Weekly High-dose 5-Fluorouracil (5-FU), Leucovorin (LV) and Bimonthly Cisplatin in Patients with Advanced Gastric Cancer

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Background: A phase II clinical trial was performed to evaluate the activity and toxicity of bimonthly cisplatin and weekly 24-h infusion of high-dose 5-fluorouracil and leucovorin in patients with advanced gastric cancer.

Patients and methods: From September 1997 to March 1998, 23 chemo-naive patients of advanced gastric cancer were enrolled in this study. The regimen consisted of weekly 24-h infusion of 5-FU (2600 mg/m²) and LV 150 mg and bimonthly cisplatin (25–50 mg/m²) bolus for 12 weeks followed by a 2-week break.

Results: There were 10 male and 13 female patients with a median age of 52 years. A total of 428 chemotherapy treatments were given with a mean of 11. Seventeen patients were evaluable for response. There were 41% (7/17) partial response, 18% (3/17) stable disease and 41% (7/17) progressive disease. The grade III or IV toxicity included anorexia 35% (8/23), fatigue 26% (6/23), vomiting 17% (4/23) and mucositis 9% (2/23). One patient developed perforated duodenal stump after chemotherapy. One patient died of hyperammonemia-related coma. The median times to disease progression and overall survival were 3.5 and 7 months, respectively.

Conclusions: This regimen showed modest activity against gastric cancer. However, there was no survival advantage and there was greater toxicity than with weekly high-dose 5-FU–LV alone.

Key words: chemotherapy – stomach neoplasms – fluorouracil – cisplatin

INTRODUCTION

Gastric cancer is the second leading cancer worldwide, with a current 5-year survival rate of <20% (1,2). About 25% of patients with gastric cancer are associated with disseminated disease at presentation and more than half of patients with localized disease recur within 5 years (1–6). Advanced disease is incurable and patients will be treated by chemotherapy if their condition allows. A number of effective chemotherapy combination regimens have been developed in advanced and metastatic gastric cancer, but there is no worldwide consensus regarding a standard regimen. 5-Fluorouracil (5-FU)-based regimens, used either alone or in combination with other drugs, are commonly used in general clinical practice, but the response rate is only 20–50% with very few complete responses (6–11). To date, most of the chemotherapy to patients with metastatic gastric cancer has been for palliation only.

Our previous studies using weekly high-dose 24-h infusion of 5-FU and leucovorin (LV) to chemotherapy-naive patients with gastric cancer revealed a partial response rate of 33% (95% confidence interval: 18–50%) and a median survival of 7 months (12). This regimen was considered to be effective and with acceptable toxic profiles for patients with gastric cancer, even in patients with poor performance status. However, there were no complete responses and the responses were not durable. We therefore suggest that this regimen should be modified as a basis for combination trials to improve the response rate and survival duration by overcoming the drug resistance of 5-FU. Cisplatin is probably the second most common agent employed for gastric cancer in Europe, much more common.
than anthracyclines. The combination of 5-FU and cisplatin in patients with gastric cancer has been tested (13–15). Cisplatin was found to have a synergistic effect when combined with 5-FU in experimental models. Administration of cisplatin inhibited intracellular L-methionine metabolism, thus resulting in a several-fold increase in reduced folate and enhanced the 5-FU cytotoxicity (16). The 5-FU and cisplatin combination is considered to be one of the standards or reference regimens for gastric cancer in many centers. There have been three phase II studies in Europe, using infusional 5-FU with cisplatin; the response rates ranged from 41 to 48% and median overall survivals were 9–10 months (13–15). In addition, a randomized phase III study in Korea showed that the 5-FU and cisplatin combination was better than 5-FU, adriamycin, mitomycin C (FAM) or 5-FU alone in terms of response rate and time to progression (17). We therefore suggest that cisplatin is a reasonable agent to combine with the weekly high-dose 5-FU–LV regimen to yield a higher response rate and longer duration than with 5-FU–LV alone. The original 5-FU–cisplatin combination usually gives cisplatin at a dose of 100 mg/m² every 3–4 weeks. Because we intended to use this regimen on an outpatient basis, we split the dose of cisplatin to 50 mg/m² twice a month. Actually, the dose intensity is equal to the common 5-FU–cisplatin combination. Consequently, we designed this phase II prospective clinical trial by using weekly high-dose 5-FU–LV and bimonthly cisplatin combination in patients with gastric cancer.

PATIENTS AND METHODS

All patients were required to have a known primary gastric cancer beyond hope of cure, that is, histological proof of residual primary, recurrent or metastatic disease. The tumors were required to be radiologically measurable or evaluable. Patients should have no prior chemotherapy, a Karnofsky performance status ≥30, absolute granulocyte count ≥1500/ml, platelet count ≥100 000/ml, serum creatinine concentration ≤2 mg/dl and serum bilirubin ≤3.0 mg/dl. Written informed consent was obtained prior to therapy.

All patients received a central vascular device through subclavian vein for outpatient infusion therapy. The chemotherapy consisted of 5-FU 2600 mg/m² with LV 150 mg, which was infused simultaneously through a portable pump for 24 h. It was preceded by a bolus infusion of cisplatin 25–50 mg/m² in 0.9% saline, 500 ml for 3 h every other week. The first eight patients were treated with cisplatin at a dose of 50 mg/m². However, because unacceptable toxicity occurred in all of these patients, the dosage of cisplatin was reduced to 25 mg/m² on subsequent patients. Standard pre-medication with antiemetics such as steroids and serotonin antagonist was given. Patients were planned to have chemotherapy every week for 12 weeks, then a 2-week rest. If a grade III hematomlogical or gastrointestinal toxicity (according to the WHO Toxicity Guidelines) was observed, the dose of cisplatin was reduced to 25 mg/m². The course of chemotherapy was repeated every 14 weeks until disease progression, unacceptable toxicity or patient refusal.

Prior to the therapy, all patients were evaluated by a complete history review, physical examination, complete blood counts, biochemistry profile, serum tumor marker, chest roentgenogram and abdominal computed tomography (CT) scan. Patients were re-assessed after 12 weeks by the same procedures. In instances of clinical suspicion of progressive disease (PD) during treatment, the evaluation was performed immediately. Complete response (CR) was defined as the disappearance of all measurable disease based on the image studies. Partial response (PR) was defined as a ≥50% decrease in the sum of the products of the largest perpendicular diameters of all the measurable lesions or a decrease of at least 50% of the one dimension of the evaluable lesions for at least 4 weeks without the appearance of the new lesions. Stable disease (SD) was defined as a decrease of the lesions for at least 4 weeks, which did not reach the criteria of PR or a <25% increase of lesions. PD was defined as a ≥25% increase in the size of one or more evaluable lesions or the appearance of new lesions. The presence of ascites was not considered to be a criterion of measuring response; however, a new appearance of ascites was considered to be a progression.

The estimated sample size was 29 patients under an expected response rate of 30% using Simon’s two-stage design. However, because of the toxicity, this study was terminated early after internal review. The time to progression was measured from the start of the therapy to the date of progression. One patient who died without observing evidence of disease progression was treated as an ‘event’ at the time of death. Otherwise, such a patient was censored at the time of latest examination certifying no evidence of progression. The survival time was calculated from the start of the therapy to the date of death and survival time was established by the Kaplan–Meier method.

RESULTS

From September 1997 to March 1998, 23 consecutive patients were registered in this study. The patients’ characteristics are summarized in Table 1. There were 10 males and 13 females with a median age of 52 years (range, 24–70 years). The mean Karnofsky performance status was 65.7% (range, 50–80%). The sites of diseases included stomach (14), peritoneum (11), intra-abdominal lymph nodes (6), liver (3), bone (1) and ovary (1).

A total of 428 chemotherapy treatments were given (range, 1–19) with a mean of 11. Dose reduction of cisplatin or termination of the studies due to unacceptable toxicity was required for the first eight patients using cisplatin at 50 mg/m². The toxicities included WHO grade III or IV thrombocytopenia (one patient), nausea or vomiting (three patients), mucositis (one patient), hand–foot syndrome (one patient), consciousness change (two patients) and grade II or III fatigue (five patients). Among them, one patient died of consciousness disturbance from hyperammonemia. Therefore, we decided to reduce the
dose of cisplatin to 25 mg/m² for the following 15 patients. After dose reduction, none of the patients left the study due to toxicity, only one patient had grade III vomiting and one had grade III mucositis.

Only 17 patients were eligible for analyzing response. The overall response rate was 41% (7/17) (95% confidence interval: 17–67%) without any complete response; 18% of the patients showed stable disease and 41% developed progressive disease. All of the responders were in the group of patients receiving 25 mg/m² cisplatin. The response rate in this subset, therefore, was 47%. However, the study’s intend-to-treat response rate was 30%. The median follow-up period was 7 months. The overall median time to disease progression was 3.5 months. The overall median survival was 7 months (Fig. 1).

**DISCUSSION**

The present study revealed a 41% response rate but a significant toxicity compared with the previous 5-FU–LV trial, while the survival was the same (12). Most of the grade III or IV side effects occurred in the first eight patients who received bimonthly 50 mg/m² cisplatin prior to 5-FU–LV infusion. Among these patients, fatigue was the most common toxicity, followed by nausea and vomiting. The most disturbing adverse effect, fatigue, led to the reduction of cisplatin to 25 mg/m² on the subsequent 15 patients. After the reduction, the toxicity was manageable and the patient compliance improved. In addition, four patients survived longer than 18 months, which was not frequently seen in patients received 5-FU–LV alone (12). The durable responses were attributed to the inhibition of resistant clones by combination chemotherapy.

In comparison with those of the 5-day infusion of 5-FU and cisplatin combination, the response rate and the survival of the present study did not differ, but the toxic profile was better (13–15). Chi et al. (18) used weekly 24-h infusion of high-dose 5-FU–LV with cisplatin, epidoxorubicin and etoposide and

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**Table 1.** Patients’ characteristics (n = 23)

<table>
<thead>
<tr>
<th>Gender</th>
<th></th>
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<tbody>
<tr>
<td>Male</td>
<td>10</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>52 (range 24–70)</td>
</tr>
<tr>
<td>Performance status (Karnofsky)</td>
<td>65.7 (mean, range 50–80)</td>
</tr>
<tr>
<td>80–90%</td>
<td>7</td>
</tr>
<tr>
<td>60–70%</td>
<td>12</td>
</tr>
<tr>
<td>40–50%</td>
<td>4</td>
</tr>
<tr>
<td>Tumor site</td>
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<tr>
<td>Loco-regional</td>
<td>14</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>11</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>6</td>
</tr>
<tr>
<td>Liver</td>
<td>3</td>
</tr>
<tr>
<td>Bone</td>
<td>1</td>
</tr>
<tr>
<td>Ovary</td>
<td>1</td>
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</table>

**Table 2.** Maximum toxicity grade (WHO) (n = 23)

<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
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<tbody>
<tr>
<td>Leukocytes</td>
<td>19 (83%)</td>
<td>1 (4%)</td>
<td>3 (13%)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Platelets</td>
<td>20 (87%)</td>
<td>1 (4%)</td>
<td>2 (9%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mucositis</td>
<td>12 (52%)</td>
<td>5 (22%)</td>
<td>4 (17%)</td>
<td>2 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>8 (35%)</td>
<td>6 (26%)</td>
<td>5 (22%)</td>
<td>3 (13%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (22%)</td>
<td>5 (22%)</td>
<td>7 (30%)</td>
<td>6 (26%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20 (87%)</td>
<td>3 (13%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neurotoxicity*</td>
<td>21 (91%)</td>
<td>0</td>
<td>0</td>
<td>2 (9%)</td>
<td></td>
</tr>
<tr>
<td>Hand–foot syndrome</td>
<td>19 (83%)</td>
<td>0</td>
<td>3 (13%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
</tbody>
</table>

*Hyperammonemia-associated toxicity.

The toxicity profiles are summarized in Table 2. Grade III or IV toxicity included fatigue 26% (6/23), vomiting 17% (4/23) and mucositis 9% (2/23). In addition, one patient had a perforated duodenal stump immediately after the first dose of chemotherapy. Two patients showed hyperammonemia-associated consciousness changes. One patient developed visual hallucination and incoherent speech during infusion, but recovered spontaneously after chemotherapy. The other patient showed consciousness disturbance, fever and hypotension with an elevation of serum ammonia level during chemotherapy, and died later due to uncontrolled shock. His case was considered to be treatment-related death. A patient complained of acute upper abdominal pain with a standing chest film of subphrenic free air 4 days after the first dose of chemotherapy. An emergency laparotomy was performed which revealed a perforated peptic ulcer at the duodenum. He survived after surgery but was removed from the study later.
reported <10% grade III or IV toxicity. The favorable toxicity profile may attributed to the different cisplatin infusion schedule and low-dose chemotherapy (18). Kretzschmar et al. (19) applied a weekly 24-h infusion of high-dose 5-FU plus LV in combination with mitomycin C; a response rate of 37% was reported without complete response. There were 23% grade III neutropenia and 13% grade III thrombocytopenia. However, the median time to disease progression and overall survival were only 5 and 7 months, respectively. In addition, Boke-meyer et al. (20) reported a combination of weekly high-dose 5-FU–LV and paclitaxel. Among the 26 patients with gastric cancer, the response rate was 32% without complete response. However, the progression-free survival and median overall survival were up to 8 and 11 months, respectively. There were 14% grade III/IV neutropenia and 45% alopecia from the toxicity of paclitaxel. The combination was suggested to be comparable to ELF or FAMTX and the toxicity allowed administration on an outpatient basis (20). However, there was no randomized comparison to confirm the superiority of weekly high-dose 5-FU–LV combination over others. There is an ongoing randomized trial of a weekly high-dose 5-FU–LV-based regimen, which may answer this question (21).

The unusual complication of fatigue was not seen with the 5-FU–cisplatin combination when the 5-FU was given as a 5-day continuous infusion and 100 mg/m² cisplatin as a 3-h infusion in patients within the same ethnic population (22), but was seen in patients with weekly high dose 5-FU–LV alone, where 90% of patients experienced a mild degree of fatigue (12). However, the severity of fatigue was much higher in the present trial where 26% of the patients experienced WHO grade II or III fatigue and five patients dropped out owing to fatigue. The increased frequency and severity of fatigue may be related to the addition of cisplatin to the 5-FU–LV-based regimen. However, a weekly high-dose 5-FU–LV and cisplatin combination has been reported in patients with gastric cancer and nasopharyngeal carcinoma in the same patient ethnic group, but the cisplatin was administered as a 24-h continuous infusion (18,23). The authors did not report the toxicity of fatigue and claimed that the overall toxicity was minimal. Whether the change of cisplatin infusion schedule results in decreased fatigue in patients with gastric cancer remains elusive. 5-FU chemotherapy-related hyperammonemia was a complication from high-dose 5-FU infusion therapy. It has been reported in the literature, but its mechanism remains unclear (24). In our previous study, three patients had similar hyperammonemia-associated consciousness changes; two recovered spontaneously after discontinuation of the therapy and the third died owing to profound consciousness changes. The present study did not show an increase in the frequency of hyperammonemia compared with the previous 5-FU–LV alone therapy.

Weekly high-dose 5-FU–LV has a modest response for patients with gastric cancer and with acceptable toxicity. This promising regimen has been increasingly used as a base of combination chemotherapy for gastric cancer, although it has not been proved by randomized trials. We added cisplatin to this regimen and obtained an equal response rate but increased toxicity compared with 5-FU–LV alone. We conclude that there was no advantage in combining 25–50 mg/m² of bimonthly cisplatin with high dose 5-FU–LV. We should look for other active agents to combine with the 5-FU–LV-based regimen such as taxanes, CPT-11 and oxaliplatin.

Acknowledgment

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References


