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Clinical Trial Results

S-1 plus Raltitrexed for Refractory Metastatic Colorectal Cancer: A Phase II Trial

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Trial Information

- **ClinicalTrials.gov Identifier:** ChiCTR-OPC-15006819
- **Sponsor(s):** Ji-Yan Liu
- **Principal Investigator:** Ji-Yan Liu
- **IRB Approved:** Yes

Lessons Learned

- The upregulation of dihydropyrimidine dehydrogenase (DPD) and thymidylate synthase (TS) are important mechanisms of resistance to 5-fluorouracil (5-FU) in metastatic colorectal cancer (mCRC) after long exposure to 5-FU.
- S-1 (containing a DPD inhibitor) combined with raltitrexed (a TS inhibitor) showed a moderate effect, which needs further study as a third- or later-line therapy in mCRC.

Abstract

Background. 5-fluorouracil (5-FU) is a fundamental drug in the treatment of metastatic colorectal cancer (mCRC). Patients with mCRC are often exposed to 5-FU and/or its analogues for a long time because of its central role in treatment regimens. The upregulation of dihydropyrimidine dehydrogenase (DPD) and/or thymidylate synthase (TS) are important mechanisms of resistance of 5-FU. To evaluate the efficacy and safety of S-1 (containing a DPD inhibitor) and raltitrexed (a TS inhibitor) for refractory mCRC, a one-center, single-arm, prospective phase II trial was conducted.

Methods. Patients who had mCRC that had progressed after treatment with fluoropyrimidine, irinotecan, and oxaliplatin and who had at least one measurable lesion were eligible for this trial. Patients received oral S-1 (80–120 mg for 14 days every 3 weeks) plus an intravenous infusion of raltitrexed (3 mg/m^2 on day 1 every 3 weeks). The primary endpoint was objective response rate (ORR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), and toxicity.

Results. In total, 46 patients were enrolled. Three patients did not complete the first assessment because of adverse events and unwillingness, leaving tumor response evaluation available in 43 patients. Of 43 evaluable patients, the ORR was 13.9% and disease control rate was 58.1%. In the intention-to-treat population (n = 46), the ORR was 13.0% and disease control rate was 54.3%. Median PFS and median OS were 107 days (95% confidence interval [CI], 96.3–117.7) and 373 days (95% CI, 226.2–519.8), respectively. Most of the adverse effects were mild to moderate.

Conclusion. S-1 combined with raltitrexed for refractory mCRC showed moderate effect, and it is worthy of further study as third- or later-line therapy in mCRC. ***The Oncologist*** 2019;24:591–e165

Discussion

The incidence and mortality of colorectal cancer has increased rapidly over the past few decades in China. Chemotherapy, combined with surgery, radiotherapy, and other treatment, is the key therapeutic strategy for mCRC. The addition of irinotecan or oxaliplatin to 5-FU and folinic acid, in combination with either a vascular endothelial growth factor inhibitor or an epidermal growth factor inhibitor, is considered the standard therapy for mCRC patients. After failure of the first and second lines of treatment, there are still a large number of patients with good performance status who could tolerate further treatment. However, effective drugs and regimens are lacking. Although regorafenib and TAS-102 were recently approved by

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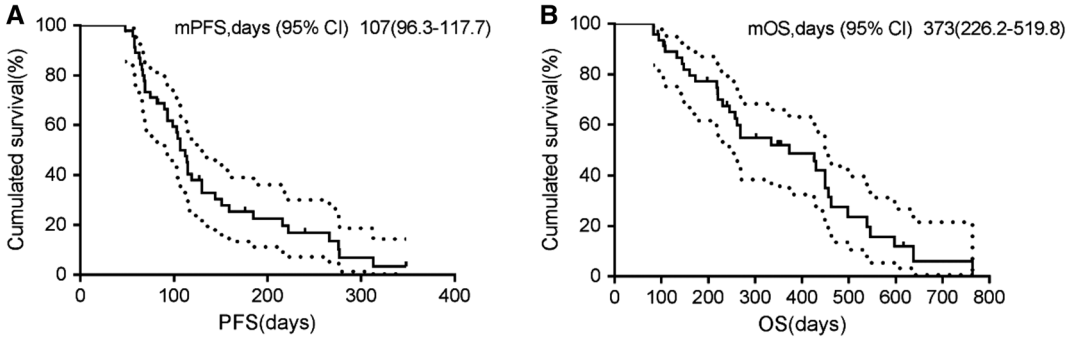


Figure 1. Survival graphs. **(A):** Progression-free survival. **(B):** Overall survival.
Abbreviations: CI, confidence interval; mOS, median overall survival; mPFS, median progression-free survival.

the U.S. Food and Drug Administration for refractory mCRC, treatment efficacy is limited.

5-FU and its analogues are the basic chemotherapy drugs for the treatment of colorectal cancer. Patients with mCRC were often exposed to 5-FU and/or its analogues for a long time. DPD is the rate limiting enzyme of 5-FU catabolic pathway. TS plays a key role in DNA synthase, which is the target of 5-FU in its antitumor mechanism. Our previous research and other studies have shown that both enzymes are often upregulated after the use of 5-FU in colorectal cancer and could mediate 5-FU resistance [1, 2].

Several studies have demonstrated the activity of S-1 in mCRC, including those resistant to 5-FU. In previous small sample trials, the ORR of S-1 monotherapy or S-1 combined with gemcitabine (GS) in the treatment of patients with mCRC after failure of both irinotecan- and oxaliplatin-containing regimens was 0%–14.3% [3, 4]. Raltitrexed is a specific inhibitor of TS, which has a fundamental role in the de novo synthesis of the nucleotide thymidine triphosphate. This agent is an alternative to 5-FU/leucovorin for the treatment of advanced colorectal cancer. The combination of S-1 and raltitrexed may play a synergistic inhibitory effect on TS, especially in the condition of DPD and TS upregulation after long-term exposure of 5-FU, which could reverse resistance to 5-FU [5]. There was no prior report about the effect of S-1 in combination with raltitrexed in mCRC.

Our study demonstrates the efficacy and safety of S-1 plus raltitrexed in refractory mCRC. Compared with the low ORR (1%–2.2%) of regorafenib and TAS-102 and the ORR (0%–14.3%) of S-1 monotherapy or GS, our study showed a relatively higher ORR of 13% (6/46), numerically superior to most prior studies, and side effects were tolerable, which indicates that this combination might be another option for refractory mCRC after the failure of 5-FU, irinotecan, and oxaliplatin.

Trial Information	
Disease	Colorectal cancer
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	More than two prior regimens
Type of Study - 1	Phase II
Type of Study - 2	Single arm
Primary Endpoint	Overall response rate
Secondary Endpoint	Progression-free survival
Secondary Endpoint	Overall survival
Secondary Endpoint	Safety

Additional Details of Endpoints or Study Design

Patient Eligibility: This study was a single-center, single-arm, prospective phase II trial, initiated by the investigator, carried out in the Cancer Center, West China Hospital, Sichuan University, China, which was approved by the ethics committee and registered in clinical trials. Patients were included in this study based on the following criteria: pathologic diagnosis confirming metastatic and unresectable colorectal adenocarcinoma with at least one measurable lesion according to RECIST version 1.1 criteria; age more than 18 years; expected survival more than 12 weeks; failure of 5-fluorouracil (or capecitabine), oxaliplatin, and irinotecan, with or without targeted therapies, such as cetuximab or bevacizumab and so on; Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; adequate bone-marrow, liver, and renal function.

Treatment Plan: Patients received raltitrexed 3 mg/m^2 intravenous infusion on day 1 plus S-1 on days 1–14 every 3 weeks. 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. Treatment was continued until documented disease progression (PD), unacceptable toxicity, or unwillingness to continue the treatment.

Assessment: Patients were evaluated by physical examination, vital signs, and clinical laboratory tests, including full hematology and chemistry panels every 3 weeks while receiving treatment. Radiologic assessments of tumors were

performed every 6 weeks by investigators according to RECIST version 1.1. Adverse events were assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Survival follow-up was carried out every 12 weeks from the time patients stopped treatment until their death or the trial cutoff date for data collection.

Endpoints and Statistical Analysis: The primary endpoint was objective response rate ORR. The sample size was based on Simon's two-stage designs with p0 = 5%, p1 = 20%, α = .05, and β = .10. In the first stage, 21 patients would be registered. At the end of the first stage, the observation of one objective response or more would have led to the total inclusion of more than 41 patients. Secondary endpoints included PFS, OS, and toxicity. 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 CI of 95%. Statistical analysis was performed with SPSS software 25.0 (IBM Corporation, Armonk, NY).

Investigator's Analysis	Active and should be pursued further

Drug Information

Drug 1	
Generic/Working Name	S-1
Trade Name	Tegafur, gimeracil, and oteracil potassium capsules
Company Name	Shandong New Time Pharmaceutical Co., Ltd.
Drug Type	Small molecule
Drug Class	Antimetabolite
Dose	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, milligrams (mg) per flat dose
Route	Oral (p.o.)
Schedule of Administration	Patients received S-1 on days 1–14 every 3 weeks
Drug 2	
Generic/Working Name	Raltitrexed
Trade Name	Raltitrexed
Company Name	Nanjing CHIA TAI Tianqing Pharmaceutical Co. Ltd.
Drug Type	Other
Drug Class	Antimetabolite
Dose	3 milligrams (mg) per squared meter (m^2)
Route	IV
Schedule of Administration	Patients received raltitrexed 3 mg/m^2 on day 1 every 3 weeks

Patient Characteristics

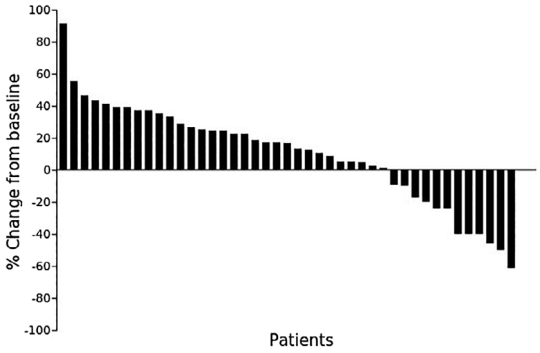
Number of Patients, Male	22
Number of Patients, Female	24
Stage	Eligibility required pathologic diagnosis confirming metastatic and unresectable colorectal adenocarcinoma
Age	Median (range): 57 (29–78) years
Number of Prior Systemic Therapies	Median (range): 2 (2–3)
Performance Status: ECOG	0 — 18 1 — 25 2 — 3 3 — 0 Unknown — 0

Other

Primary site of disease: right side, 8; left side, 38. Differentiation of tumors: poor, 11; moderate, 29; well, 0; unknown, 6. The number of metastatic organs: single, 19; multiple, 27. Prior targeted therapy: cetuximab, 13; bevacizumab, 8; KH903 (VEGF receptor-antibody fusion protein), 2.

Cancer Types or Histologic Subtypes	Colorectal adenocarcinoma, 46

Primary Assessment Method	
Title	Total Patient Population
Number of Patients Screened	46
Number of Patients Enrolled	46
Number of Patients Evaluable for Toxicity	46
Number of Patients Evaluated for Efficacy	43
Evaluation Method	RECIST version 1.1
Response Assessment CR	*n* = 0 (0%)
Response Assessment PR	*n* = 6 (13.0%)
Response Assessment SD	*n* = 19 (41.3%)
Response Assessment PD	*n* = 18 (39.1%)
Response Assessment OTHER	*n* = 3 (6.5%)
(Median) Duration Assessments PFS	107 days; CI, 96.3–117.7
(Median) Duration Assessments OS	373 days; CI, 226.2–519.8



Waterfall plot of evaluable patients (*n* = 43) showing the largest decrease in the sum of the target lesions compared with baseline.

Adverse Events

All Cycles

Name	NC/NA, %	Grade 1, %	Grade 2, %	Grade 3, %	Grade 4, %	Grade 5, %	All grades
Hypoalbuminemia	69	20	11	0	0	0	31
Diarrhea	81	11	4	4	0	0	19
ALT, SGPT	59	30	9	2	0	0	41
AST, SGOT	63	26	11	0	0	0	37
Weight loss	85	15	0	0	0	0	15
Pruritus/itching	91	9	0	0	0	0	9
Platelets	75	11	7	7	0	0	25
Fatigue	87	13	0	0	0	0	13
Leukocytes (total WBC)	61	20	15	4	0	0	39
Anorexia	67	33	0	0	0	0	33
Vomiting	85	11	4	0	0	0	15
Mucositis/stomatitis (functional/symptomatic)	74	17	7	2	0	0	26
Hemoglobin	55	30	11	4	0	0	45
Nausea	56	33	11	0	0	0	44
Neutrophils/granulocytes (ANC/AGC)	69	15	7	9	0	0	31
Bilirubin (hyperbilirubinemia)	89	9	2	0	0	0	11
Hyperpigmentation	57	17	26	0	0	0	43

Abbreviations: AGC, absolute granulocyte count; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate transaminase; NC/NA, no change from baseline/no adverse event; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; WBC, white blood cell.

Assessment, Analysis, and Discussion	
Completion	Study completed
Investigator's Assessment	Active and should be pursued further

Although the combination of chemotherapy (5-fluorouracil [5-FU]/oxaliplatin/ irinotecan) and targeted therapy (a vascular endothelial growth factor inhibitor or an epidermal growth factor inhibitor) have proven efficacy in metastatic colorectal cancer (mCRC), little improvement has been achieved in the outcomes of refractory mCRC [6, 7]. Some patients might be able to tolerate further treatment after failure of the first- and second-line treatment. However, there is a lack of effective drugs and regimens. Although regorafenib and TAS-102 were newly approved by the U.S. Food and Drug Administration for refractory mCRC, they only improve median progression-free survival by 0.2–0.3 months and median overall survival by 1.4–1.8 months, respectively [8, 9]. Furthermore, the expensive price is often unaffordable in developing countries. So there is an urgent need to find more drugs and regimens with practical application value.

As we know, patients with mCRC are often exposed to 5-FU and/or its analogues for a long time. The upregulation of dihydropyrimidine dehydrogenase (DPD) and thymidylate synthase (TS) has been found to be an important mechanism of 5-FU resistance, especially in secondary resistance, and the inhibition of these enzymes may reverse resistance [1, 2, 10, 11]. S-1 contains an inhibitor of DPD, whose activity in mCRC patients has been demonstrated in several studies. Furthermore, a few small-scale trials have explored the effectiveness of S-1 as a third-line regimen for patients who were 5-FU, oxaliplatin, and irinotecan refractory [3, 4, 12, 13]. Raltitrexed is a specific inhibitor of TS, and some clinical studies have shown that the combination of 5-FU and raltitrexed may improve the therapeutic activity in advanced colorectal cancer with mild to moderate adverse events [14–17]. However, the combination of S-1 and raltitrexed has not been reported for refractory mCRC.

The results of our single-arm phase II trial showed the effectiveness and safety of S-1 plus raltitrexed for refractory mCRC. Three patients (6.5%) treated with fewer than two cycles were not eligible for tumor response assessments. Among them, one was because of adverse events, and the other two were unwilling to proceed with the treatment. Tumor response evaluation was available in 43 patients at the time of the analysis, no patient achieved complete response, six patients (13.9%) achieved partial response, 19 patients (44.2%) achieved stable disease, and 18 patients (41.9%) showed disease progression. The objective response rate (ORR) was 13.9%, and the disease control rate was 58.1%. In the intention-to-treat population (n = 46), the ORR was 13.0% and disease control rate was 54.3%. Among patients with stable disease, six patients (13.0%) showed minor response (MR) in lesion size compared with baseline values (Table 1). The median follow-up period was 14.3 months (range, 2.8–44.9 months). At the end of the observation period, three patients were still undergoing chemotherapy, six patients were lost to follow-up for survival visit, and seven patients were still alive, who were all censored on the Kaplan-Meier curve. The median progression-free survival (PFS) and overall survival (OS) were 107 days (95% confidence interval [CI], 96.3–117.7) and 373 days (95% CI, 226.2–519.8), respectively, shown in Figure 1. Nine of 46 (19.6%) patients had PFS of more than 6 months. Sixteen of 46 (34.8%) patients had overall survival of more than 1 year.

Compared with the low ORR (1%–2.2%) and small survival benefit of regorafenib and TAS-102, our study showed a relatively higher objective response rate of 13.0%, a longer median PFS of 3.6 months, and a median OS of 12.4 months. Nineteen of 46 (41.3%) patients achieved stable disease; of those, six patients showed MR in lesion size compared with the baseline value.

As previous studies reported, the most frequent adverse events of S-1 were diarrhea, nausea, leucopenia, neutropenia, thrombocytopenia, and hyperpigmentation [3]. Compared with 5-FU, raltitrexed has a lower incidence of mucositis, diarrhea, and leukopenia and greater incidence of anemia, thrombocytopenia, and transaminase increase [17]. In this study, the toxicity of S-1 plus raltitrexed for refractory mCRC was considered to be acceptable, not superimposed. The most common adverse events of any grade in our research were anemia (45%), hyperpigmentation (43%), nausea (44%), increase in alanine aminotransferase level (41%), and leukopenia (39%). The incidence of grade 3–4 toxicity was not high. The most common grade 3–4 hematological toxicities were neutropenia (9%) and thrombocytopenia (7%). There was no grade 4 hematological toxicity. Compared with 38% of patients treated with TAS-102 for whom grade 3–4 neutropenia occurred, the 9% in our study was relatively lower. The most common grade 3–4 nonhematological toxicity was diarrhea (4%), which seems higher than TAS-102 (<1%) [9]. However, only one patient in our study stopped the treatment because of grade 3 diarrhea. In general, the toxicities of S-1 plus raltitrexed were mild to moderate, which is a tolerable combination.

This is a small-sample-size, single-arm, single-center, prospective analysis. Five patients ceased chemotherapy for reasons other than disease progression and so were censored on the PFS Kaplan-Meier analysis, which makes us less confident in the PFS result.

In conclusion, our trial is the first research about the efficacy and safety of S-1 plus raltitrexed in refractory mCRC. It is active and tolerable, an economic and convenient combination. S-1 plus raltitrexed might be an option for mCRC after failure of fluoropyrimidine, irinotecan, and oxaliplatin, which is worthy of further study as third- or later-line therapy in mCRC.

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Disclosures

The authors indicated no financial relationships.

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Tables

Table 1. Objective response rate of intention-to-treat population (*n* = 46)

Best response	*n* (%)
CR	0 (0)
PR	6 (13.0)
SD	19 (41.3)
MR	6 (13.0)
NC	13 (28.3)
PD	18 (39.1)
Unevaluable	3 (6.5)
ORR	6 (13.0)
DCR	25 (54.3)

Abbreviations: CR, complete response; DCR, disease control rate; MR, minor response; NC, no change; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Table 2. Baseline characteristics of the intention-to-treat population (*n* = 46)

Characteristic	*n* (%)
Age, median (range), yr	57 (29–78)
Sex	
Male	22 (47.8)
Female	24 (52.2)
ECOG performance status	
0–1	43 (93.5)
2	3 (6.5)
Primary site of disease	
Right side	8 (17.4)
Left side	38 (82.6)
Differentiation of tumors	
Poor	11 (24.0)
Moderate	29 (63.0)
Well	0 (0)
Unknown	6 (13.0)
Number of metastatic organs	
Single	19 (41.3)
Multiple	27 (58.7)
Time from diagnosis of metastases	
≤12 months	18 (39.1)
>12 months	28 (60.9)
Number of prior regimens	
2	44 (95.7)
≤3	2 (4.3)
Prior targeted therapy	
Cetuximab	13 (28.2)
Bevacizumab	8 (17.4)
KH903 (VEGF receptor-antibody fusion protein)	2 (4.3)
Chemotherapy cycles, median (range)	3 (1–13)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; VEGF, vascular endothelial growth factor.