Phase II study of combination therapy with S-1 and irinotecan in patients with advanced colorectal cancer


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Background: A combination of irinotecan with continuous intravenous infusions of 5-fluorouracil (5-FU) and leucovorin (LV) is often used to treat advanced colorectal cancer. However, recent concerns about safety and convenience have prompted the development of new oral fluoropyrimidine derivatives and improved regimens. This phase II study evaluated the efficacy and safety of the oral fluoropyrimidine S-1 plus irinotecan in patients with previously untreated advanced or recurrent colorectal cancer.

Patients and methods: Forty eligible patients with histologically confirmed colorectal adenocarcinoma received this treatment. S-1 was administered orally on days 1 to 14 of a 21-day cycle. Patients were assigned on the basis of body surface area (BSA) to receive one of the following oral doses twice daily: 40 mg (BSA < 1.25 m²), 50 mg (BSA 1.25 to < 1.50 m²), or 60 mg (BSA ≥ 1.50 m²). Irinotecan (150 mg/m²) was administered by intravenous infusion on day 1.

Results: A total of 327 courses of treatment were administered to 40 patients. Five patients had complete responses, and 20 had partial responses. The overall response rate was 62.5% (95% confidential interval, 47.5%–77.5%). Median progression-free survival was 8.0 months (95% confidential interval, 5.2–11.4 months). The rates of grade 3 or 4 toxicity were as follows: neutropenia, 15%; anemia, 7.5%; anorexia, 12.5%; and diarrhea, 7.5%.

Conclusions: Combined treatment with S-1 and irinotecan is an effective, well tolerated, and convenient regimen in patients with advanced colorectal cancer. Our findings suggest that combined treatment with S-1 and irinotecan is a promising regimen, offering benefits in terms of safety and survival as compared with conventional regimens in patients with advanced colorectal cancer.

Key words: S-1, irinotecan, colorectal cancer, phase II study

Introduction

Irinotecan, a potent inhibitor of topoisomerase I, extends survival significantly as compared with best supportive care or 5-fluorouracil (5-FU) infusion as second-line therapy for advanced colorectal cancer. Two randomized phase III trials have shown that a combination of irinotecan plus intravenous infusion of 5-FU and leucovorin (LV) as first-line treatment provides a survival benefit, with a median overall survival time (MST) of 14.8 to 17.4 months in patients with advanced colorectal cancer [1]. However, recent reports have expressed concern about high rates of toxicity and early treatment-related mortality among patients receiving combined treatment with irinotecan plus bolus 5-FU and LV [2-3]. Meta-analysis has shown that infusional 5-FU regimens may be a safer option and are superior to bolus 5-FU regimens in terms of tumor response [4]. Consequently, irinotecan plus infusional 5-FU and LV has been considered superior to irinotecan plus bolus 5-FU and LV. However, administration of infusional 5-FU is becoming more complex because of the need for vascular access devices and portable delivery systems. The use of an indwelling central venous catheter and a portable pump may also lead to problems such as infection, thrombosis, and higher health-care costs. Such problems have increased the need for new oral fluoropyrimidine agents and safer and more effective combination regimens for advanced colorectal cancer.

S-1 is an oral fluoropyrimidine preparation developed by Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan) that combines tegafur with two 5-FU modulators, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo), in a molar ratio of 1:0.4:1 [5]. Tegafur, a prodrug of 5-FU, is converted to 5-FU mainly in liver and tumor cells. CDHP, a reversible inhibitor of dihydropyrimidine dehydrogenase, suppresses the degradation of 5-FU, thereby maintaining high concentrations of 5-FU in plasma and tumor cells. CDHP, a reversible inhibitor of dihydropyrimidine dehydrogenase, suppresses the degradation of 5-FU, thereby maintaining high concentrations of 5-FU in plasma and tumor cells [5-6]. CDHP also decreases cardiotoxic and neurotoxic effects by reducing the production of F-β-alanine (FBAL), the main catabolite of 5-FU [7-8]. After oral administration, Oxo is selectively distributed to the small and large bowel. High concentrations of Oxo in these organs inhibit the phosphorylation of 5-FU to fluoropyrimidine monophosphate, catalyzed by orotate phosphoribosyltransferase within...
gastrointestinal mucosal cells, thereby reducing the incidence of diarrhea [9].

Several clinical trials of S-1 monotherapy have been conducted. Dose-limiting toxicity was myelosuppression in Japanese studies and diarrhea in European and North American studies [10–13]. In phase II trials of S-1 as a single agent, response rates ranging 19% to 39% were obtained in patients with advanced colorectal cancer [14–16]. These studies demonstrated that S-1 had a high response rate and good compliance in patients with advanced colorectal cancer treated on an outpatient basis. Several regimens combining S-1 and irinotecan were subsequently developed. Yamada et al. conducted a phase I and pharmacokinetic study to assess the maximum tolerated dose and recommended dose of S-1 combined with irinotecan [17]. That study recommended that 150 mg/m² of irinotecan is given on day 1 with 40 mg/m² of S-1 twice daily on days 1 to 14 of a 21-day cycle. We conducted this phase II study to validate the safety profile and effectiveness of S-1 combined with irinotecan in patients with advanced colorectal cancer.

**patients and methods**

**eligibility**

To be eligible for this study, patients had to have histologically or cytologically confirmed advanced or recurrent colorectal adenocarcinoma with metastatic measurable lesions. Other eligibility criteria included an age of ≥20 to <75 years, an Eastern Cooperative Group (ECOG) perfor-

mance status (PS) of ≤2, a leucocyte count of ≥3000 to ≤12 000/μl, a hemoglobin of ≥8 g/dl, a platelet count of ≥100 000/μl, a serum bilirubin level of ≤1.1 mg/dl, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels of ≤1 U/L, a serum creatinine level of ≤1.1 mg/dl (for men) or ≤0.7 mg/dl (for women), the ability to ingest food, and no high medical risks. Patients who had received prior chemotherapy or radiotherapy were excluded; however, those who had received adjuvant chemotherapy completed at least 6 months before study entry were eligible. All patients gave written informed consent before enrolment.

**treatment schedule**

S-1 was available as capsules containing 20 or 25 mg of tegafur. Patients were assigned on the basis of body surface area (BSA) to receive one of the following oral doses twice daily, within an hour after breakfast and supper: 40 mg (BSA <1.25 m²), 50 mg (BSA ≥1.25 to <1.50 m²), or 60 mg (BSA ≥1.50 m²). S-1 was given for 14 consecutive days followed by a 7-day rest period. Irinotecan was administered as a 90-minute intravenous infusion in a dose of 150 mg/m² on day 1, after the initial oral dose of S-1. Courses of treatment were repeated every 21 days until confirmation of either disease progression or unacceptable toxicity.

If laboratory abnormalities not meeting the eligibility criteria developed after the start of treatment, subsequent courses of treatment were withheld until the resolution of such abnormalities to the levels defined in the eligibility criteria. If grade 2 non-hematological toxicity other than constipation, alopecia, pigmentation, or taste disturbance occurred, subsequent courses of treatment were also withheld until symptoms resolved. If the eligibility criteria were not met by day 35 of a cycle, the patient was excluded from further study. If the serum bilirubin level exceeded 1.5 mg/dl, the serum creatinine level exceeded the eligibility criteria, or if grade 3 toxicity developed, the treatment course was interrupted until symptoms, laboratory abnormalities, or both had resolved. If treatment was resumed, S-1 was given until day 14 of the cycle, not for the full 14 days. If the previous treatment course was delayed or interrupted because of toxicity, the dose of irinotecan was reduced by 25 mg/m² for subsequent courses. If 125 mg/m² of irinotecan was not tolerated, the dose was reduced to 100 mg/m². If 100 mg/m² of irinotecan was poorly tolerated, the patient was excluded from further study. The dose of S-1 was unchanged if the dose of irinotecan was reduced. Only if skin reactions occurred, the dose of S-1 was reduced in subsequent courses as follows: 60 mg, 50 mg, and 40 mg of S-1 twice daily were reduced to 50 mg, 40 mg, and 25 mg twice daily, respectively. Once lowered, the doses of S-1 and irinotecan were not increased.

Supportive treatments were given as required. The use of colony-stimulating factors was allowed if medically justified. A 5-hydroxytryptamine-3-receptor antagonist and dexamethasone were given to all patients in a 30-min intravenous infusion before administration of irinotecan. All patients received oral dexamethasone on days 2 and 3 of each cycle.

**evaluation**

Patients who received at least one treatment course were included in safety and efficacy analyses. Before study entry, patients underwent physical examination, chest X-ray, and computed tomographic scans of the abdomen and chest. Patients were re-examined at 6-week intervals to evaluate target lesions. Responses were evaluated according to the RECIST criteria [18]. Complete and partial responses required subsequent confirmation of response after an interval of at least 4 weeks. Pretreatment evaluations comprised an electrocardiogram, urinalysis, and laboratory tests, including a complete blood cell count and serum chemistry profiles. Toxicity was assessed according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 3.0. Toxicity and laboratory variables were assessed weekly during the first treatment course and on days 1 and 15 from the second through sixth treatment courses. Safety profiles and dose intensity were determined for up to six courses of treatment per patient.

**statistical methods**

Response rates with 5-FU plus LV, or with irinotecan as a single agent were approximately 20% in previous clinical trials in patients with advanced colorectal cancer. With a combination of irinotecan, S-5FU, and LV as first-line treatment for advanced colorectal cancer, the response rate was about 40%. We calculated the required sample size for this study on the basis of a target activity level of 40% and a minimum activity level of 20%, with α and β error of 0.1. The required number of patients was estimated to be 36. A stopping rule was included in this study. This trial would have been stopped if there were less than four patients with response among the first 19 patients. Survival was calculated by the Kaplan-Meier method from the date of starting treatment.

**results**

**patients’ characteristics**

Between April 2004 and February 2005, we enrolled 41 patients with advanced colorectal carcinoma. One patient was excluded from the study because of another active malignancy. The other 40 patients met all eligibility requirements. Their characteristics are shown in Table 1. All eligible patients received at least one course of treatment. Three patients had received prior adjuvant chemotherapy (bolus 5-FU and LF-LV in 2, and an oral fluoropyrimidine derivative in 1). Nine patients had primary sites with metastatic lesions at study entry. The median follow-up time was 12 months. The 40 patients had received...
a total of 327 treatment courses (median, nine courses; range, one to 16+ courses).

response
All 40 patients had at least one measurable lesion. Responses to treatment are shown in Table 2. Five patients had a complete response (CR). Two of these patients had lung metastasis, one had lung and liver metastases, and two had liver and abdominal lymph node metastases. Response was not evaluated in two patients. One patient refused to continue treatment, and another discontinued treatment because of toxicity before the initial evaluation of response. At a median follow-up time of 12 months, the median progression-free survival (PFS) time was 8.0 months (range, 1.4 to 13.8+ months; 95% confidence interval, 5.2 to 11.4 months) (Figure 1). Because there were only seven deaths, the median overall-survival time could not be calculated. Among 25 patients who had complete or partial responses, the median time to response was 1.5 months (range, 1.2 to 4.2 months). The median duration of response was 8.0 months (range, 2.8 to 11.9+ months).

toxicity
A total of 200 treatment courses were administered to the 40 eligible patients to define safety profiles for up to six treatment courses per patient. Toxicity is summarized according to the worst grade per patient in Table 3. There were no treatment-related deaths. The most common type of hematological toxicity was anemia; however, the incidence of grade 3 or 4 anemia was very low. The most common type of non-hematological toxicity was fatigue, which was usually mild. Toxicity is summarized according to the worst grade for the 200 courses of treatment in Table 4. Cumulatively, myelosuppression and gastrointestinal toxicity were most common reactions, but were generally mild. The incidence of grade 3 or 4 toxicity was less than 5% for all events. Treatment was discontinued because of toxicity in seven of the 40 patients. The reasons for discontinuing treatment were as follows: grade 3 anorexia or nausea, 3 patients; grade 3 diarrhea, one; grade 3 elevation of AST, one; grade 2 cardiac ischemia, one; and refusal to continue treatment because of prolonged mild fatigue and nausea, one. The patient with the grade 3 elevation of AST was confirmed to have severe multiple liver metastasis at study entry. There was no evidence of disease.
medial PFS of 8.0 months. In previous phase III studies of irinotecan was very effective, with a response rate of 62.5% and untreated colorectal cancer. Our results showed that S-1 plus treatment with S-1 and irinotecan in patients with previously discussion

The mean dose intensity of irinotecan was 130 mg/m²/3 weeks. The mean relative dose intensity of irinotecan was 87%. The dose of irinotecan was reduced according to the study protocol in five of the 40 patients (12.5%). The reasons for reducing the dose of irinotecan were as follows: diarrhea, three patients; anorexia, one; and hyperbilirubinemia, one. The mean relative dose intensity of S-1 was 82%. S-1 had good compliance: 96% of the scheduled dose was administered during one to six treatment courses. The dose of S-1 was reduced according to the study protocol in three of the 40 patients (7.5%). The reasons for dose reduction were as follows: stomatitis, 1 patient; ocular diseases, 1; and anorexia, 1. During one to six treatment courses (a total of 200 courses), treatment was delayed for at least 1 week because of toxicity in 12 of the 40 patients (25%). The incidences of toxic reactions responsible for treatment delays were as follows: neutropenia or leukopenia, 3%; diarrhea, 2%; hyperbilirubinemia, 2%; and other reactions, 4.5%.

discussion

This study assessed the efficacy and safety of combined treatment with S-1 and irinotecan in patients with previously untreated colorectal cancer. Our results showed that S-1 plus irinotecan was very effective, with a response rate of 62.5% and median PFS of 8.0 months. In previous phase III studies of irinotecan with infusional 5-FU and LV, response rates ranged from 31% to 62% [1, 19–22]. Median time to progression (TTP) or PFS in our study were similar to those reported in previous studies of irinotecan with infusional 5-FU and LV.

Toxicity was generally mild and manageable on an outpatient basis. The most common hematological toxicity was anemia, because the baseline hemoglobin level was grade 1 or less than the lower limit of normal in nearly all patients. Meanwhile, neutropenia was considered the most frequent type of treatment-related hematological toxicity. The most common type of non-hematological toxicity was fatigue, which was not severe but prolonged. The incidences of grade 3 or 4 diarrhea and anorexia were low. However, patients with anorexia had other related toxic reactions, such as diarrhea, dehydration, fatigue, and neutropenia. In patients who had moderate anorexia or diarrhea, treatment with S-1 was temporarily discontinued, or the start of the next treatment course was delayed at least 1 week. Consequently, either neutropenia or leukopenia was the most common reason for delaying subsequent courses of treatment. Neutropenia, diarrhea, nausea, and vomiting frequently occurred in previous studies of combined treatment with irinotecan plus infusional 5-FU and LV [1, 19–22]. Our results suggested that both the incidences and intensities of these toxic reactions with S-1 plus irinotecan were similar to those with a combination of irinotecan plus infusional 5-FU and LV.

Prolonged mild ocular toxicity, including epiphora and blurred vision, was relatively frequent, especially in patients who received long-term treatment. Such toxicity occasionally led to delay of treatment and was most likely caused by 5-FU. The safety database of the manufacturer of S-1 indicates that the incidence of ocular toxicity is less than 5%. Systemic therapy with 5-FU has been reported to cause epiphora due to stenosis and fibrosis of tear ducts [23]. Another study has suggested that epiphora is often reversible on stopping treatment [24]. Subsequent courses of treatment should therefore be delayed and appropriate local therapy administered in patients with ocular toxicity. Unfortunately, one patient in our study underwent surgery of the tear ducts. Patients who have persistent ocular toxicity should therefore be referred to an ophthalmologist.

The mean relative dose intensity of both S-1 and irinotecan in our study exceeded 80%. We calculated the dose intensity of S-1 in a similar manner to S-1 as a single agent. The dose intensity of irinotecan in our study was less than that of irinotecan combined with infusional 5-FU plus LV. In another phase I study of S-1 plus irinotecan, S-1 was administered twice daily for 3 weeks in combination with irinotecan on days 1 and 15 of a 5-week cycle [25]. The recommended dose was 80 mg/m² of irinotecan. The dose intensity of irinotecan in a 5-week schedule was very similar to that with our regimen. These findings suggest that the use of higher doses of irinotecan would probably require a lower dose of S-1 to maintain toxicity, especially neutropenia, diarrhea, or prolonged fatigue, within acceptable levels. Overall, compliance with a combination of S-1 and irinotecan was good; in addition, our regimen was more convenient and easier to administer than a combination of

Table 3. Toxicity in all 40 patients during one to six treatment courses

<table>
<thead>
<tr>
<th>Toxicity (n = 40)</th>
<th>Grade (NCI-CTC, ver. 3.0)</th>
<th>All grades (%)</th>
<th>Grade ≥3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Anemia</td>
<td>28</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>13</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>20</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Nausea</td>
<td>22</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>21</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>8</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Ocular diseases</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>16</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Elevation of AST/ALT</td>
<td>20</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>
irinotecan plus infusional 5-FU and LV. Our results indicate that most patients can receive S-1 plus irinotecan on an outpatient basis.

Capecitabine is also an oral fluoropyrimidine derivative. Studies of a combination of capecitabine plus irinotecan reported response rates ranging from 47% to 61% and a median PFS or TTP of 6.1 to 8.3 months in patients with colorectal cancer [26–27]. The incidence of grade 3 or 4 diarrhea with capecitabine plus irinotecan was greater than 20% in both studies, clearly higher than that with S-1 plus irinotecan. Moreover, both irinotecan and capecitabine are metabolized by carboxylesterases in the liver to an active metabolite, SN-38, and to an intermediate metabolite, 5′-deoxy-5-fluoropyrimidine, respectively. The complex metabolism of both capecitabine and irinotecan can thus theoretically lead to pharmacokinetic drug–drug interactions [28]. In contrast, both capecitabine and irinotecan can thus theoretically lead to pharmacokinetic drug–drug interactions [28].

A combination of oral uracil/tegafur (UFT) and irinotecan is better tolerated than a combination of S-1 and irinotecan. Available evidence thus indicates that S-1 plus irinotecan may be better tolerated than capecitabine plus irinotecan. Moreover, both irinotecan and capecitabine are more convenient than a combination of capecitabine and irinotecan. Studies of a combination of capecitabine plus irinotecan was higher than that with S-1 plus irinotecan. Moreover, both irinotecan and capecitabine are metabolized by carboxylesterases in the liver to an active metabolite, SN-38, and to an intermediate metabolite, 5′-deoxy-5-fluoropyrimidine, respectively. The complex metabolism of both capecitabine and irinotecan can thus theoretically lead to pharmacokinetic drug–drug interactions [28].

In conclusion, our results suggest that combined treatment with S-1 and irinotecan is a promising regimen, offering benefits in terms of safety and survival as compared with conventional regimens in patients with advanced colorectal cancer. Future studies must objectively confirm that S-1 plus irinotecan can replace a combination of infusional 5-FU and LV plus irinotecan, without negatively affecting efficacy or safety. We firmly believe that further trials comparing S-1 plus irinotecan with a combination of irinotecan plus infusional 5-FU and LV are warranted.

acknowledgements

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references