Phase I dose-escalating study of S-1 in combination with oxaliplatin for patients with advanced and/or metastatic colorectal cancer

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The purpose of this study was to determine the optimal dose of oxaliplatin, when combined with a fixed dose of S-1 (40 mg/m^2 twice daily on days 1–14) on a 3-week schedule, for patients with advanced and/or metastatic colorectal cancer. Patients were required to have a histologically proven advanced or metastatic colorectal cancer for which they had received no previous chemotherapy. Oxaliplatin was administered intravenously on day 1 every 3 weeks. Patients were divided into two groups to receive two doses of oxaliplatin – 100 mg/m^2 or 130 mg/m^2. Ten patients were enrolled in the study between March 2006 and July 2006, and were followed up until 50% of the patients progressed. All patients were evaluated for chemotherapy-related toxicity. The maximum tolerated dose was not reached during the first course. One of six patients experienced grade 3 thrombocytopenia at dose level 2 of oxaliplatin. Nonhematological toxicity was mild and tolerable. During the full course of treatment, complete response was achieved in two of the nine evaluated patients and partial response was achieved in one patient. The remaining six patients achieved stable disease during first two courses of therapy, and four patients remained stable at the time of the last follow-up. The median time to progression-free survival was 8.3 months. When combined with a fixed dose of S-1 80 mg/m^2, oxaliplatin administered at a dose of 130 mg/m^2 is tolerable and recommended for phase II study.

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Introduction

Colorectal cancer (CRC) is one of the most common cancers of the digestive tract, and the global incidence has increased in recent years, including in China [1]. The mortality rate for colon cancer increased from 2.55/100 000 in 1981 to 3.02/100 000 in 2000 [2]. The primary treatment method for metastatic CRC (mCRC) for many years has been 5-fluorouracil (5-FU) with leucovorin (LV) [3]. In the past 10 years, the widespread use of newer chemotherapeutic drugs and monoclonal antibodies such as oxaliplatin, irinotecan, and bevacizumab/cetuximab has resulted in increased overall response rates and a longer time to progression, but 5-FU/LV remains the basis of almost all treatment regimens [4,5].

S-1 is an oral pyrimidine fluoride-derived drug with low toxicity and high efficacy. S-1 is being developed to enhance the clinical advantages of an oral fluoropyrimidine and ameliorate gastrointestinal toxicity [6–8]. S-1 has a broad spectrum of antitumor activity against various solid tumors such as gastric [9], colorectal [10], and lung cancers [11]. During preclinical testing in the human colorectal adenocarcinoma xenograft mice model, Nukatsuka reported that the S-1 plus oxaliplatin therapy had a superior antitumor effect to the XELOX regimen (capecitabine plus oxaliplatin), with comparable toxicity [12]. Based on these results, the combination of oxaliplatin with S-1 was expected to become the optimal treatment for CRC, but has not yet been assessed. Therefore, a phase I study was conducted to determine the feasible dose of oxaliplatin when combined with a fixed dose of S-1 (80 mg/m^2/day on days 1–14) on a 3-week schedule for patients with mCRC and to determine the relationship between dose and toxicity for S-1 and oxaliplatin combination chemotherapy. The secondary objective was to evaluate the antitumor activity of this regimen on mCRC.

Methods

Study design

This was an open-label, dose-finding study, designed to establish the optimal dose of oxaliplatin in combination with a fixed dose of S-1 (40 mg/m^2 twice daily) for patients with advanced and/or mCRC. The study was

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designed to have a minimum of three patients and a maximum of six patients evaluated at each oxaliplatin dose level. The dose of oxaliplatin was scheduled to be increased by approximately 30% for each cohort of patients at each dose level, starting at 100 mg/m^2 (level 1) and increasing to 130 mg/m^2 (level 2). In the case of dose-limiting toxicity (DLT) occurring at dose level 1, an additional dose level of 85 mg/m^2 would be introduced. Intrapatient dose escalation was not permitted.

DLT was defined, based on the common terminology criteria for adverse events, as one of the following: any study medication-related grade 3 or greater nonhematological toxicity, any study medication-related grade 4 hematological toxicity or grade 3 febrile neutropenia, or any study medication-related grade 3 or greater neuropathy. Exceptions included nausea and/or vomiting that was not treated with optimal antiemetic prophylactic or therapeutic treatment, and hyperbilirubinemia without an increase in aspartate aminotransferase or alanine aminotransferase, or clinical liver function failure.

Eligibility criteria

Patients eligible for this study were required to be aged 18 years or older and younger than 75 years, able to take medications orally, and have histologically proven CRC with measurable lesions, and no other cancers. Patients must have had no prior chemotherapy or radiotherapy, except for adjuvant chemotherapy (including 5-FU-containing and/or oxaliplatin-containing regimens) completed at least 6 months before selection. Patients were required to have a performance status ≤ 2 according to the Eastern Cooperative Oncology Group scale, with a life expectancy of ≥ 3 months, and be sufficiently fit to receive chemotherapy. Eligibility for the study also required adequate organ function as follows: hemoglobin, ≥ 90 g/l; neutrophils, $\geq 2.0 \times 10^9$/l; platelets, $\geq 100 \times 10^9$/l; and aspartate aminotransferase and alanine aminotransferase ≤ 100 U/l, serum alkaline phosphatase within twice the normal upper limit, serum bilirubin ≤ 17.1 μmol mg/l, and creatinine within the normal upper limit.

Written informed consent was obtained from all patients. The Fudan University Cancer Hospital Ethics Committee for clinical investigation approved the study.

Treatment schedule

Oxaliplatin was administered intravenously over 2 h on day 1 at 3-weekly intervals. S-1 40 mg/m^2 was administered orally twice daily for 14 days of a 3-week cycle. This cycle was repeated until disease progression or serious adverse events developed, or until a patient refused further treatment. Drug administration was suspended if a patient developed neutropenia of < 1000/mm^3, thrombocytopenia of $< 50\,000$/mm^3, or nonhematological toxicity of grade 2 or greater.

If a patient required a recovery period of more than 3 weeks from the scheduled start date of the next cycle or had grade 4 neuropathy, the patient was withdrawn from the study. If a patient was withdrawn from the study before the end of the treatment period, the patient was requested to return for a final follow-up visit.

Evaluation of response and toxicity

Physical examination, complete blood cell count, serum chemistry, and urinalysis were performed at baseline and at least once per week after initiating treatment. Patients underwent dynamic computed tomography (CT) at 8-week intervals after the start of treatment to evaluate their response to treatment. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors. Progression-free survival (PFS) was calculated from the first day of treatment until evidence of tumor progression, clinical progression, or death due to any cause.

Results

Patients' characteristics

Ten patients were enrolled in the study between March and July 2006. The first administration of S-1 40 mg/m^2 for one patient receiving the level 1 oxaliplatin dose (100 mg/m^2) was later found to be incorrect. As a result, an additional patient was enrolled in the level 1 group. As the three patients who were treated at the level 2 oxaliplatin dose (130 mg/m^2) did not experience any DLT after administration of the first cycle, an additional three patients were treated at the level 2 dose. The patients' characteristics are shown in Table 1.

Nine patients received a total of 74 cycles of chemotherapy. The median number of cycles administered per patient was 7.8 (range, 3–18). All 10 patients were evaluated for toxicity, nine of whom were evaluable for efficacy.

Toxicity

All 10 patients were evaluated for DLT during the first treatment cycle. None of the patients experienced DLT at either dose level. The toxicities experienced by the patients during the treatment period are listed in Table 2. The grade 3/4 hematological toxicity profile showed that three had thrombocytopenia (30%), one had neutropenia (10%), and one had lymphocytopenia (10%). Nonhematological toxicities were generally mild at both dose levels, and toxicity greater than grade 3 was not experienced; none of the patients experienced grade 4 toxicity at either dose level. No patient experienced toxicity necessitating discontinuation of therapy. The dose of 130 mg/m^2 was considered the highest safe dose, and the dose was not increased further.

Tumor response and survival

Complete responses were achieved for two of the nine patients (22.2%), and a partial response was achieved for

Table 1 Characteristics of patients receiving S-1 and oxaliplatin 100 mg/m^2 or 130 mg/m^2

Variable	No. of patients ($n=10$)
Sex	
Male	8
Female	2
Median age (range)	56.7 (46–74) years
ECOG PS score	
0	1
1	9
2	0
Disease stage	
Locally advanced	1
Metastatic	9
Site of metastatic disease	
Liver	3
Lung	4
Distant lymph nodes	1
Pelvis	1
Multiple metastasis	1

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Table 2 Toxicities experienced during the treatment period ($n=10$)

	Grade 1 (No.)	Grade 2 (No.)	Grade 3 (No.)	Total (No.)
Anorexia	6	0	0	6
Nausea/vomiting	4	2	0	6
Abdominal pain	1	1	0	2
Diarrhea	4	0	0	4
Constipation	3	0	0	3
Dental ulcer	1	0	0	1
Fatigue	4	0	0	4
Acroanesthesia	4	0	0	4
Fever	1	3	1	5
Neutropenia	3	3	1	7
Thrombocytopenia	2	3	3	8
Lymphocytopenia	0	2	1	3
Anemia	0	1	0	1
Hyperbilirubinemia	4	1	0	5
Elevated LDH	7	1	0	8
Hypersensitivity	0	1	0	1
Elevated BUN	2	0	0	2
Elevated ALT	1	0	0	1
Hyperglycemia	0	2	0	2
Skin rash	2	0	0	2
Peripheral neuropathy	4	0	0	4

ALT, alanine aminotransferase; BUN, blood urea nitrogen; LDH, lactate dehydrogenase.

one patient (11.1%). Therefore, the overall response rate was 33.3%. Progressive disease was noted in five patients (55.5%) at the latest follow-up visit. The median PFS was 8.3 months (95% confidence interval, 2.2–14.3 months), and the overall median survival time was not reached by the last follow-up visit.

Discussion

Remarkable advances in chemotherapy for mCRC have occurred since the 1990s. 5-FU/LV has become the standard treatment for mCRC [13]. In the past 10 years, many studies have been conducted to optimize the dose and delivery method of 5-FU/LV. These studies have led to the widespread clinical use of the Mayo Clinic, Roswell Park, AIO (Arbeitsgemeinschaft Internistische Onkologie), and de Gramont regimens [14–16]. The average response rate to 5-FU/LV for the treatment of mCRC is approximately 20% and the median survival time is approximately 12–15 months. With the addition of oxaliplatin and irinotecan to the basic 5-FU/LV regimen in the late 1990s, the response rate increased to 50% and the median survival time to approximately 20 months [17,18].

The efficacy and widespread use of 5-FU for the treatment of cancer has encouraged scientists to develop new derivatives. S-1 is a 5-FU derivative, in which tegafur was combined with two classes of modulators, gimeracil and oteracil potassium [19]. The development of S-1 is intended to prolong the concentration of 5-FU in plasma and tumor tissue over an equitoxic dose of tegafur uracil, but with less gastrointestinal toxicity [20].

In December 2003, S-1 was approved for use in Japan for the treatment of CRC. Two late phase 2 studies were conducted for chemotherapy-naive patients with advanced CRC. In the report by Shirao *et al.* [10], 173 courses of S-1 were administered to 38 patients. Fifteen patients had partial responses (response rate, 39.5%), and the 1-year survival rate was 47.4%. In the study by Ohtsu *et al.* [21], S-1 was administered orally twice daily at a standard dose of 80 mg/m^2/day for 28 days followed by 14 days of rest to 63 patients with mCRC. S-1 was continued until disease progression, unacceptable toxicity, or patient refusal. Twenty-two of the 62 eligible patients (35%) achieved a partial response with a 95% confidence interval of 25–48%. Five of the 10 patients with a history of adjuvant chemotherapy achieved a partial response. The median survival time was 12 months. Major adverse reactions included myelosuppressive and gastrointestinal toxicities, although the incidence of grade 3 or 4 toxicity was 13% for neutropenia and $< 10\%$ for other toxicities. None of the 53 patients treated as outpatients required admission to hospital owing to adverse reactions. These results suggest that S-1 achieves similar responses to those of 5-FU/LV, and shows the potential for another form of biochemical modulation with manageable toxicity.

Trials performed in the past few years show the benefit of combining oxaliplatin with 5-FU/LV or capecitabine in both a first-line and second-line setting for mCRC. It is, therefore, reasonable to investigate the possibility of combining S-1 with oxaliplatin to further improve the treatment efficacy for mCRC. The current study evaluated the safety of oxaliplatin administered with a fixed S-1 dose, and identified the optimal dose of oxaliplatin in this combination regimen for patients with mCRC.

S-1 monotherapy with a 4-week administration followed by a 2-week rest (6-week regimen) is used as the

community standard treatment for metastatic gastric cancer in some Asian countries. However, from the historical data, the incidence of adverse reactions to S-1 has been reported to be around 80%. Comparing with the 6-week regimen, in Kimura's study [22], a 3-week regimen (2 weeks on/1 week off schedule) may mitigate adverse reactions and prolong the medication period. This 3-week regimen provided a similar survival time to a 6-week regimen in a recent report [23]. In this dose-escalating study, oxaliplatin was administered at dose levels of 100 mg/m^2 or 130 mg/m^2 on day 1 of a 21-day cycle, with a fixed S-1 dose. DLT was not observed in patients at either dose level, and the maximally tolerated dose was not reached during the first cycle. The chemotherapy regimen was continued until progressive disease or intolerable toxicity was experienced. Seventy-four cycles of chemotherapy were given with a mean of 7.8. Three patients (30%) were found to have thrombocytopenia, one (10%) had neutropenia, and one (10%) had anemia. No patient experienced grade 4 hematological toxicity during the full course of the treatment. Nonhematological toxicities were generally mild at all levels, and toxicity greater than grade 3 was not experienced.

In this study, the S-1-oxaliplatin regimen was administered successfully, with good treatment compliance. It is clear that good compliance increases the likelihood of a favorable therapeutic response. The overall response rate was 33.3%, with a PFS of 8.3 months. This result is comparable with the CapeOX (capecitabine and oxaliplatin) regimen [24] and the FOLFOX (LV/5-FU/oxaliplatin) regimen [25] for patients with mCRC. Based on these results, the recommended dose of oxaliplatin for the phase II or III study to compare with the standard CapeOX regimen should be 130 mg/m^2.

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