selected based on the traditional 3 + 3 dose escalation design, which is a mainstay for dose-finding studies. However, when evaluating triplet combinational therapy, more sophisticated strategies, such as the continual reassessment method, which can provide more precise dose-toxicity curves and recommended phase II dose, might be an alternative dose-finding design [21].

Toxicity analysis during the entire treatment period revealed grade 3/4 neutropenia (33.3 %), febrile neutropenia (12.5 %), grade 3 nausea (8.3 %) and anorexia (4.2 %), and some other low-grade non-hematological toxicities, such as diarrhea or peripheral neuropathy; most of these

Table 7 Univariate analyses of the factors that might influence the response rate

Variables	*n*	Response rate (%)	*P* value
Sex			
Male	9	58.3	0.256
Female	12	33.3	
Age (years)			
<65	17	47.1	0.916
≥65	4	50.0	
ECOG PS*			
0	9	55.6	0.528
≥1	12	41.7	
Primary cancer site			
Stomach	7	57.1	0.816
Colorectal	5	40.0	
Biliary tract	9	44.4	
Liver metastasis			
Present	6	33.3	0.407
None	15	53.3	
Peritoneal metastasis			
Present	8	37.5	0.466
None	13	53.8	

* *ECOG PS* Eastern Cooperative Oncology Group performance status

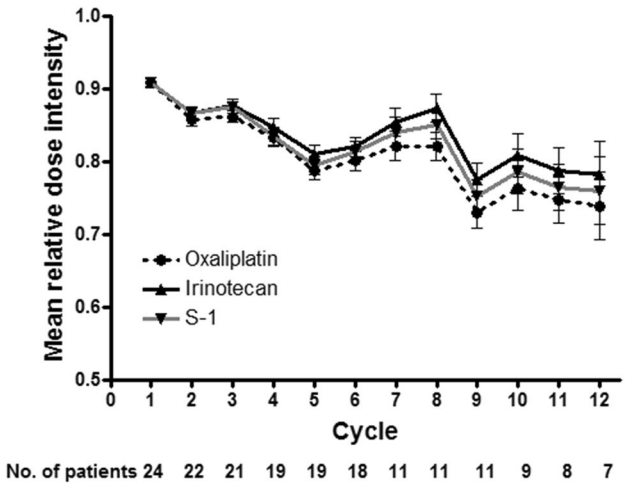

Fig. 4 Mean relative dose intensities of oxaliplatin, irinotecan, and S-1 according to treatment cycle

toxicities were relatively tolerable. These toxicities were observed at rates that are comparable to the rate of grade 3/4 toxicities from previous studies of the FOLFOXIRI regimen in various GI cancers, such as neutropenia (35.0–56.0 %), diarrhea (10.0–27.7 %), nausea (2.8–43.8 %), peripheral neuropathy (2.0–9.0 %), stomatitis (2.0–8.8 %), and infusion-related adverse events (4.0 %) [4–7, 22–24]. Although oxaliplatin-induced cumulative peripheral neuropathy is an expected adverse effect of treatment, and occurred 70.8 % of our patients, most of these patients only experienced grade 1 neuropathy. This favorable neurotoxicity profile may be related to our strict adherence to the protocol for dose reduction or delay. Oxaliplatin was delayed in patients with grade 2 or higher toxicity until the neuropathy had resolved to less than grade 1, and the dose was reduced by 25 % of the original doses. Thus, strict adherence to our dose modification or delay protocol may have reduced the likelihood of worsened toxicity (grade 3/4) in subsequent cycles.

In other recently reported trials, S-1 was incorporated as the 5-FU component in triplet regimens with a schedule of 2 weeks on and 1 week off in patients with GC and CRC [16, 17, 25]. Most of these studies reported toxicity rates (26.3–65.9 % for grade 3/4 neutropenia and 10.5–15.9 % for febrile neutropenia) that were comparable to our results. In particular, a phase II trial of a 3-week TIROX triplet combination with a similar median follow-up of 7 cycles also revealed rates of 45.2 % for grade 3/4 neutropenia and 9.5 % for febrile neutropenia [18]. The reason for the lower rate of severe toxicities in our study, despite the older median age (59 years vs. 50–54 years), may be related to our S-1 dose schedule, as a shorter cycle with 1 week of administration and 1 week of rest might be more tolerable than regimens with 2 weeks of continuous administration, especially among older patients. Alternative strategies, such as metronomic chemotherapy regimens, may also be considered to reduce the serious effects of cytotoxic chemotherapy at the MTD on the host's immune system [26]. In the present study, the daily oral administration of S-1 provided the advantage of short drug-free interruptions. Given the toxicity of biweekly, intravenous bolus administration of oxaliplatin and irinotecan, further investigation for other intravenous chemotherapy schedules is warranted.

In the present study, the drugs' RDIs exhibited gradually decreasing trends with a greater number of cycles, and the mean RDI decreased sharply after the administration of the ninth dose (out of a maximum of 12 cycles). The main reasons for the lower RDI in our study were dose delays in 33.7 % of the patients and dose reductions in 27.5 % of the patients; most of these events were due to neutropenia or febrile neutropenia. Therefore, careful monitoring and proper management are necessary for subsequent phase II trials, especially in the later treatment period. Previous phase I/II trials of capecitabine as a substitute for 5-FU (XELOXIRI) in patients with CRC have also revealed similar RDIs (76.0–81.0 % for oxaliplatin, 81.0–85.0 % for irinotecan, and 69.0–84.0 % for capecitabine) [12, 14]. However, common adverse events in the studies with the XELOXIRI regimen were not limited to hematological toxicities and also included grade 3/4 non-hematological toxicities, such as diarrhea (11.0–40.0 %), peripheral

neuropathy (2.0–20.0 %), and low-grade capecitabine-induced hand-foot syndromes (13.3–25.0 %) [12–15]. Thus, the subjective symptoms of the XELOXIRI regimen tend to be somewhat more obvious than those of our OIS regimen.

The confirmed ORR among all patients in the present study was 47.6 % (95 % CI, 28.3–67.6 %). Although ORR was not the primary endpoint, and we only examined a small number of patients, this result is acceptable, as the treatment of advanced GI cancer remains challenging.

As has been noted for many years, 5-FU is a mainstay of treatment and is usually combined with newer cytotoxic drugs, such as oxaliplatin and irinotecan. Furthermore, molecular targeted agents have become a focus of treatment for advanced GI cancer, along with considerable advances in the field of palliative chemotherapy. However, the effective use of targeted agents has been limited to patients with GI cancer and specific predictive biomarkers [27, 28]. Thus, conventional cytotoxic drugs remain the mainstay of frontline treatment, and highly active triplet cytotoxic chemotherapy combinations may be a viable treatment option. Because these triplet chemotherapies provide promising antitumor activity in patients with CRC or GC, there have been increasing efforts to identify the optimal regimen to safely, easily, and effectively administer these chemotherapies. Several trials have demonstrated that the triplet combination of oxaliplatin, irinotecan, and 5-FU/leucovorin (FOLFOXIRI) provides an ORR of 31.6–66.7 %, a median PFS of 6.4–12.1 months, and a median OS of 11.1–22.6 months in patients with various advanced GI cancers [4–7, 21–23]. However, FOLFOXIRI also has considerable toxicities and is not well tolerated by patients.

S-1 is an oral anticancer drug that consists of tegafur (as a 5-FU prodrug), 5-chloro-2,4-dihydroxypyridine, and potassium oxonate, which inhibits the orotate phosphoribosyl transferase enzyme in intestinal tissues and decreases the occurrence of diarrhea [29, 30]. Furthermore, the efficacy of S-1 is non-inferior to that of infused 5-FU or capecitabine [11, 31]. Therefore, OIS could be considered as a substitute for FOLFOXIRI or XELOXIRI, as it alleviates GI toxicities and hand-foot syndromes and eliminates the need for prolonged intravenous infusions and frequent hospitalizations.

Another interesting finding of the present study is that the ORR was 44.4 % in cases of BTC, which is more favorable than the ORR in previous reports. In this context, a meta-analysis of BTC (104 phase II and III trials that included 2,810 patients with BTC) revealed that gemcitabine with cisplatin provided a better response rate and survival outcomes, compared to the other regimen. Therefore, gemcitabine with cisplatin is currently considered a standard first-line treatment for advanced BTC [32, 33]. However, patients with advanced BTC still experience poor survival outcomes with a median OS of <1 year [32–34]. Furthermore, combinations of S-1 and oxaliplatin have yielded modest response rates (24.5 %) and tolerable toxicity profiles, and another phase II trial of irinotecan and oxaliplatin reported an ORR of 17.9 % [35, 36]. Therefore, the triplet combination of OIS could be an effective therapeutic strategy for patients with advanced BTC.

In conclusion, among patients with advanced GI cancer, the RD of OIS triplet chemotherapy was oxaliplatin at 85 mg/m^2 and irinotecan at 180 mg/m^2 on day 1, and S-1 at 100 mg/m^2 on days 1–7, every 2 weeks. This regimen provided acceptable antitumor activity and a favorable toxicity profile. Therefore, we are currently performing a phase II study using this OIS regimen in patients with advanced GC and BTC.

Acknowledgments This work was supported by a Grant (15182MFDS512) from Ministry of Food and Drug Safety and Hallym University Research Fund, HURF-2015-38.

Compliance with ethical standards

Conflict of interest The authors have declared that no competing interest exists.

References

1. Souglakos J, Mavroudis D, Kakolyris S, Kourousis Ch, Vardakis N, Androulakiset N, Agelaki S, Kalbakis K, Tsetis D, Athanasiadis N, Smnonis G, Gerogoulias V (2002) Triplet combination with irinotecan plus oxaliplatin plus continuous-infusion fluorouracil and leucovorin as first-line treatment in metastatic colorectal cancer: a multicenter phase II trial. J Clin Oncol 20:2651–2657
2. Masi G, Allegrini G, Cupini S, Marcucci L, Cerri E, Brunetti I, Fontana E, Ricci S, Andreuccetti M, Falcone A (2004) First-line treatment of metastatic colorectal cancer with irinotecan, oxaliplatin and 5-fluorouracil/leucovorin (FOLFOXIRI): results of a phase II study with a simplified biweekly schedule. Ann Oncol 15:1766–1772
3. Conroy T, Paillot B, François E, Bugat R, Jacob JH, Stein U, Nasca S, Metges JP, Rixe O, Michel P, Magherini E, Hua A, Deplanque G (2005) Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer: a Groupe Tumeurs Digestives of the Fédération Nationale des Centres de Lutte Contre le Cancer study. J Clin Oncol 23:1228–1236
4. Falcone A, Ricci A, Brunetti I, Pfanner E, Allegrini G, Barbara C, Crino L, Bendetti G, Evangelista W, Fanchini L, Cortesi E, Picone V, Vitello S, Chiara S, Granetto C, Porcile G, Fioretto L, Orlandini C, Andreuccetti M, Masi G (2007) Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol 25:1670–1676
5. Lee J, Kang WK, Kwon JM, Oh SY, Lee HR, Kim HJ, Park BB, Lim HY, Han MJ, Park JO, Park YS (2007) Phase II trial of irinotecan plus oxaliplatin and 5-fluorouracil/leucovorin in patients with untreated metastatic gastric adenocarcinoma. Ann Oncol 18:88–92

6. Cao W, Yang W, Lou G, Jianga J, Genga M, Xi W, Li H, Ma T, Jin Y (2009) Phase II trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) as first-line treatment for advanced gastric cancer. Anticancer Drugs 20:287–293
7. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Bouragade SG, Fouchardiere C, Bennouna J, Bachet JB, Akouz FK, Verge DP, Delbaldo C, Assenat E, Chauffert B, Michel P, Grillot CM, Ducreux M (2011) FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817–1825
8. Cassidy J, Twelves C, Van Cutsem E, Hoff P, Bajetta E, Boyer M, Bugat R, Burger Y, Garin A, Graeven U, McKendrick J, Maroun J, Marshall J, Osterwalder B, Manga GP, Rosso R, Rougier P, Schilsky RL (2002) First-line oral capecitabine therapy in metastatic colorectal cancer: a favorable safety profile compared with intravenous 5-fluorouracil/leucovorin. Ann Oncol 13:566–575
9. Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, Maroun J, Salde D, Weaver C, Harrison E, Burger HU, Osterwalder B, Wong AO, Wong R (2001) Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. J Clin Oncol 19:2282–2292
10. Van Cutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M, Bugat R, Findlay M, Frings S, Jahn M, McKendrick J, Ostersalder B, Manga GP, Rosso R, Rougier P, Schmiegel WH, Seitz JF, Thompson P, Vieitez JM, Weitzel C, Harper P (2001) Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol 19:4097–4106
11. Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, Miyashita K, Nishizaki T, Kobayashi O, Takiyama W, Toh Y, Nagaie T, Takagi S, Yamamura Y, Yanaka K, Orita H, Takeuchi M (2008) S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 9:215–221
12. Bajetta E, Celio L, Ferrario E, Di Bartolomeo M, Denaro A, Dotti K, Mancin M, Bajetta R, Colombo A, Pusceddu S (2007) Capecitabine plus oxaliplatin and irinotecan regimen every other week: a phase I/II study in first-line treatment of metastatic colorectal cancer. Ann Oncol 18:1810–1816
13. Fornaro L, Masi G, Bursi S, Loupakis F, Vasile E, Antonuzzo A, Chiara S, Pfanner E, Paolo D, Bocci G, Tacca D, Falcone A (2009) A dose finding and pharmacokinetic study of capecitabine in combination with oxaliplatin and irinotecan in metastatic colorectal cancer. Cancer Chemother Pharmacol 63:965–969
14. Vasile E, Masi G, Fornaro L, Cupini S, Loupakis F, Bursi S, Petrini I, Donato S, Brunetti IM, Ricci S, Antonuzzo A, Chiara S, Amoroso D, Andreuccetti M, Falcone A (2009) A multicenter phase II study of the combination of oxaliplatin, irinotecan and capecitabine in the first-line treatment of metastatic colorectal cancer. Br J Cancer 100:1720–1724
15. Zarate R, Rodriguez J, Bandres E, Patino-Garcia A, Ponz-Sarvise M, Viudez A, Ramirez N, Bitarte N, Chopitea A, Gardia-Foncillas J (2010) Oxaliplatin, irinotecan and capecitabine as first-line therapy in metastatic colorectal cancer (mCRC): a dose-finding study and pharmacogenomic analysis. Br J Cancer 102:987–994
16. Park SR, Kong SY, Rhee J, Park YI, Ryu KW, Lee JH, Kim YW, Choi IJ, Kim CG, Lee JY, Cho SJ, Kim NK (2011) Phase II study of a triplet regimen of S-1 combined with irinotecan and oxaliplatin in patients with metastatic gastric cancer: clinical and pharmacogenetic results. Ann Oncol 22:890–896
17. Kim SY, Hong YS, Kim BC, Park JW, Choi HS, Jeong SY, Kim DY, Hong CW, Sohn DK, Jung KH (2009) A phase II study of S-1 plus irinotecan and oxaliplatin in heavily-treated patients with metastatic colorectal cancer. Investig New Drugs 27:269–274
18. Kim SY, Hong YS, Shim EK, Kong SY, Shin A, Baek JY, Jung KH (2013) S-1 plus irinotecan and oxaliplatin for the first-line treatment of patients with metastatic colorectal cancer: a prospective phase II study and pharmacogenetic analysis. Br J Cancer 109:1420–1427
19. Eisenhauer EA, Therasse P, Bogaerts J, Schwartzd LH, Sargente D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar K, Dodd L, Kaplan R, Lacombe D, Verweij J (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228–247
20. Hryniuk WM (1987) Average relative dose intensity and the impact on design of clinical trials. Semin Oncol 14:65–74
21. Tourneau CLT, Lee JJ, Siu LL (2009) Dose escalation methods in phase I cancer clinical trials. J Natl Cancer Inst 101:708–772
22. Comella P, Lorusso V, Maiorino L, Casaretti R, Cannone M, Massidda B, Putzu C, Leo S, Roselli M, Mancarella S, Palmeri S, Greco E, Vessia G, Sandomenico C, Franco L (2009) Oxaliplatin, irinotecan, and fluorouracil/folinic acid in advanced gastric cancer: a multicenter phase II trial of the Southern Italy Cooperative Oncology Group. Cancer Chemother Pharmacol 64:893–899
23. Souglakos J, Androulakis N, Syrigos K, Polyzos A, Ziras N, Athanasiadis A, Kakolyris S, Tsousis S, Kouroussis Ch, Vamvakas L, Kalykaki A, Samonis G, Mavroudis D, Georgoulias V (2006) FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) versus FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG). Br J Cancer 94:798–805
24. Loupakis F, Cremolini C, Masi G, Lonardi S, Zagonel V, Salvatore L, Cortesi E, Tomasello G, Ronzoni M, Spadi R, Zaniboni A, Tonini G, Buonadonna A, Amoroso D, ChiaraS Carlomagno C, Boni C, Allegrini G, Boni L, Falcone A (2014) Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. N Engl J Med 371:1609–1618
25. Park SR, Hong YS, Lim HS, Seong MW, Kong SY, Kim SY, Park YI, Jung KH (2013) Phase I clinical and pharmacokinetic/pharmacogenetic study of a triplet regimen of S-1/irinotecan/oxaliplatin in patients with metastatic colorectal or gastric cancer. Cancer Chemother Pharmacol 72:953–964
26. Lien K, Georgsdottir S, Sivananthan L, Chan K, Emmenegger U (2013) Low-dose metronomic chemotherapy: a systematic literature analysis. Eur J Cancer 49:3387–3395
27. Van Cutsem E, Bang YJ, Feng-yi F, Xu JM, Lee KW, Jiao SC, Chong JL, Lopez-Sanchez RI, Price T, Gladkov O, Stoss O, Hill J, Ng V, Lehle M, Thomas M, Kiermaier A, Ruschoff J (2015) HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. Gastric Cancer 18:476–484
28. Van Cutsem E, Lenz HJ, Köhne CH, Heinemann V, Tejpar S, Melezínek I, Beier F, Stroh C, Rougier P, Krieken HV, Ciardiello F (2015) Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. J Clin Oncol 33:692–700
29. Shirasaka T, Shimamato Y, Ohshimo H, Yamaguchi M, Kato T, Yonekura K, Fukushima M (1996) Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. Anticancer Drugs 7:548–557
30. Peters GJ, Noordhuis P, Van Kuilenburg ABP, Schornagel JH, Gall H, Turner SL, Swart MS, Soorn D, Van Gennip AH, Wanders J, Holwerda U, Smid K, Giaccone G, Fumoleau P, Groeningen CJ (2003) Pharmacokinetics of S-1, an oral formulation of ftorafur, oxonic acid and 5-chloro-2,4-dihydroxypyridine (molar

ratio 1:0.4:1) in patients with solid tumors. Cancer Chemother Pharmacol 52:1–12
31. Lee JL, Kang YK, Kang HJ, Lee KH, Zang DY, Ryoo BY, Kim JG, Park SR, Kang WK, Shin DB, Ryu MH, Chang HM, Kim TW, Baek JH, Min YJ (2008) A randomised multicentre phase II trial of capecitabine versus S-1 as first-line treatment in elderly patients with metastatic or recurrent unresectable gastric cancer. Br J Cancer 99:584–590
32. Eckel F, Schmid RM (2007) Chemotherapy in advanced biliary tract carcinoma: a pooled analysis of clinical trials. Br J Cancer 96:896–902
33. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, Madhusudan S, Iveson T, Hughes S, Pereira SP, Roughton M, Bridgewater J (2010) Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 362:1273–1281
34. Jang JS, Lim HY, Hwang IG, Song HS, Yoo N, Yoon S, Kim YH, Park E, Byun JH, Lee MA, Oh SJ, Lee KH, Kim BS, Oh SC, Kim SY, Lee SJ (2011) Gemcitabine and oxaliplatin in patients with unresectable biliary cancer including gall bladder cancer: a Korean Cancer Study Group phase II trial. Cancer Chemother Pharmacol 65:641–647
35. Kim KP, Jang G, Hong YS, Lim HS, Bae KS, Kim HS, Lee SS, Shin JG, Lee JL, Ryu MH, Chang HM, Kang YK, Kim TW (2011) Phase II study of S-1 combined with oxaliplatin as therapy for patients with metastatic biliary tract cancer: influence of the CYP2A6 polymorphism on pharmacokinetics and clinical activity. Br J Cancer 104:605–612
36. Karachaliou N, Polyzos A, Kentepozidis N, Kakolyris S, Ziras N, Vardakis N, Kalykaki A, Milaki G, Georgoulias V, Androulakis N (2010) A multicenter phase II trial with irinotecan plus oxaliplatin as first-line treatment for inoperable/metastatic cancer of the biliary tract. Oncology 78:356–360