Purpose: To evaluate the antitumor effect and feasibility of a combination of irinotecan (CPT-11) and 5-day infusional 5-fluorouracil (5-FU) in a sequential schedule based on our previous combination phase I studies in patients with metastatic colorectal cancer.

Patients and Methods: Forty chemotherapy-naive patients with metastatic colorectal cancer received 90-min infusion of CPT-11 at a dose of 150 mg/m² on days 1 and 15 and 120-h protracted infusion of 5-FU at 600 mg/m²/day on days 3–7, which were repeated every 4 weeks.

Results: The median number of actually administered courses was five, ranging from one to 14. There were 16 (40%) patients who developed grade 3 or 4 neutropenia. Grade 3 or 4 nausea/vomiting and diarrhea were seen in three (8%) and seven (18%) patients, respectively. Only one early death not related to treatment occurred during the study. There was one complete response and 17 partial responses with a response rate of 45% (95% confidence interval: 29.3–61.5%). With a median follow-up period of 22.5 months for survivors, the median survival and median progression-free survival times were 15.9 and 7.0 months, respectively.

Conclusions: Although the toxicities were modest, this sequentially combined regimen is active and feasible in patients with metastatic colorectal cancer.

Key words: irinotecan – 5-fluorouracil – colorectal cancer

INTRODUCTION

Irinotecan (CPT-11) is a camptothecin derivative and is a potent inhibitor of topoisomerase I, a nuclear enzyme involved in the unwinding of DNA (1). CPT-11 was originally developed in Japan and has demonstrated antitumor activity against metastatic colorectal cancer in a single-agent phase II study with a response rate of 27% (2). This activity was confirmed by other studies (3,4). Based on the promising results, we conducted a phase I/II study in combination with 5-fluorouracil (5-FU). At that time, leucovorin had not been commercially available in Japan and we chose a protracted infusion schedule of 5-FU. At first, we used a simultaneous schedule, which consisted of 90-min infusion of CPT-11 immediately followed by 7-day continuous infusion of 5-FU at a fixed dose of 400 mg/m²/day (5). However, this study demonstrated an unexpected lower response rate of 11% (4/36) and lower incidence of toxicities such as leukopenia and diarrhea than those observed in the previous single-agent study. This failure appeared to be caused by a pharmacokinetic interaction between CPT-11 and 5-FU: the plasma area under the concentration × time curve (AUC) of SN-38, an active metabolite of CPT-11, in patients treated with this regimen was 29% lower than the historical control in patients treated with CPT-11 alone. This interaction might be caused by reducing carboxylesterase, a converting enzyme from CPT-11 to SN-38, in patients treated with this regimen.

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and 15 and 5-FU was continuously infused for 120 h from day 3 to day 7 at a fixed dose of 600 mg/m²/day. This study was carried out as a phase I/II setting with a starting dose of CPT-11 at 100 mg/m² and determined a recommended dose of CPT-11 at 150 mg/m². In contrast to the previous study, this study demonstrated promising results with a response rate of 32% (8/25) in total and of 42% (8/19) for patients who received a dose of CPT-11 of 125 mg/m² or more. This study also showed a promising survival rate with a median response duration of 177 days and no interactions in pharmacokinetic parameters between the two agents as seen in the previous study (7). Based on the results, we conducted a phase II study to estimate the efficacy of this combination regimen. Primary endpoints of this study were response rate and incidence of serious adverse reactions.

PATIENTS AND METHODS

PATIENT ELIGIBILITY

Patients eligible for this study were required to have histologically proven colorectal carcinoma with measurable metastatic lesions. No prior chemotherapy or radiotherapy was allowed. Patients were required to have a 2 or better performance status on the Eastern Cooperative Oncology Group scale with a life expectancy of 8 weeks or longer and to be between 20 and 75 years old. Eligibility also required adequate organ functions as follows: WBC >4000/µl, platelets >100 000/µl, AST and ALT <2.5 times the normal upper limits (except for cases with liver metastasis), serum bilirubin <2.0 mg/dl, blood urea nitrogen <25 mg/dl, creatinine <1.5 mg/dl, creatinine clearance >50 ml/min, normal electrocardiogram and written informed consent from the patients. Exclusion criteria consisted of large amounts of ascites or pleural effusion, brain metastasis, serious complications and any active malignancies at other sites. Pretreatment evaluations included physical examinations, abdominal CT scan, abdominal ultrasonography and chest X-ray. This study protocol was approved by the Japan Clinical Oncology Group (JCOG) Clinical Trial Review Committee and by the institutional review board in each participating institution.

TREATMENT SCHEDULE

The treatment schedule of this regimen comprised CPT-11 at a dose of 150 mg/m² with 90-min infusion on days 1 and 15 and 120-h protracted infusion of 5-FU at 600 mg/m²/day on days 3–7. This schedule was repeated every 4 weeks until the occurrence of disease progression, unacceptable toxicities or patient’s refusal. On every occasion of CPT-11 administration, patients had to fulfill the following criteria: WBC >3000/µl, platelets >100 000/µl, AST and ALT <2.5 times the normal upper limits (except for cases with liver metastasis), serum bilirubin <2.0 mg/dl, blood urea nitrogen <25 mg/dl, creatinine <1.5 mg/dl, no evidence of diarrhea or infectious fever. Patients had to wait to receive CPT-11 until recovery from any of the above adverse events. If grade 4 hematological toxicity or diarrhea were seen in the previous course or if intervals between any of the two CPT-11 administrations exceeded 21 days owing to any adverse events, then the subsequent dose of CPT-11 was reduced to 120 mg/m². Whenever any of the above toxicities occurred despite the dose reduction of CPT-11, the protocol treatment was terminated for the subjects.

EVALUATION OF RESPONSE AND TOXICITY

The measurable lesions were evaluated by abdominal CT scan and/or chest X-ray, which were carried out in each course. Antitumor activity was evaluated in accordance with standard WHO criteria. Briefly, complete response (CR) was defined as the complete disappearance of all measurable and assessable disease for a minimum of 4 weeks. A partial response (PR) was defined as a 50% or more reduction in the sum of the products of the longest diameter of measurable lesions for a minimum of 4 weeks. No change (NC) was defined as the failure to observe a partial or complete response and progressive disease for at least 4 weeks. Progressive disease (PD) was defined as a 25% or more increase in the sum of the products of the longest diameter of measurable lesions or the appearance of new lesions. Objective responses were confirmed by extramural review.

Physical examinations, blood cell counts, hepatic and renal tests were assessed on a weekly basis in the first course followed by every 2 weeks in the subsequent courses. Toxicity was evaluated according to the toxicity criteria of the JCOG (8), which were based on National Cancer Institute common toxicity criteria.

STATISTICAL CONSIDERATIONS

The sample size for the study was calculated from an expected response rate of 40% and a minimum of 20% with an α and β error of 0.1, using Simon’s two-stage minimax design (9). The estimated sample size was 36 and adding 10% of expected ineligible cases, then a total of 40 patients including 19 patients for the first stage were required. Overall survival was calculated from the date of registration to death due to any cause or to the last contact date, using the Kaplan–Meier method. Progression-free survival was analyzed from the date of registration to date of documented disease progression or, if patients died without disease progression, to date of death.

RESULTS

PATIENTS’ CHARACTERISTICS

During the period between October 1997 and May 1999, a total of 40 patients were enrolled and the study was completed without early termination at the first stage. All patients were eligible and their characteristics are listed in Table 1. There were 22 patients with colon and 18 with rectal carcinoma as the primary site. Twenty-six patients had synchronous metastatic diseases at diagnosis and the remaining 14 patients had recurrent metastatic diseases after surgery. Major metastatic sites were liver and lung. Thirty-six patients had received surgical
rescue for primary tumors before registration. The median number of treatment courses was five, ranging from one to 14. All patients discontinued the treatment and the reasons for leaving the protocol were as follows: 20 patients by disease progression, three by toxicity, nine by patient’s refusal related to toxicity of the treatment, seven by refusal not related to toxicity and one by death during the treatment period due to disease progression. There were six patients associated with major deviations: two patients with delay of initiating 5-FU administration on day 3, two with shortened duration of 5-FU administration, and two with delay of CPT-11 administration.

**ADVERSE EVENTS**

Major adverse events of this combination were hematological and gastrointestinal toxicities. There were five (12.5%), 16 (40.0%) and five (12.5%) patients who developed grade 3 or 4 leukopenia, neutropenia and anemia, respectively. Grade 3 or 4 nausea/vomiting and diarrhea were seen in three (7.5%) and seven (17.5%) patients. Grade 3 liver injury and hyponatremia were observed in one patient each and no other grade 3 or worse toxicities occurred. Discontinuations of the treatment by patient’s refusal, described as above, were mostly caused by the gastrointestinal toxicity. However, there was only one early death, within 30 days of the last treatment date. The patient had multiple liver metastases with tumor thrombus on the portal vein at registration and died of hepatic failure 17 days after the last treatment date due to tumor progression. No treatment-related deaths occurred during the study.

**RESPONSE AND SURVIVAL**

Of the 40 patients, 18 (45%) achieved objective responses including one CR, with a 95% confidence interval (CI) of 29.3–61.5%. The CR case had liver metastasis before registration and showed complete disappearance of metastatic lesion after six courses, which lasted for 1 month. There were 17 (43%) patients with NC and only three (8%) patients showed PD. No significant differences in response rates between metastatic sites were observed: 45.5% (10/22) in liver, 45.0% (9/20) in lung and 50.0% (9/18) in abdominal nodes metastases.

With a median follow-up period of 22.5 months for survivors, the median survival time of the 40 patients was 15.9 months (95% CI: 11.5–19.6 months) with 1-year survival of 62.5% (95% CI: 47.5–77.5%). Median progression-free survival was 7.0 months (95% CI: 5.9–8.3 months) with 1-year progression free survival of 17.5% (95% CI: 5.7–29.3%).

**DISCUSSION**

CPT-11 has provided survival benefit in patients with metastatic colorectal cancer. First, CPT-11 alone achieved survival prolongation when used as second-line treatment after 5-FU failure as compared with both best supportive care (10) and another scheduled 5-FU treatment (11). These results support the suggestion that CPT-11 can be considered to be the standard treatment after failure of 5-FU-based treatments. Additionally, as first-line therapy, two large randomized studies comparing CPT-11 plus 5-FU–leucovorin with 5-FU–leucovorin in patients with metastatic colorectal cancers have already been reported from Europe (12) and the USA (13). Both studies demonstrated that CPT-11 in addition to 5-FU–leucovorin provided significant prolongation of survival as compared with 5-FU–leucovorin alone: median survival times of the combination arms and 5-FU–leucovorin arms were 17.4 vs 14.1 months in the European study and 14.8 vs 12.6 months in the US study; their median progression-free survivals were 6.7 vs 4.4 and 7.0 vs 4.3 months, respectively. These results suggest that this combination can be a standard treatment for metastatic colorectal cancer.

In our previous combination phase I study of CPT-11 and infusional 5-FU, a simultaneous schedule revealed an antagonism on both toxicity and efficacy (5). We then revised the administration schedule to a sequential format, which was associated with no pharmacokinetic interaction (7). The present phase II study demonstrated efficacy of this combination in terms of median survival and response rate. With respect to the pharmacokinetic and/or pharmacodynamic interaction, Saltz et al. reported that no pharmacokinetic interaction between CPT-11 and 5-FU–leucovorin was observed in their combination phase I study (14). They used a CPT-11 and 5-FU administration schedule in two opposite sequences as 90-min and brief infusions, respectively. The peak plasma concentration and AUC of SN-38 in CPT-11 administration immediately followed by 5-FU and leucovorin were only slightly lower by 13.2 and 8.2%, respectively, than in CPT-11 alone, which showed no significant differences and less clinical importance of the sequence. This combination regimen was then developed into a phase III study showing a survival advantage as compared with 5-FU plus leucovorin. Based on these favorable clinical results, there seems to be no meaningful interactions when 5-FU is used as a bolus infusion. Recently, however, Falcone et al. reported a sequence effect of CPT-11 and 5-FU treatment on the pharmacokinetics and toxicity profile (15). In that study, patients received a 60-min infusion of CPT-11

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**Table 1. Patients’ characteristics**

<table>
<thead>
<tr>
<th>Metastatic site:</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal lymph nodes</td>
<td>18</td>
</tr>
<tr>
<td>Liver</td>
<td>22</td>
</tr>
<tr>
<td>Lung</td>
<td>20</td>
</tr>
<tr>
<td>Others</td>
<td>14</td>
</tr>
</tbody>
</table>

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Falcone et al. reported a sequence effect of CPT-11 and 5-FU when 5-FU is used as a bolus infusion. Recently, however, clinical results, there seems to be no meaningful interactions when 5-FU is used as a bolus infusion. Recently, however, Falcone et al. reported a sequence effect of CPT-11 and 5-FU treatment on the pharmacokinetics and toxicity profile (15). In that study, patients received a 60-min infusion of CPT-11
before or after a 48-h infusional schedule of 5-FU was comparable to that of Saltz et al.’s regimen (13) with a 48-h interval. There were no pharmacokinetic interactions. Additionally, the efficacy parameters seemed to be comparable to those of Saltz et al.’s regimen (13) with regard to response rate, 45 vs 39%, and median survival, 15.9 vs 14.8 months. In terms of toxicity, the incidences of grade 3 or 4 diarrhea and neutropenia were slightly lower in the present study than in Saltz et al.’s study; 17.5 vs 22.7% for diarrhea and 40 vs 53.8% for neutropenia. More recently, two large randomized studies revealed that the combined CPT-11 + 5-FU–leucovorin arm developed threefold higher treatment-related deaths than other arms such as 5-FU–leucovorin or oxaliplatin + 5-FU–leucovorin (16). Although the number of the patients in the present study was small, no treatment-related deaths occurred with the present regimen and it appeared to be more manageable than Saltz et al.’s regimen. On comparing the present results with those of Douillard et al.’s regimen (12) using continuous infusion of 5-FU with leucovorin, the efficacy parameters were also similar; response rates 45 vs 41% and median survival times 15.9 vs 17.4 months in our study and in Douillard et al.’s study, respectively, while grade 3 or 4 diarrhea seemed to be less frequent with our regimen than Douillard et al.’s regimen (17.7 vs 44.4%). These results suggested that our regimen had potentially an efficacy comparable to those of both Saltz et al.’s and Douillard et al.’s regimens without increasing the rate of severe diarrhea. However, in 12 (30%) of the 40 patients in the present study, the treatments were discontinued owing to the toxicity or the patient’s refusal related to toxicities. This high incidence of discontinuation related to toxicities appears to be resolved in a future study, partly by using intensive support with anti-emetic or diarrheal agents.

The present study clinically confirmed the efficacy of this combination probably without pharmacokinetic interaction of the two agents. Based on the recent promising results of this combination including leucovorin (12,13), it is now becoming a mainstream treatment for advanced colorectal cancer. However, this study suggested that CPT-11 and a 5-day infusion of 5-FU without leucovorin achieved a favorable response and survival, which were comparable to those with CPT-11 + 5-FU–leucovorin. Additionally, based on our experiences with this combination study series, the timing of administration of each agent should be carefully planned when using an infusional schedule of 5-FU.

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