Phase I—II study of irinotecan combined with mitomycin-C in patients with advanced gastric cancer*


1Department of Internal Medicine, Cancer Institute Hospital, Tokyo; 2Department of Gastrointestinal Oncology, National Cancer Center Hospital, Tokyo, Japan

Summary

Background: Irinotecan (CPT-11) shows synergism with mitomycin-C (MMC) in a preclinical setting. The goals of this study were to determine the maximum tolerated dose (MTD), the dose limiting toxicity, the recommended dose (RD), and preliminary anti-tumor activity in a combined CPT-11 and MMC treatment of advanced gastric cancer.

Patients and methods: The study was designed to evaluate escalated doses of CPT-11 and MMC administered every two weeks. Five escalating dose levels were studied (CPT-11/MMC: 100/5; 125/5; 150/5; 150/7; 150/10 mg/m²).

Results: Thirty-one patients were enrolled. Thirty patients were assessable for toxicity and tumor response for 89 treatment cycles. The median age was 60 years (32-73 years), and most patients (90%) had a performance status of 0 to 1. Fourteen patients were previously treated and 17 were chemotherapy-naive. The MTD was CPT-11 150 mg/m² plus MMC 10 mg/m², in which all three patients experienced grade 4 neutropenia, including one episode of prolonged and one of febrile neutropenia, and one patient experienced grade 3 diarrhea during the first cycle. Fifteen partial responses were observed.

Conclusions: The RD based on this phase I—II study was CPT-11 150 mg/m² plus MMC 5 mg/m² administered every two weeks. This combination demonstrates promising activity against advanced gastric cancer and warrants further investigation in another phase II study.

Key words: chemotherapy, clinical trial, gastric cancer, irinotecan (CPT-11), mitomycin-C, phase I—II study

Introduction

Despite a declining incidence in many industrial countries, gastric cancer remains one of the most common malignancies worldwide. Although this tumor is potentially curable with surgery when diagnosed at an early stage, the prognosis in patients with unresectable or metastatic disease is very poor, with a median survival of 3–4 months when they receive the best supportive care alone, and of 7–10 months when they were treated with palliative chemotherapy [1–3]. Metastatic or unresectable gastric cancer is a systemic disease and combination chemotherapy has been extensively investigated. For the last decade, 5-fluorouracil (5-FU) has been the mainstay of systemic chemotherapy against advanced gastric cancer, and other active drugs such as mitomycin C (MMC), doxorubicin and cisplatin are commonly used as part of combination chemotherapy regimens [4]. Various combinations of active drugs have been investigated to determine whether the high response rate reported for some combination chemotherapies translates into improved survival [5–8]. However, some randomized control trials failed to demonstrate the superiority of 5-FU-based combination chemotherapy compared with 5-FU monotherapy [9–11]. In a randomized controlled trial by the European Organization for Research and Treatment of Cancer, investigators compared three commonly used regimens of FAMTX (a high-dose methotrexate followed by 5-FU in combination with doxorubicin) with ELF (etoposide, leucovorin, and bolus 5-FU) and FUP (an infusional 5-FU plus cisplatin). The findings of this trial demonstrated modest clinical efficacy for all three investigated regimens with no significant difference in overall survival [12]. In a recent randomized controlled trial in advanced gastric cancer, an infusional 5-FU-based combination chemotherapy with cisplatin and epirubicin (ECF) proved to be significantly superior to the FAMTX in terms of response rate, quality of life, and survival, suggesting that the ECF could be a new standard treatment in further clinical trials [13]. However, from the point of view of median survival in those large-scale randomized controlled trials, little substantial difference exists between one regimen and another. Therefore, there is a clear need for the clinical application of new agents with novel mechanisms of action that may improve the clinical outcome of this disease.

Irinotecan hydrochloride (CPT-11) is a semi-syn-
thetistic, water-soluble analog of camptothecin, which shows an anti-tumor activity through the inhibition of DNA-topoisomerase-I [14–17]. CPT-11 acts as a prodrug, i.e. CPT-11 is rapidly converted in vivo to its active metabolite SN38 by the function of carboxylesterase. Topoisomerase-I is a nuclear enzyme that induces single-stranded DNA breaks, relieving torsional strain during replication and transcription. SN38 binds to topoisomerase-I/DNA complex, preventing religation of DNA after cleavage by topoisomerase-I, which leads to cell death. CPT-11 shows the anti-tumor activity against various solid tumors, such as respiratory tract, gynecological, lymphoma, head and neck, urological and gastrointestinal tract cancers [18–21]. A Japanese phase II trial demonstrated that CPT-11 has an effect in advanced gastric cancers with the overall response rates of 23% (14 partial responses of 60 patients) and with the response rate of 16% (nine partial responses of 45 patients) for the previously treated patients [22]. In addition, a preclinical study demonstrated that CPT-11 shows synergism with cisplatin, Ara-C and MMC [23]. Among these drugs, cisplatin and MMC are active drugs against advanced gastric cancer. Boku et al. reported a high response rate in their phase II trial of CPT-11 combined with cisplatin in advanced gastric cancer with the overall response rate of 48% (21 of 44 patients) and the response rate of 27% (four of 15 patients) in previously treated patients [24]. The major toxicity was neutropenia and diarrhea. Although the combination of CPT-11 and cisplatin was effective, this combination was toxic and required aggressive hydration to reduce cisplatin-associated renal toxicity, and made it difficult to administer on an out-patient basis.

In the present study, we describe the phase I–II trial of CPT-11 combined with MMC, an active and widely-used drug in the treatment of advanced gastric cancer, to determine the maximum tolerated dose (MTD), the dose limiting toxicity (DLT) and preliminary anti-tumor activity.

Patients and methods

Eligibility

Patients enrolled in this study were required to fulfill the following eligibility criteria: (1) histological confirmation of gastric cancer; (2) unresectable or metastatic disease, or recurrence after gastrectomy; (3) measurable lesion; (4) age $\leq$ 75 years; (5) performance status (PS) $\leq$ 2 on the Eastern Cooperative Oncology Group (ECOG) scale; (6) no prior chemotherapy or prior-treated with less than two regimens not including MMC, although prior use of CPT-11 was allowed; (7) no chemotherapy within four weeks before entry; (8) adequate bone marrow function (WBC $\geq$ 4000 cells/mm$^3$ and platelet $\geq$ 100,000 cells/mm$^3$) (9) adequate liver function (serum bilirubin level $< 1.5$ mg/dl and serum transaminase level $< 2.5$-fold the upper limit of normal); (10) adequate renal function (serum creatinine level $< 1.5$ mg/dl, blood urea nitrogen level $\leq$ 25 mg/dl); (11) no other serious medical condition; (11) no other active malignancies; (12) written informed consent

This study was approved by the Institutional Review Board in the Cancer Institute Hospital, Tokyo, Japan and the National Cancer Center Hospital, Tokyo, Japan.

Pretreatment evaluation and follow-up

Pretreatment evaluation consisted of a complete history and physical examination, complete blood cell count (CBC), serum chemistry including electrolytes, liver and renal function test, tumor markers, ECG, chest X-ray, and computed tomography (CT) scan of the abdomen/pelvis and chest (if indicated), all sites of measurable lesions were initially documented using a CT scan. If indicated, upper GI endoscopy was performed. During the study period, patient monitoring included the assessment of clinical toxicities, CBC count, serum chemistry, and physical examination before each dose of chemotherapy. In addition, ECG, chest X-ray and measurement of the target lesions by CT scan were performed before each cycle and at the end of treatment. During the follow-up period, patients were evaluated every two months after the end of the study treatment, including physical examination, CBC count, serum chemistry, ECG, chest X-ray and CT scan of the measurable lesions in the case of tumor response or stable disease until documented disease progression

Treatment plan

On day 1 and day 15, mitomycin-C (Kyowa-hakko Co. Ltd, Tokyo, Japan) dissolved in 20 ml physiologic saline was administered as a bolus infusion and was immediately followed by a 90 min intravenous infusion of CPT-11 (Camptos, Yukaft Honsha Co. Ltd, Tokyo, Japan and Topotecin, Daiichi Pharmaceutical Company, Tokyo, Japan) diluted in 250 ml of 5% glucose solution. All patients received premedication with the antiemetic drug, granisetron, which was administered as an intravenous infusion. No other prophylactic treatment was used (e.g. anticholinergic drugs, granulocyte colony stimulating factor, corticosteroids or antibiotics). The first cycle of treatment was administered in the hospital to monitor the toxicity, and subsequent cycles were only administered on an outpatient basis. The second administration of MMC and CPT-11, scheduled on day 15, was withheld in instances of grade 2 or greater leukopenia, grade 1 thrombocytopenia, or grade 1 or greater diarrhea until their recovery. Before the next cycle was started, the leukocyte count had to be $\geq 3000$ cells/mm$^3$, and platelet count $\geq 100,000$ cells/mm$^3$, with no diarrhea observed, and the liver and renal function of eligibility criteria had to be within acceptable limits. The treatment was repeated until disease progression or severe toxicity was observed. The total dose of MMC had to be less than $50$ mg/m$^2$ in each patient to prevent the delayed cumulative toxicity due to MMC, such as thrombocytopenia, hemolytic uremic syndrome or pulmonary fibrosis [25–27]. In patients who had tumor response or stable disease after receiving the full dose of MMC, the treatment with CPT-11 alone was continued.

Dose escalation plan and toxicity evaluation

The starting doses of MMC and CPT-11 were 5 mg/m$^2$ and 100 mg/m$^2$, respectively, and the two drugs were administered on the same day every two weeks (day 1 and day 15). Five escalating dose levels of CPT-11 / MMC (100/5 mg/m$^2$, 125/5, 150/5, 150/10) were studied (Table 1). Intra-patient dose escalation was not permitted. Toxicities were evaluated weekly and graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC). The DLT was defined as any grade 3 or higher non-hematological toxicity (except alopecia, nausea or vomiting) and hematological toxicity of neutropenia grade 4 (duration $\geq 4$ days or association with fever) or thrombocytopenia grade 4. Delay of administration due to toxicity of more than eight days was regarded as a DLT. At each dose level, three patients were initially enrolled, and if none of them experienced DLT during the first treatment cycle, the next cohort of three patients was tested at the next higher dose level. If any DLT was observed in one of the three patients, an additional three patients were enrolled at the same dose level. If two of the first three patients or three or more of six patients at any dose level experienced any DLT, the MTD had been reached and the dose level below the MTD was considered to be the recommended dose for further study. The determination of MTD was based on the toxicity observed in the first cycles of each patient.
Table 1  Patient characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dose level</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td>60</td>
<td>62</td>
<td>58</td>
<td>60</td>
<td>46</td>
<td>60</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td>49-73</td>
<td>56-70</td>
<td>37-69</td>
<td>47-71</td>
<td>32-66</td>
<td>32-73</td>
</tr>
<tr>
<td>ECOG performance status score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>2</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intestinal type</td>
<td></td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Diffuse type</td>
<td></td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>7</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>Previous chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>5</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>5-FU</td>
<td></td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>CDDP</td>
<td></td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

Patients who experienced DLTs in the first cycle at each dose level subsequently had their CPT-11 doses reduced in decrement of 25 mg/m² when the treatment was continued.

Response and survival evaluation

Tumor response was assessed by CT scan of the target lesions before each cycle of chemotherapy and at the end of treatment. Complete remission (CR), partial remission (PR), no change (NC) and progressive disease (PD) were defined according to the standardized response criteria of the WHO [29]. Tumor response was confirmed by an extramural review. The overall survival was calculated from the date of initiation of treatment to the date of death. The progression-free survival was calculated from the date of initiation of treatment to the date of disease progression assessed by the investigators. The duration of response was defined as the interval from the onset of PR to the first day when progression was noted. The time to remission was calculated from the date of initiation of treatment to the onset of PR.

Results

Patient population

Between March 1998 and August 1999, 31 patients with advanced gastric cancer were enrolled in this trial at the Department of Internal Medicine, Cancer Institute Hospital, Tokyo (15 patients) and Department of Gastrointestinal Oncology, National Cancer Center Hospital, Tokyo (16 patients), Japan. The characteristics of the patients are listed in Table 1. Twenty-three males and eight females were treated at five different dose levels. The median age of the patients was 60 years (range, 32 to 73 years), and the majority of the patients (90%) had a good performance status of 0 to 1. Fourteen patients had previously received chemotherapy, mainly in the form of 5-FU-based chemotherapy.

Treatment under study

In total, 89 cycles of therapy over five dose levels were administered (Table 2). Twenty-nine of 31 enrolled patients received at least one complete cycle of chemotherapy, and 30 patients were assessable for toxicity and tumor response. One patient was not assessable for toxicity during the first treatment cycle because the treatment was terminated after the first administration as a result of rapid tumor progression, and this patient was not involved in the assessment of toxicity (dose level 2). The tumor response of one patient treated with dose level 4 was not assessed because of the absence of any measurable lesion, as he/she only presented an evaluable primary gastric tumor. There were no treatment-related deaths. Two early deaths occurred due to disease progression, one which was a rapid progression (brain metastasis) and the other a progressive peritoneal carcinomatosis associated with perforation of the jejunum and fistula to the abdominal wall. Twenty-two patients (70%) received more than two cycles of treatment on an out-patient basis without any treatment-related hosp-
talizations during the treatment period. The treatment was terminated after the first cycle in nine patients according to the protocol, as they presented progressive disease (eight patients) or refused further treatment (one patient). Eight patients received the maximum dose of MMC (50 mg/m² per patient) allowed in this protocol.

Toxicity observed in the first cycle of treatment

The toxicities observed in the first cycle of treatment are summarized in Table 3. Neutropenia and diarrhea were the principal dose-limiting toxicities of this drug combination. At dose level 1, one patient experienced grade 4 neutropenia in the first cycle and recovered within three days. Non-hematological toxicity was limited to mild nausea and vomiting, and no diarrhea was observed at dose level I. At dose level 2, seven patients were enrolled, and two episodes of grade 4 neutropenia occurred in the first cycle, both of which were resolved within three days. However, the treatment was delayed (> 8 days; DLT) in one patient, in whom the second administration scheduled on day 15 was given on day 26 because of a prolonged leukocytopenia. Severe diarrhea (grade 4) was observed in one patient. At dose level 3, one patient experienced the prolonged (>4 days) neutropenia grade 4, and another patient experienced severe diarrhea (grade 4). At dose level 4, none of three patients initially enrolled experienced any hematological toxicity, and non-hematological toxicity was also mild. However, at dose level 5, all three patients experienced grade 4 neutropenia, which included prolonged or febrile grade 4 neutropenia in two patients. In addition, one patient experienced severe diarrhea (grade 3). This precluded dose escalation above this dose level, and we determined that the dose level 5, in which MMC 10 mg/m² and CPT-11 150 mg/m² were administered, was the maximum tolerated dose with the dose-limiting toxicity being neutropenia. Consequently, an additional nine patients were enrolled onto dose level 4 (12 patients in total). Two of these patients experienced grade 4 neutropenia and one patient experienced grade 3 diarrhea.

In general, the median nadir neutrophil count was 1.072 cells/mm³ (range; 30–3520 cells/mm³). It typically occurred by day 15 (median; range 7–31 days) and was resolved shortly thereafter. The effects on platelets were modest. The effects on RBCs were also mild. Mild nausea and vomiting (≤ grade 2) was observed at all dose levels, but never prevented the continuation of treatment.

Toxicity observed in overall treatment cycles

The toxicities observed in all treatment cycles are summarized in Table 4. Eighty-nine cycles in total were administered to 31 patients. Neutropenia and diarrhea were the major toxicities of this drug combination. The
incidence of grade 4 neutropenia and severe diarrhea (grades 3 and 4) were 11.2% (10 episodes in 89 cycles) and 4.4% (4 episodes in 89 cycles), respectively. The majority of episodes of grade 4 neutropenia (nine of 10 episodes of grade 4 neutropenia) and severe diarrhea (all four episodes of grades 3 and 4) were observed in the first cycles of treatment. This indicates that dose reduction of CPT-11 was effective in preventing the recurrence of toxicity in an individual patient. Anemia requiring RBC transfusions did not occur. The acute cholinergic syndrome was not observed in this study. The diarrhea observed in the present study was all delayed diarrhea which generally developed 5 to 10 days after the administration of CPT-11. Delayed diarrhea was successfully managed with loperamide, and all patients could continue treatment with CPT-11. The non-hematological toxicity other than diarrhea was mild to moderate. Nausea and vomiting were uncommon and mild with the routine use of a prophylactic antiemetic therapy involving granisetron. Grade 2 emesis was observed in 10% of patients overall (10 episodes in 89 cycles). Fatigue was mild and infrequent. Mild and transient increase in hepatic enzymes (GOT, GPT) were rarely observed during treatment. Increase in creatinine and BUN occurred in one patient (grade 2). Twenty patients had alopecia (grade 1 in 14 patients, grade 2 in 6 patients).

**Antitumor activity and survival**

Although antitumor activity was not the primary endpoint, significant antitumor activity was seen at all dose levels. (Table 5) Fifteen of 30 response-assessable patients achieved an objective response, including one complete response, resulting in an overall response rate of 50% (95% confidence interval (95% CI): 32%–67%). Five of 14 patients (36%; 95% CI: 11%–61%) with prior chemotherapy and 10 of 16 chemotherapy-naïve patients (62.5%; 95% CI: 39%–86%) achieved an objective response. Fourteen of 27 patients who received a dose of MMC and CPT-11 below the MTD (dose levels 1 to 4) achieved objective responses (response rate 51.8%; 95% CI: 33%–71%). The median time to response was 41 days (range: 20–83 days) and the median response duration was 124 days (range: 39–297 days). The median overall survival time was 260 days, and the one-year survival rate was 36% (median follow-up time: 545 days). The median progression-free survival time was 135 days.

**The maximum tolerated dose and the recommended dose for further trials**

Based on findings obtained during the first cycle of treatment, it was suggested that the MTD is MMC 10 mg/m² and CPT-11 150 mg/m² with a bi-weekly schedule and that the dose-limiting toxicity is neutropenia. The toxicity observed at dose levels 3 and 4, in which the doses of MMC were different but the doses of CPT-11 were similar, were both acceptable, and the antitumor activity equivalent between them. Therefore, it was suggested that the recommended dose for the phase II study is dose level 3 (MMC 5 mg/m² plus CPT-11 150 mg/m²) which had more substantial benefit context an outpatient setting.

**Discussion**

In this dose determination study, we found that a combination of CPT-11 and MMC is feasible. The primary endpoint of this study was to determine the maximum tolerated dose, the dose limiting toxicity and the recommended dose in CPT-11 combined with MMC administered according to a bi-weekly schedule in patients with advanced gastric cancer. The MTD was determined to be dose level 5 (CPT-11 150 mg/m² and MMC 10 mg/m²), and the dose-limiting toxicity was neutropenia. The recommended dose for further study was dose level 3 (CPT-11 150 mg/m² and MMC 5 mg/m²). Neutropenia was observed at all dose levels evaluated but was brief and reversible without serious sequelae except at the highest dose level, where all patients experienced grade 4 neutropenia and two of them experienced prolonged or febrile neutropenia. At the recommended dose, the main toxicities per patient were neutropenia (grade 4, 17%) and diarrhea (grade 4, 17%). Patients who experienced DLTs in the first cycle subsequently had CPT-11 doses reduced by 25 mg/m², and did not experience severe toxicity again. Diarrhea was frequent but manageable using an early antidiarrheal therapy involving loperamide. It was therefore not judged to be dose-limiting. The severity of diarrhea was not associated

**Table 5. Objective response.**

<table>
<thead>
<tr>
<th>Dose level</th>
<th>No. of patients</th>
<th>No. of responders</th>
<th>Response rate (%)</th>
<th>Time to remission (days)</th>
<th>Response duration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>1</td>
<td>33</td>
<td>73</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>4</td>
<td>57</td>
<td>26</td>
<td>25–70</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>3</td>
<td>50</td>
<td>43</td>
<td>27–73</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>6</td>
<td>54</td>
<td>57</td>
<td>20–83</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>1</td>
<td>33</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>30</td>
<td>15</td>
<td>50</td>
<td>41</td>
<td>20–83</td>
</tr>
</tbody>
</table>
with the CPT-11 dose. Nausea and vomiting were mild with prophylactic use of antiemetic therapy. Since MMC has a cumulative toxicity in the form of delayed thrombocytopenia or anemia, pulmonary fibrosis and hemolytic uremic syndrome, the total dose of MMC was kept to less than 50 mg/m² per patient to avoid those toxicities in the present study. Within the dose range and follow-up period evaluated in the present study, this measure was effective in preventing these toxicities.

In the present study, CPT-11 and MMC were administered on the same day of a bi-weekly schedule. CPT-11 is an inhibitor of DNA topoisomerase-I, an enzyme responsible for variations of the topological form of DNA during replication and transcription [30]. The cytotoxic effect of CPT-11, and especially of its active metabolite SN38, is specific to the S-phase of the cell cycle. Theoretically, the activity of cell-cycle specific drugs is postulated to be exposure time-dependent rather than concentration-dependent, and frequent or prolonged administration is recommended because such administration schedules could increase the likelihood that the exposure of tumor cells to drugs while in the S-phase results in increasing antitumor activity [31]. However, in vitro preclinical studies of CPT-11 have yielded conflicting results in terms of its schedule-dependency. Several studies have shown that camptothecin analogs are more effective when administrated in prolonged low-dose schedules in a preclinical setting than when given at higher doses for shorter duration despite the similarity of the similar total doses [32, 33]. Others have reported that the activity of CPT-11 was not apparently schedule-dependent [34]. The schedule-dependent cytotoxicity of CPT-11 is also not known in the clinical setting. Phase I studies of CPT-11 in metastatic colorectal cancer in Japan, Europe and the United States were performed using different administration schedules including weekly, bi-weekly and once every three weeks, resulting in different recommended dosages and schedules [20, 35–37]. In terms of efficacy, however, the different administration schedules have demonstrated comparable antitumor activity in phase II studies in metastatic colorectal cancer. Therefore, the optimal clinical administration schedule of CPT-11 is still uncertain at present. From the practical point of view, bi-weekly administration of CPT-11, the procedure used in the present study, appears to be a good compromise between the weekly and once every three weeks schedule, at least with respect to compliance of both patient and physician, operating on an easily handled outpatient basis.

A recommended dose of CPT-11 as a bi-weekly monotherapy for Japanese patients is 150 mg/m². In the phase I–II study of CPT-11 combined with cisplatin of 80 mg/m²/course in patients with advanced gastric cancer reported by Shirao et al., the recommended dose of CPT-11 was 70 mg/m² administered in a bi-weekly schedule, a dosage which was 46% of the recommended dose in the monotherapy [38]. However, CPT-11 and MMC could be combined without a dose-reduction of each drug and an almost full-dose combination of CPT-11 (150 mg/m² bi-weekly) and MMC (5–7 mg/m² bi-weekly) was shown in the present study to be possible and to have acceptable toxicity. One possible explanation of this finding is that the pattern of hematological toxicity is different for CPT-11 and for MMC; it is typically acute leukocytopenia in CPT-11 and delayed thrombocytopenia in MMC, and there is no overlap in acute non-hematological toxicity between CPT-11 and MMC. The present findings suggest that the full-dose combination of this regimen should provide considerable advantages in the clinical setting in terms of maximizing synergism between the two drugs and their dose intensities, and determining their compatibility with additional drugs.

Although tumor response was not the primary endpoint in the present dose-finding study, sufficient activity has been observed in advanced gastric cancer to encourage further clinical investigations of this chemotherapy combination. Among 30 assessable patients, 15 objective responses including one complete response was achieved and the overall response rate was 50% with a 95% CI of 32 and 68%. The response rate in chemotherapy-naive and prior treated patients was 65% and 36%, respectively. Objective responses were obtained at all dose levels. Tumor responses were observed in all disease sites including primary lesions, liver and lymph node metastases. This response suggests that CPT-11 combined with MMC is very active against advanced gastric cancer and that there is little cross-resistance with 5-FU-based regimens. This combination therapy should be clinically investigated as a first line chemotherapy as well as second line chemotherapy for 5-FU-failure. Although this was a dose-finding study involving small numbers of patients of various dose levels, significant antitumor activity was observed to warrant further evaluation. Evaluation of this combination chemotherapy for colorectal and gastric cancer is currently underway in the Japan Clinical Oncology Group.

Acknowledgements

This study was supported, in part, by a Grant-in-Aid for Cancer Research (11S-3) from Ministry of Health and Welfare, Japan. The authors thank Dr Mace L. Rothenberg for his fruitful discussion and for comments about the manuscript.

References

3 Pyrhönen S, Kuitunen T, Nyandoto P et al. Randomized comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX)


Received 28 May 2001; accepted 28 June 2001

Correspondence to:
T. Yamao, MD, PhD
Dept. of Internal Medicine
Cancer Institute Hospital
1-37-1 Kami-ikebukuro Toshima-ku, Tokyo 170-8455
Japan
E-mail: tyamao-gi@umin.ac.jp