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Original Article

Gemcitabine plus S-1 versus cetuximab as a third-line therapy in metastatic colorectal cancer: an observational trial

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Abstract: Background and aim: After failure of oxaliplatin, irinotecan, and 5-fluorouracil (5-FU), there is no effective and low-cost therapy for metastatic colorectal cancer (mCRC). The purpose of this study was to assess the efficacy and safety of gemcitabine plus S-1 (GS) versus cetuximab as a third-line chemotherapy for mCRC patients. Methods: Patients with previous failure of oxaliplatin, 5-FU, and irinotecan chemotherapy were included. The patients received GS or cetuximab until disease progression or intolerable toxicity occurred. The regimen that was selected by the patient depended on their economic ability. Results: In all, 38 patients were enrolled between October 2009 and October 2012, and the patients were divided into 2 groups of 19 patients each. The median overall survival (OS) was 10 months for the GS group and 6.9 months for the cetuximab group (P = 0.047). The median progression-free survival (PFS) was 79 days and 78 days (P = 0.344), respectively. The disease control rate (DCR) was 42.11% and 47.37%, respectively (P = 0.985). The overall response rate was 0% and 10.52%, respectively (P = 0.169). Adverse events related to chemotherapy were mild to moderate. Only grade 3-4 neutropenia was found in the GS group at a rate of 21.1%. In the cetuximab group, the rash incidence rate was 89.6%, with 1 patient reaching grade 3. Conclusions: GS has benefits in OS compared with cetuximab, and is a promising and safe regimen as a third-line chemotherapy for oxaliplatin- and irinotecan-refractory mCRC with good performance status for mCRC patients.

Keywords: Metastatic colorectal cancer, gemcitabine, S-1, cetuximab, third-line

Introduction

Colorectal cancer (CRC) is the leading cause of cancer-related death in Western countries [1], and the morbidity and mortality of CRC has increased rapidly over the past few decades in China as lifestyles have changed. Data [2] obtained in 2008 from 56 cancer registries in China showed that the incidence and mortality rates of CRC ranked third and fifth among cancers of men and women, respectively.

Palliative chemotherapy is the main treatment for metastatic CRC (mCRC). The combination of 5-fluorouracil (5-FU) with irinotecan or oxaliplatin is considered the standard chemotherapy regimen for mCRC patients [3], and may be combined with targeted drugs such as bevacizumab [4], cetuximab, [5] or panitumumab [6]. To date, however, there is no effective treatment for good performance status in patients after failure of first-line and second-line treatments. In general, it is suggested that patients take part in clinical trials or use single-targeted drugs.

Gemcitabine is a nucleoside analog of deoxycytidine that inhibits ribonucleotide reductase, an enzyme that is important for producing the deoxynucleotides for DNA synthesis and repair. S-1 is an oral pyrimidine fluoride-derived anticancer agent in which 5-fluoro-1-(tetrahydro-2-furanyl)-2,4(1H,3H)-pyrimidinedione is combined with 2 classes of modulators, 5-chloro-2,4-dihydroxypyridine and oteracil potassium, to enhance antitumor effects and decrease gastrointestinal toxicity [7]. A previous study has shown that the combination of 5-FU and

Table 1. Baseline characteristics

	GS	Cetuximab	*P*
	n (%)	n (%)	value
Sex			1.000
Male	10 (52.6)	10 (52.6)	
Female	9 (47.4)	9 (47.4)	
Median age	56	59	0.516
Range	40-71	48-72	
ECOG PS			0.632
0	9 (47.4)	12 (63.2)	
1	8 (42.1)	6 (31.6)	
2	2 (10.5)	1 (5.3)	
Site of primary tumor			0.516
Rectum	11 (57.9)	8 (42.1)	
Colon	8 (42.1)	11 (57.9)	
TNM stage			0.673
IIb	4 (21.1)	2 (10.5)	
III	7 (36.8)	8 (42.1)	
IV	8 (42.1)	9 (47.4)	
Management of primary tumor			0.311
Resected	18 (94.7)	19 (100.0)	
Not resected	1 (5.3)	0 (0.0)	
Metastatic sites			
Liver	11 (57.9)	14 (73.7)	0.494
Lung	6 (31.6)	8 (42.1)	0.737
Peritoneum	4 (21.1)	2 (10.5)	0.656
Pelvis	3 (15.8)	2 (10.5)	0.631
Uterus or ovary	2 (10.5)	0 (0.0)	0.146
Lymph node	3 (15.8)	7 (36.8)	0.141

gemcitabine may stabilize thymidylate synthase and, therefore, enhance inhibition of DNA synthesis [8]. In addition, small-scale trials have shown that S-1 is also effective in gastric [9] and breast [1] cancer patients who exhibit resistance to 5-FU or capetabine. Thus, it is possible that gemcitabine combined with S-1 would be effective as a third-line treatment for CRC.

The aim of this study was to evaluate the efficacy, safety, and cost-effectiveness of gemcitabine plus S-1 (GS) as a third-line chemotherapy in Chinese mCRC patients who experienced previous treatment failure with oxaliplatin, irinotecan, and 5-FU.

Methods

Eligibility

This trial was an open-label, non-random, and control observational trial in our department. Patients were included in the study based on the following criteria: age > 18 years; pathologic diagnosis confirming colorectal adenocarcinoma; metastatic and unresectable CRC with at least 1 measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.0); failure of oxaliplatin, 5-fluorouracil, and irinotecan regardless of use with bevacizumab; Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1; adequate organ function [leukocyte ≥ 3.5 × 10^9/L; neurocyte ≥ 1.5 × 10^9/L; hemoglobin ≥ 80 g/L; platelet ≥ 100 × 10^9/L; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN (upper limits of normal) or ≤ 5 × ULN if liver metastasis was present; total bilirubin level ≤ 1.5 × ULN; and a normal serum creatinine level].

Patients were excluded based on the following criteria: previous use of cetuximab; other malignancy (with the exception of basal cell carcinoma of the skin and *in situ* cancer of the cervix); brain metastases; surgical or other treatments within 28 days; inadequately controlled cardiovascular disease, hypertension, hepatitis, or ulcer; bleeding tendency; and previous adverse events ≥ grade 2.

Treatment

The patients selected the treatment regimen based on whether they could afford the fee. The GS regimen was administered every 3 weeks and consisted of 1000 mg/m^2 gemcitabine on days 1 and 8, and S-1 on days 1-14. The S-1 dose was calculated according to body surface area (BSA) as follows: BSA < 1.25 m^2, 80 mg/day; BSA ≥ 1.25 m^2 but < 1.5 m^2, 100 mg/day; and BSA ≥ 1.5 m^2, 120 mg/day. The patients received their assigned dose of S-1 in 2 separate oral administrations as follows: 1 after breakfast and 1 after dinner. Cetuximab was infused at a first dose of 400 mg/m^2 and then at 250 mg/m^2 every week. Antiemetic prophylaxis with a $5HT_3$-receptor antagonist was administered. The regimens were continued until disease progression, intolerant toxicity, or patient refusal.

Assessments

Efficacy assessments were conducted by computed tomography (CT) or magnetic resonance

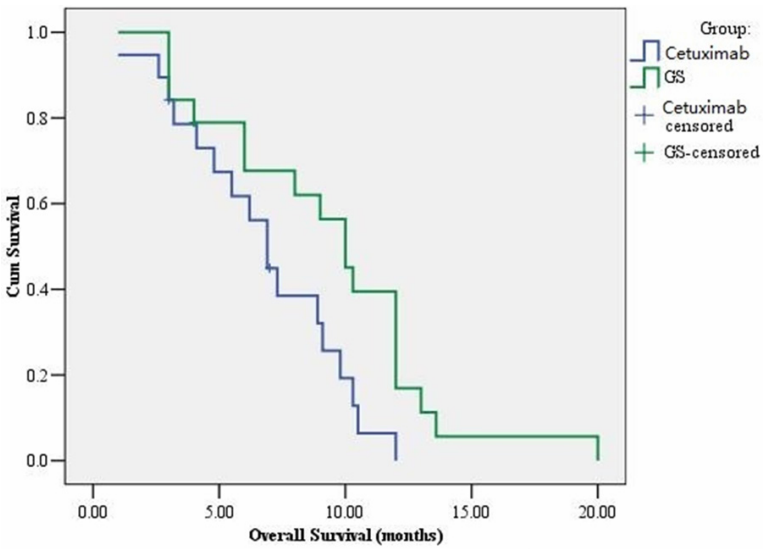

Figure 1. Overall survival in the two study groups.

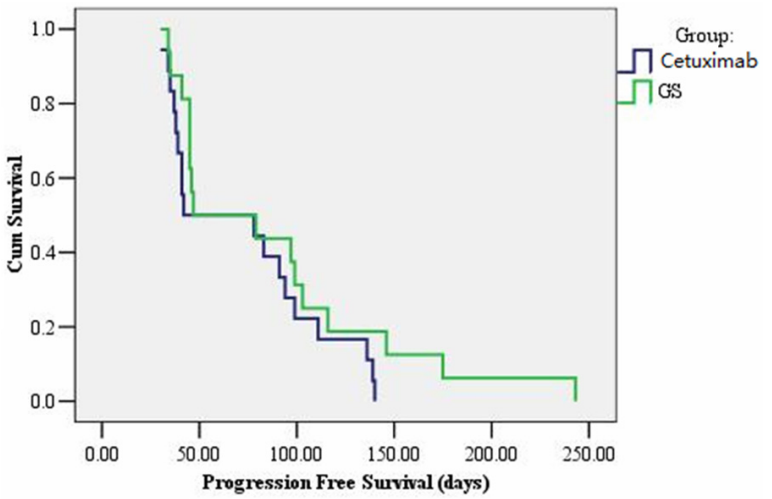

Figure 2. Progression-free survival in the two study groups.

Table 2. Response assessment

Assessment	N (%)		*P* value
	GS	Cetuximab	
CR	0 (0.00)	0 (0.00)	
PR	0 (0.00)	2 (10.52)	
SD	8 (42.11)	7 (36.84)	
PD	10 (52.63)	10 (52.63)	
NA	1 (5.26)	0 (0.00)	
RR (%)	0.00	10.52	0.169
DCR (%)	42.11	47.37	0.985

CR, complete response; PR, partial response; SD, stable disease; PD, disease progression; NA, not available; RR, response rate; DCR, disease control rate.

imaging (MRI) every 6 weeks, according to RECIST (version 1.0). Adverse events were assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTC, version 3.0).

Statistical analysis

The primary endpoint was overall survival (OS). The secondary endpoints were response rate (RR), progression-free survival (PFS), toxicity, and cost-effectiveness. The dates of the last follow-up were recorded as censored data for the survival analysis when the time of death or progression could not be confirmed or if the patient was still alive. OS and PFS were analyzed using the Kaplan-Meier method with a confidence interval (CT) of 95%. The significance of the correlation between the GS group and the cetuximab group was assessed by the chi-square test (Fisher's exact test). Statistical analysis was performed with SPSS software 17.0 (SPSS Inc., Chicago, IL).

Results

In all, 38 patients with oxaliplatin, irinotecan, and 5-FU chemotherapy failure were enrolled in this observational cohort trial between October 2009 and October 2012, and the patients were divided into 2 groups of 19 patients each. Thirty-seven patients were evaluated in the study. Of the evaluated patients, 18 patients received GS and 19 received cetuximab. The median follow-up time was 12 months (range of 1-20 months).

The basic patient characteristics of the groups were similar (**Table 1**). The groups consisted of 52.6% males, and almost all patients had a good performance status (PS 0-1). More than 80% of the patients had locally advanced or

Table 3. Adverse event assessment

Adverse event	NCI-CTC grade, N (%)				*P* value
	GS		Cetuximab		
	1/2	3/4	1/2	3/4	
Non-hematological					
Nausea	10 (52.6)	1 (5.3)	0 (0)	0 (0)	0.001
Vomiting	7 (36.9)	1 (5.3)	0 (0)	0 (0)	0.017
Diarrhea	4 (21.1)	0 (0)	0 (0)	0 (0)	0.034
Fatigue	10 (52.6)	0 (0)	1 (5.3)	0 (0)	0.005
Fever	1 (5.3)	1 (5.3)	1 (5.3)	0 (0)	0.598
Rash	5 (26.3)	0 (0)	16 (84.3)	1 (5.3)	0.001
Hematological					
Leukopenia	12 (63.1)	2 (10.5)	0 (0)	0 (0)	< 0.001
Neutropenia	10 (52.6)	4 (21.1)	0 (0)	0 (0)	< 0.001
Thrombocytopenia	6 (31.6)	0 (0)	0 (0)	0 (0)	0.028

metastatic cancer when first diagnosed. Nearly all of the patients (97.4%) had undergone a radical or palliative operation of the primary tumor. The KRAS status of the cetuximab group was all wild type, and that of the GS group was unknown.

The median OS of the GS group was 10 months, and that of the cetuximab group was 6.9 months (P = 0.047) (**Figure 1**). The median PFS was 79 days and 78 days, respectively (P = 0.344) (**Figure 2**). The disease control rate of the GS group versus the cetuximab group was 42.11% vs. 47.37%, respectively (P = 0.985) (**Table 2**). The overall response rate was 0% vs. 10.52%, respectively (P = 0.169) (**Table 2**).

The adverse events are listed in **Table 3**. For all events (either hematological or non-hematological), the incidence in the GS group was higher than in the cetuximab group, except for the incidence of rash. The overall incidence of grade 3-4 adverse events was not high. The most common events (incidence rate > 20%) in the GS group were neutropenia (73.6%), nausea (57.9%), fatigue (52.6%), vomiting (42.2%), thrombocytopenia (31.6%), rash (26.3%), and diarrhea (21.1%). Most of these adverse events were mild to moderate. In the cetuximab group, the rash incidence rate reached 89.6%, and the other adverse events were rare.

One patient in the cetuximab group died within 30 days of the last treatment. Severe adverse events occurred in 2 patients as follows: one was a myocardial infarction in the GS group, and the other was a perforation in the cetuximab group. None of these events was drug related.

Discussion

Phase III trials [11-13] have confirmed that oxaliplatin, irinotecan, and 5-FU are the most effective cytotoxic drugs for mCRC. Either a sequential [3] or a synchronous [14] scheme can provide patients with optimal clinical benefits. Tournigand [3] et al. demonstrated that FOLFIRI followed by mFOLFOX6 or the reverse sequence produced comparable efficacy in prolonging survival in advanced CRC. The introduction of targeted drugs, such as bevacizumab [4], cetuximab [5], and panitumumab [6], will increase the efficacy of chemotherapy alone and thus prolong OS.

After the failure of an irinotecan-based regimen, cetuximab plus irinotecan presented a better outcome compared with cetuximab alone [15]. It is worth noting that the clinical trial mentioned above focused on a second-line setting, and the median OS obtained in this trial was only 8.6 months vs. 5.9 months. Since this clinical trial, small-scale trials [16-18] have explored the effectiveness of a cetuximab plus irinotecan-based regimen as a third-line regimen for patients who were oxaliplatin and irinotecan refractory. The results of these trials reported an RR of 25.4%-30.8%, a median PFS of 2.9-4.7 months, and a median OS of 8.8-10.9 months. A head-to-head trial for cetuximab or panitumumab as a third-line monotherapy is ongoing in China. Our results for the cetuximab group were comparable to those of other reported trials, and these patients all showed KRAS wild type. However, most patients with wild-type KRAS tumors do not respond. New research [19] has shown that BRAF, NRAS, and PIK3CA exon 20 mutations are significantly associated with a lower response rate. KRAS was not the only predictive biomarker [20]. We hope that the development of new biomarker screening will aid in the selection of better responding patients.

The FDA has approved regorafenib [21] as a third-line therapy in CRC even though it provides only a 1.4-month added survival benefit. The results of the phase III trial of this drug in Asia have not yet been published. As these tar-

geted drugs are not covered by medical insurance in China, the financial burden for these patients is large (beyond the economic ability of many), which has resulted in only approximately 5% of CRC patients being able to afford these drugs. For patients with a good performance status who have failed second-line chemotherapy, a more effective therapy with reduced cost is needed.

Compared with cetuximab, GS significantly prolonged median OS from 6.9 months to 10 months. The response rate and median PFS were similar between the 2 groups. Gemcitabine has also been proven effective in pancreatic cancer [22] and lung cancer [23], and preclinical data [24] have suggested that the combination of 5-FU and gemcitabine is active against CRC cells *in vitro*. The combination of these 2 drugs has also shown significant antitumor activity in advanced CRC cancer [25]. S-1 is an effective drug for mCRC, and some trials [9, 10] have confirmed that a fraction of 5-FU-refractory patients show sensitivity to S-1 with a response rate of approximately 10%. Based on our results, GS is a promising regimen as a third-line chemotherapy for mCRC patients.

In this trial, the side effects of cetuximab were mild, with an acne-like rash being the most common side effect. With regard to subgroup imbalance, an association between cutaneous toxicity and response rate was not observed. In the GS group, the most common adverse events were nausea, vomiting, fatigue, leucopenia, neutropenia, and thrombocytopenia. These events were all statistically significant when compared with those in the cetuximab group. In general, this regimen was well tolerated with all adverse events under control.

We also evaluated the cost-effectiveness of these 2 regimens. For example, we assumed that for a patient with a BSA of 1.5 m^2, a minimal cost analysis showed that the GS regimen had a cost of RMB 27684 for each RECIST evaluation period and that the cetuximab regimen had a cost of RMB 112752 for each RECIST evaluation period. An incremental analysis showed that the GS regimen could prolong OS by 1 month, with a cost of RMB 27441 less in each evaluation period compared with the cost of cetuximab. However, the incidence of adverse events with the GS regimen was higher than that with cetuximab, including hematological and gastrointestinal events. Adverse event lab exam fees and adjuvant drugs would result in additional costs. Overall, the cost-effectiveness of the GS regimen is higher than that of cetuximab monotherapy.

In conclusion, the encouraging results of our study could represent a basis for future trials. We provide a new option for oxaliplatin- and irinotecan-refractory mCRC with good performance status for mCRC patients.

Disclosure of conflict of interest

None.

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