A Phase II Study of Sequential Methotrexate and 5-fluorouracil Chemotherapy in Previously Treated Gastric Cancer: A Report from the Gastrointestinal Oncology Group of the Japan Clinical Oncology Group, JCOG 9207 Trial

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Objective: As prognosis of advanced gastric cancer is still poor, a standard regimen after first-line fluorouracil (FU)-based chemotherapy has not yet been established. Therefore, we conducted a phase II study to evaluate the efficacy and toxicity of sequential treatment with methotrexate (MTX) and also 5-FU as second-line chemotherapy in patients with advanced gastric cancer.

Methods: Treatment consisted of weekly doses of MTX (100 mg/m², i.v. bolus), followed by 5-FU (600 mg/m², i.v. bolus) 3 h after MTX administration. Leucovorin rescue therapy (six doses of 10 mg/m², given at 6-h intervals) was commenced 24 h after a treatment with MTX. The primary endpoint was the response rate.

Results: Between December 1992 and June 1995, 56 patients were registered in this study and one was ineligible. All registered patients were included in all analyses. The median age of the patients was 60 (20–75 years). Most patients (75%) had a performance status of 0 or 1, and 51 (90%) received 5-FU-based chemotherapy as first-line treatment. The major adverse events were myelosuppression and gastrointestinal toxicity. Grade 4 neutropenia occurred in 6.3% of the patients. The overall objective response rate was 9.0% [five partial responses among 56 patients, 95% confidence interval (CI): 3.0–20%]. The median overall survival time was 237 days, and the 1-year survival proportion was 21.4%.

Conclusions: Sequential MTX/5-FU therapy provides good survival outcomes with tolerable toxicity despite a limited response in patients with previously treated advanced gastric cancer. This regimen is now being evaluated in a randomized study in patients with pretreated advanced gastric cancer, by the Japan Clinical Oncology Group.

Key words: methotrexate – 5-fluorouracil – gastric cancer – second-line chemotherapy
INTRODUCTION

Gastric cancer is the most common cancer in Japan and many other Asian countries. Mortality statistics show that around 50,000 patients die from gastric cancer every year in Japan (1). Primary tumor resection is the best strategy for the treatment of gastric cancer. In patients with curatively resected Stages I–III gastric cancer, the 5-year survival proportion is ≥50%, but remains ≤10% in Stage IV or recurrent disease. Some randomized trials have demonstrated that fluorouracil (FU)-based regimens improve survival proportions in patients with advanced gastric cancer, as compared with supportive care alone (2–4). Although this survival advantage is significant as first-line treatment, no randomized study has shown a survival benefit of any second-line regimen for patients with metastatic gastric cancer failed to first-line FU-based chemotherapy, as compared with best supportive care.

Methotrexate (MTX) enhances the cytotoxicity of 5-FU by inhibiting the synthesis of DNA, RNA or both when 5-FU is administered several hours after MTX (5,6). A meta-analysis of randomized trials of sequential MTX/5-FU therapy revealed a higher response rate and longer survival as compared with single-agent bolus 5-FU chemotherapy in patients with colorectal cancer. Toxicity with these sequential MTX/5-FU regimens was similar to that with 5-FU alone (i.e. vomiting, stomatitis, diarrhea and leukopenia) (7,8). The sequential MTX/5-FU therapy was also found to be effective against advanced gastric cancer as shown in phase II trials (9,10). One Japanese phase II trial of sequential MTX/5-FU therapy in advanced gastric cancer reported response rates of 23% [13 partial responses (PRs)/56 patients] and 41% (15 PRs/37 patients) with low- and intermediate dose MTX regimens, respectively (11). Several reports indicated that a 7- to 24-h interval between MTX and 5-FU may provide an advantage of efficacy. However, a longer than 7-h interval cannot be used on an outpatient basis. In Japan, a 3-h interval between MTX and 5-FU regimens has been verified to be safe and oncologic in patients with advanced gastric cancer (11). Therefore, we decided to adopt a 3-h interval in the present study.

In 1990s, the sequential MTX/5-FU therapy was widely used as an option for advanced gastric cancer in Japan. At that time, however, other active drugs, such as irinotecan (CPT-11) and taxanes, were unavailable. The results of in vitro studies showed that bolus and continuous administrations of FU had different mechanisms of cytotoxicity and resistance, thereby resulting in incomplete cross-resistance between pulse and prolonged exposure to FU (18,19). Therefore, the sequential MTX/5-FU therapy, in which 5-FU was given by bolus infusion, was used empirically without clinical evidence in patients who failed to respond to infusional FU-based regimens, such as 5-FU alone or 5-FU/cisplatin. This background led to the present phase II clinical trial assessing the efficacy and toxicity of sequential MTX/5-FU chemotherapy in patients with pretreated advanced gastric cancer, conducted by the Japan Clinical Oncology Group (JCOG 9207 study).

PATIENTS AND METHODS

ELIGIBILITY

All patients enrolled in this trial fulfilled the following eligibility criteria: (i) histologically confirmed gastric cancer, (ii) unresectable or recurrent disease, (iii) treated with one prior regimen until disease progression or unacceptable toxicity after discontinuing palliative or adjuvant chemotherapy, (iv) a wash-out period of at least 4 weeks since the last chemotherapy treatment, (v) measurable or assessable disease, (vi) age ≤75 years, (vii) performance status (PS) ≤3 on the Eastern Cooperative Group (ECOG) scale, (viii) adequate bone marrow function (WBC ≥ 4000/mm³, platelets ≥ 100 000/mm³), (ix) adequate liver function (serum total bilirubin level ≤ 2.0 mg/dl, transaminase level ≤ 2.5-fold the upper limit of normal), (x) adequate renal function [serum creatinine ≤ 1.5 mg/dl, blood urea nitrogen (BUN) ≤ 25 mg/dl, creatinine clearance ≥ 50 ml/min], (xi) a normal electrocardiogram, (xii) a life expectancy of at least 8 weeks and (xiii) provision of written informed consent. Patients with active gastrointestinal bleeding, synchronous carcinomas, large amounts of pleural effusion or ascites, central nervous system metastasis, concurrent uncontrolled disease, or severe psychiatric disease were excluded. Pregnant or nursing women were also excluded. The study protocol was approved by the JCOG Clinical Trial Review Committee and by the institutional review board of each participating center.

TREATMENT PLAN

The treatment schedule consisted of a weekly dose of MTX (100 mg/m², i.v. bolus) followed by 5-FU (600 mg/m², i.v. bolus) after a 3-h interval. Leucovorin rescue therapy (10 mg/100 mg/m², i.v. bolus) followed by 5-FU (600 mg/m², i.v. every 6 h, for a total of six doses) was commenced 24 h after MTX administration. To prevent MTX-induced nephrotoxicity, acetazolamide (250 mg) was given intravenously immediately after MTX infusion, and sodium bicarbonate (33.3 mEq) dissolved in 500 ml of normal saline was administered by drip infusion for urinary alkalization during the 3-h interval between the doses of MTX and 5-FU. Before each cycle, the patients had to meet the following criteria: WBC ≥ 3000/mm³, platelet count ≥ 75 000/mm³, adequate liver and renal function as defined in the eligibility criteria, a PS of 0–3 and no grade ≥ 2 toxicity. The treatment was terminated if the disease progressed within 4 weeks or if a complete response (CR), PR or minor response (MR) was not achieved within 8 weeks. Otherwise, the treatment was repeated until disease progression or severe toxicity was confirmed.

EVALUATION OF RESPONSE AND TOXICITY

Baseline evaluations included a complete medical history, physical examination, complete blood cell count, serum chemistry, creatinine clearance, urinary analysis, electrocardiography, gastroscopy, gastrography, abdominal computed
tomography, abdominal ultrasonography and chest radiography. Hematologic, serum chemical and urinary analyses and symptoms were monitored on a weekly basis during the treatment. The objective response was evaluated every 4 weeks. CR, PR, no change (NC), progressive disease (PD) or not evaluated (NE) were defined according to the response assessment criteria proposed by the Japanese Research Society of Gastric Cancer (12). The tumor response was confirmed by central review. Toxicity was evaluated according to the JCOG common toxicity criteria (13) that were established on the basis of the National Cancer Institute Common Toxicity Criteria, ver.1.

STATISTICAL METHODS

The primary endpoint of this study was the tumor response rate. The secondary endpoints were overall survival and toxicity. Sample size was determined by feasibility reasons. Within a reasonable length of time (1.5 year of accrual), 15 participating institutions can recruit 50 subjects. This produces the width of 25% of its 95% CI for a point estimate around 30%.

An interim analysis was planned to test for the treatment inefficacy by examining whether the 90% upper confidence limit of the response rate would exceed 25% for the first evaluable 20–25 patients. Overall survival was calculated from the date of registration until the date of death, using the Kaplan–Meier method, and the CIs were calculated using the Greenwood’s formula.

All the analyses were conducted using SAS software (ver. 6.12; SAS Institute, Inc., Cary, NC, USA).

RESULTS

PATIENT POPULATION AND STUDY TREATMENT

Between December 1992 and June 1995, 56 patients were enrolled in the study at 15 hospitals. Although one patient was ineligible because of no previous chemotherapy, all analyses were conducted for all registered patients. Table 1 lists the demographic data, baseline disease and pretreatment characteristics. Thirty-eight men and 18 women were registered. The median age of the patients was 60 years (range, 25–75 years), and 42 of 56 patients (75%) had a good PS of 0 or 1. Fifty-one patients (91%) had received 5-FU-based chemotherapy as first-line treatment. A total of 419 doses of sequential MTX/5-FU therapy were administered to 56 patients. The median number of doses was 5 (range, 1–31). Forty-four of the 56 enrolled patients (78%) received four or more doses of sequential MTX/5-FU therapy. Treatment was terminated because of the disease progression in 38 patients, toxicity in seven, patient refusal in four, death in four and others in three.

TOXICITY

Toxic effects occurring during the study are summarized in Table 2. The major toxicities were myelosuppression and gastrointestinal toxicity. Grade 3 and 4 neutropenia occurred in 10 and 6% of the patients, respectively. Severe thrombocytopenia was infrequent. The incidence of Grade 3/4 diarrhea was 3.6%. Mild nausea and vomiting (Grade 1 and 2) were frequent (63.6%). A Grade 4 elevation of total bilirubin was observed in one patient (2%) who was later found to have obstructive jaundice caused by disease progression. Early death, defined as death within 30 days from the last dose of chemotherapy, occurred in nine patients. The causal
The relationship between the early deaths and the study treatment was evaluated by the JCOG Data and Safety Monitoring Committee. Seven of the nine deaths were judged as ‘death due to PD’. The other two deaths were evaluated to be treatment related. One of the treatment-related deaths was caused by cardiogenic shock, probably because of a 5-FU-related ischemic cardiac event.

**Efficacy**

The tumor responses of all registered patients were assessed and confirmed by central review (Table 3). The response of the patient who had not previously received chemotherapy was classified as NE. Only five of the 56 patients had an objective PR (response rate; 9.0%, 95% CI, 3–20%). The survival curve is shown in Fig. 1. The median overall survival time was 237 days (95% CI, 145–281 days). The 1-year survival proportion was 21.4% (95% CI, 10.7–32.2%), and the 2-year survival proportion was 3.6% (95% CI, 0–8.4%).

**DISCUSSION**

5-FU-based chemotherapy is considered a standard therapy for advanced gastric cancer. However, 5-FU-based combination regimens of chemotherapy have not been shown to prolong overall survival as compared with 5-FU alone (14–17). Furthermore, the potential benefits of second-line chemotherapy for patients with pretreated gastric cancer remain unclear, and few prospective studies have been conducted.

Although this study showed that the sequential MTX/5-FU therapy possessed limited antitumor activity as second-line chemotherapy, despite an MST of 237 days (95% CI, 145–281), and 1- and 2-year survival proportions of 21.4% (95% CI, 10.7–32.2%) and 3.6% (95% CI, 0–8.4%), respectively. These survival data were similar to those obtained for first-line chemotherapy with several regimens at that time. Possible reasons for the good survival may include good patients’ clinical characteristics. At the baseline evaluation, the median age of the patients was 60 years (range, 20–75 years), and most patients had a good PS of 0 or 1. Another possible reason is a tumor stabilization effect of this combination regimen. Probably because nearly all patients had received 5-FU-based chemotherapy as first-line treatment, 56% of patients had NC, for a disease control rate (PR + NC) of 65%. The toxicity of the regimen can be considered tolerable. The proportion of patients with toxicity in our study was similar to that with the MTX/5-FU therapy used as first-line treatment (11).

Although the response rate of the present study was only 9%, the study regimen had good survival outcomes with tolerable toxicity. Given that survival with the best supportive care is ~3–4 months (3,4), this sequential MTX/5-FU therapy can be considered to be an option for standard second-line treatment.

Recently, second-line chemotherapy with paclitaxel or bi-weekly irinotecan has produced response rates of 27 and 18%, respectively (19,20), although these data were derived by subset analysis. Peritoneal dissemination of gastric cancer may cause serious complications, such as intestinal obstruction, ascites and hydronephrosis with renal dysfunction. In patients with these conditions, cisplatin or irinotecan, drugs active against gastric cancer, are difficult to use because of an

### Table 2. Toxicity profiles

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>JCOG grade</th>
<th>Total</th>
<th>Grade 3/4 (%)</th>
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<tr>
<td></td>
<td>0 1 2 3 4</td>
<td></td>
<td></td>
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<tr>
<td>Hematological toxicity</td>
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<td></td>
<td></td>
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<tr>
<td>Leucopenia</td>
<td>22 14 16</td>
<td>55</td>
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<td>Neutropenia</td>
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<td>Thrombocytopenia</td>
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<tr>
<td>Non-hematological toxicity</td>
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<td></td>
<td></td>
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<tr>
<td>Nausea/vomiting</td>
<td>18 22 13</td>
<td>55</td>
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<tr>
<td>Diarrhea</td>
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<td>Stomatitis</td>
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<tr>
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<td>Allergic reaction</td>
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<td>55</td>
<td>0</td>
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<tr>
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<td>41 8 1</td>
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<tr>
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<tr>
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<td>ECOG PS</td>
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### Table 3. Treatment response

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<th>PR</th>
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<th>PD</th>
<th>NE</th>
<th>RR</th>
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<td>5</td>
<td>31</td>
<td>14</td>
<td>6</td>
<td>9</td>
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<tr>
<td>RR</td>
<td>9.0%; 95% CI, 3–20%</td>
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</table>

CR, complete response; PR, partial response; NC, no change; PD, progressive disease; NE, not able to be evaluated; RR, response rate; CI, confidence interval.

Note: EOCG, Eastern Cooperative Oncology Group; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PS, performance status; JCOG, Japan Clinical Oncology Group; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
increased risk of toxicity. The MTX/5-FU therapy is considered to be effective and safe as first-line treatment in patients who have the advanced gastric cancer with peritoneal dissemination, especially malignant ascites (21). On the basis of these results, a randomized phase II trial comparing the MTX/5-FU therapy with paclitaxel in patients with pretreated advanced gastric cancer who have mainly peritoneal disease is now being conducted by the JCOG (protocol JCOG 0407).

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Conflict of interest statement
None declared.

References


