

Long-term Results of a Phase II Study of S-1 plus Irinotecan in Metastatic Colorectal Cancer

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Abstract. *Aim: The current study aimed to assess the long-term efficacy of combination therapy with oral S-1, a fluoropyrimidine prodrug, plus irinotecan in previously untreated patients with metastatic colorectal cancer. Patients and Methods: Between April 2004 and February 2005, 41 patients with previously untreated advanced or recurrent colorectal cancer were enrolled in the study. Chemotherapy consisted of oral administration in S-1 at 40 mg/m² twice daily on days 1 to 14 and intravenous infusion of irinotecan at 150 mg/m² on day 1 in a 21-day cycle. Results: The median patient follow-up was 78.0 months. The median survival time was 23.7 months, and the 2-year survival rate was 50%. The median time to tumor progression was 8.3 months. Conclusion: The results of this long-term update confirmed that first-line combination therapy with oral S-1 plus irinotecan was effective in patients with metastatic colorectal cancer.*

The results of systemic therapy for metastatic colorectal cancer have improved significantly with the availability of cytotoxic drugs such as irinotecan and oxaliplatin, and of monoclonal antibodies against growth factors and their receptors (1).

Irinotecan has been demonstrated to offer survival benefits compared with best supportive care and 5-fluorouracil (5-FU) as second-line treatment for metastatic colorectal cancer (2, 3). Two separate phase III trials have established its superiority when used in combination with either a bolus 5-FU/leucovorin (LV) regimen (IFL) or infusional 5-FU/LV (FOLFIRI) as first-line treatment (4, 5). FOLFIRI appears to be better-tolerated than IFL and is associated with lower

rates of toxicity and treatment-related mortality. Moreover, FOLFIRI in combination with bevacizumab has been shown to significantly improve overall survival compared with modified IFL in combination with bevacizumab (6). However, an important drawback of continuous intravenous infusion is the need for implantable access devices and portable infusion pumps. Availability of oral fluoropyrimidines has improved the feasibility of prolonged fluoropyrimidine administration (7). Most patients have a preference for oral fluorouracil therapy rather than intravenous bolus fluorouracil therapy (8). S-1 (TS-1[®]; Taiho Pharmaceutical Co. Ltd., Tokyo, Japan) is an oral fluoropyrimidine that combines tegafur and two 5-FU modulators: gimeracil (5-chloro-2,4-dihydrogenase; CDHP) and potassium oxonate (oteracil), at a molar ratio of 1: 0.4: 1. Tegafur, an oral pro-drug of 5-FU, is gradually converted to 5-FU and is rapidly metabolized by dihydropyrimidine dehydrogenase (DPD) in the liver. CDHP augments the activity of 5-FU by inhibiting DPD. Oteracil inhibits pyrimidine phosphoribosyl transferase specifically in the gastrointestinal tract and thereby reduces the phosphorylation of 5-FU in the intestine. Several phase II trials of S-1 monotherapy have demonstrated response rates ranging from 19% to 39% in metastatic colorectal cancer (9-11). Furthermore, S-1 plus irinotecan has shown non-inferiority to FOLFIRI, as second-line therapy for metastatic colorectal cancer (12). S-1 plus irinotecan is an additional treatment option, and has been tested for use with bevacizumab for previously untreated metastatic colorectal cancer (13).

However, study of S-1 plus irinotecan as first-line treatment for metastatic colorectal cancer did not have an adequate follow-up period to yield sufficient survival data. The original results demonstrated an overall response of 62.5% (14). At the time of the original publication, with a median follow-up of 12 months, the median overall survival could not be calculated because only 7 out of 40 patients had died. The current study represents the long-term follow-up of the original 40 patients on the trial, now with a median follow-up exceeding 5 years.

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Patients and Methods

Patient eligibility. Patients with histologically confirmed metastatic colorectal cancer were eligible for the study. Other enrollment criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, age 20 to 75 years, written informed consent, no concomitant or previous malignancy likely to interfere with the protocol treatment or assessment, leucocyte count of 3,000-12,000/ μ l, platelets \geq 100,000/ μ l, serum bilirubin level \leq 1.1 mg/dl, serum aspartate aminotransferase and alanine aminotransferase levels \leq 100 U/l, and serum creatinine level <upper limit of normal (ULN) range. Patients who had received prior chemotherapy or radiotherapy were excluded; however, those who had completed adjuvant chemotherapy at least six months before enrollment in the study were eligible.

Treatment design. This study consisted of a single treatment group. Patients were to receive irinotecan and S-1 combination chemotherapy until disease progression or unacceptable toxicity. Irinotecan (150 mg/m²) was administered on day 1 and S-1 [40 mg for patients with body surface area (BSA) <1.25 m²; 50 mg for BSA \geq 1.25 to <1.50 m²; 60 mg for BSA \geq 1.50 m²] was administered twice daily for two weeks from days 1 to 14, followed by a 7-day rest.

Statistical analysis. This phase II trial was approved by a local research Ethics Committee and patient enrollment began in April 2004. The primary endpoint was response. Secondary endpoints included safety, progression-free survival, and overall survival. Out of the 41 patients enrolled in this study, one patient who had a secondary cancer was excluded. The responses were assessed every six weeks, and complete and partial responses required subsequent confirmation after an interval of at least four weeks. These response rates remain unchanged subsequent to the first publication.

The current study aimed to assess long-term survival and progression-free survival. Progression-free survival was defined as the time from initiation of treatment to documented disease progression (the time-to-progression included post-study treatment if a patient discontinued the protocol treatment for a reason other than disease progression), or death due to any cause, whichever occurred earlier. Patients who did not experience disease progression or death were censored at the time of the last follow-up. Survival time was defined as the time from initiation of therapy to death due to any cause. Survival curves were estimated using the Kaplan–Meier method. The median follow-up time was calculated by using the reverse Kaplan–Meier method.

Results

Patients' characteristics. The clinical features of the 40 patients enrolled in this study are listed in Table I. All 40 eligible patients received at least one course of treatment.

Long-term efficacy. The median follow-up was 78.0 months (range 6.4 to 78.2 months). Out of the 40 patients, 38 patients developed disease progression, and two patients were lost to follow-up due to change of residence and refusal of anticancer therapy. At the time of this analysis, 37 patients had died and three patients were alive. Among the three

living patients, two had received post-study chemotherapy at the last contact (at 78 months, both patients), and one patient was lost to follow-up due to transfer to a palliative care unit at 63 months.

The median progression-free survival time was 8.3 months (95% confidence interval, 4.1 to 12.5 months) (Figure 1). The Kaplan–Meier 2-year survival rate was 50%, and the median survival time was 23.7 months (95% confidence interval 20.0 to 27.4 months) (Figure 1).

Post-study therapy. Out of 40 patients, a total of 36 received post-study chemotherapy, two patients received best supportive care only, one patient received radiotherapy for bone metastases, and one patient was lost to follow-up due to a change of residence. Oxaliplatin-containing regimens were administered to 28 patients (70%); regimens were oxaliplatin with bolus and continuous infusion 5-FU/LV (FOLFOX) in 27 patients and oxaliplatin with weekly bolus 5-FU and high-dose LV (ROX) in one patient (15); chemotherapy lines were second-line in 12 patients, third-line in 11 patients, and fourth-line in 5 patients. Bevacizumab was administered to three patients; two patients received FOLFOX with bevacizumab as second-line therapy and one patient received FOLFIRI with bevacizumab as third-line therapy after discontinuation of the protocol treatment due to fatigue, and progression on modified FOLFOX6 as second-line therapy. Anti-epidermal growth factor receptor (EGFR) monoclonal antibodies were administered to nine patients: irinotecan plus cetuximab to four patients, panitumumab alone to four patients, and cetuximab alone to one patient. Out of the nine patients that received anti-EGFR antibodies, five had wild-type v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*), and four had unknown *KRAS* status. No conversion therapy (unresectable disease becoming resectable after systemic chemotherapy) was possible in this study.

Discussion

This update of the phase II trial, after a follow-up period exceeding five years, demonstrated that S-1 plus irinotecan could be effectively combined for first-line treatment of advanced colorectal cancer. Although one limitation of this study is the possibility of selection bias, treatment with S-1 plus irinotecan led to a median survival time of 23.7 months. Recently, several standard treatments, such as FOLFOX, FOLFIRI and capecitabine plus oxaliplatin (CapeOX), have been selected based on the differences in adverse events, the necessity for ambulatory infusion devices, and the frequency of patient visits. The median survival time of patients on these regimens has reached approximately 20 months (16-21). This improvement in survival has been attributed to the increased use of three cytotoxic drugs: 5-FU, irinotecan, and oxaliplatin. In the current study, not all the patients had the

Table I. Patients' characteristics (n=40).

Category	No. of patients
Age, years	
Median (range)	60 (23-70)
Gender	
Male	27
Female	13
ECOG performance status	
0	35
1	5
Primary lesion	
Colon	25
Rectum	15
Number of organs involved	
1	13
2	16
≥3	11
Sites of metastasis	
Liver	33
Lung	17
Lymph nodes	13
Primary site	9
Abdominal mass	4
Other	3
Prior therapy	
Surgery for primary lesions	31
Surgery for metastatic lesions	3
Adjuvant chemotherapy	3
Other	1

opportunity to use the three key drugs because the introduction of oxaliplatin in Japan was delayed compared to other countries. In fact, six patients were unable to receive oxaliplatin-based regimens due to poor general condition or occurrence of death before the drug was approved. Moreover, among the 28 patients who received oxaliplatin-based chemotherapy, 16 (57%) received it as third- or fourth-line therapy, not as second-line therapy. As anti-EGFR antibodies are concerned, panitumumab was used in four patients, as a clinical trial of monotherapy, and cetuximab-based regimens were used in five patients who had wild-type KRAS and were alive at the time that cetuximab was approved in Japan (July 2008). Thus, the current study suggests that S-1 plus irinotecan can be as effective as other standard treatments when used for first-line therapy. Furthermore, to select suitable candidates for this treatment, the predictive factors for survival over 24 months were also investigated as follows: age, primary site (colon *vs.* rectum), performance status, disease status (advanced *vs.* recurrence), number of metastatic sites, white blood cell count ($\geq 10,000$ *vs.* $< 10,000$ / μ l), alkaline phosphatase (≥ 300 *vs.* < 300 IU/l), lactate dehydrogenase (\geq ULN *vs.* $<$ ULN), and carcinoembryonic antigen (≥ 5.0 *vs.* < 5.0 ng/ml). The group with the long

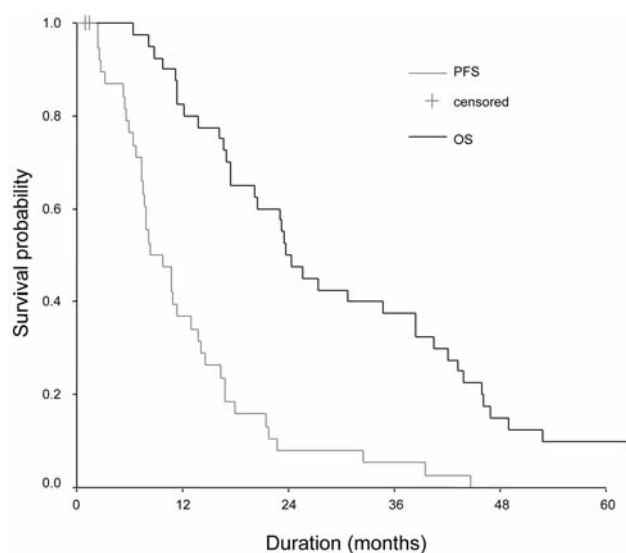


Figure 1. Overall survival and progression-free survival of the 40 patients.

survival (over 24 months) had a significantly lower value of baseline lactate dehydrogenase (LDH) than that of the group with the short survival ($p=0.026$, chi-square test). However, other factors were not statistically significant (data not shown).

Oral fluoropyrimidine plus irinotecan has been tested, as well as oral fluorouracil plus oxaliplatin, in terms of less frequent patient visits and non-necessity of ambulatory infusion devices. In Western countries, capecitabine plus irinotecan (XELIRI) induced grade 3 diarrhea in 47.5% of patients and dehydration in 19.1% of patients in a three-arm phase III trial of FOLFIRI *vs.* modified IFL *vs.* XELIRI; so XELIRI with the original starting dose of irinotecan (250 mg/m^2) revealed problems regarding safety (20). Several phase II studies of XELIRI with a reduced starting dose of irinotecan (200 mg/m^2) showed a lower incidence of grade 3, or greater, diarrhea of 16% and 12%, respectively (22, 23). In Japan, S-1 plus irinotecan for advanced colorectal cancer was tested long before the approval of capecitabine. The three-week cycle of irinotecan and S-1 was reported as follows: our phase II study of days 1 to 14 S-1 (80 mg/m^2) plus day 1 irinotecan (150 mg/m^2), another phase II study of days 3 to 16 S-1 (80 mg/m^2) plus day 1 irinotecan (150 mg/m^2), and another phase II study of days 1 to 14 S-1 (80 mg/m^2) plus day 1 and 8 irinotecan (80 mg/m^2) produced 7.5%, 0.9%, and 2.5% of grade 3 or higher diarrhea, respectively (14, 24, 25). Thus, these trials showed that S-1 plus irinotecan was well-tolerated by Japanese patients with previously untreated advanced colorectal cancer, although the schedule or dose of irinotecan differed in each trial.

In this evaluation of the long-term outcomes of patients in the phase II trial with a median follow-up period exceeding five years, combination therapy with oral S-1 plus irinotecan

was confirmed to have continued clinical benefit as first-line therapy for metastatic colorectal cancer. Recently, a phase II trial of combination therapy with oral S-1 plus irinotecan with bevacizumab (SIRB) demonstrated that this regimen is promising as a first-line treatment in patients with metastatic colorectal cancer (13). We intend to assess the SIRB regimen effectivity in relation to therapy with FOLFOX or CapeOX with bevacizumab in a randomized trial of previously untreated patients with metastatic colorectal cancer.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

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