Objective: Oral fluoropyrimidine plus cisplatin is a standard treatment for advanced gastric cancer, but patients with severe peritoneal metastasis often cannot tolerate this regimen. The aim of this study was to assess the feasibility of fluorouracil, l-leucovorin and paclitaxel therapy in such patients.

Methods: In the first phase of the study, we investigated the maximum tolerated dose and recommended dose in Cycle 1 of fluorouracil, l-leucovorin and paclitaxel, at two dose levels [Level 1 (n = 6): 5-fluorouracil/l-leucovorin/paclitaxel = 500/250/60 mg/m²; Level 2 (n = 6): 600/250/80 mg/m² on Days 1, 8 and 15, every 28 days]. Nineteen additional patients at the recommended dose level were enrolled in the second phase to investigate the feasibility of fluorouracil, l-leucovorin and paclitaxel therapy. The primary endpoint in the second phase was the completion rate of two cycles.

Results: Dose-limiting toxicities were observed in a patient at Level 1 with Grade 4 gastro-intestinal perforation (the site of primary tumor), and in two patients at Level 2 with Grade 3 febrile neutropenia and Grade 3 infection, respectively. In Cycle 2, treatment-related death occurred at Level 2 in one patient who had Grade 4 febrile neutropenia with pneumonia. The maximum tolerated dose was set at Level 1, and the recommended dose was determined as Level 1. In the second phase, the completion rate of two cycles was 92% and the ascites response was 44%. Median progression-free survival was 4.2 months and overall survival was 8.0 months. Grade 3/4 neutropenia was observed in 12% of patients.

Conclusions: Fluorouracil, l-leucovorin and paclitaxel at Level 1 is feasible as first-line treatment for peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake.

Key words: gastric cancer – peritoneal metastasis – ascites – fluorouracil – paclitaxel
INTRODUCTION

Gastric cancer remains a major cause of death in Asian countries, and this tumor type is the second leading mortality cause in Japan. The majority of gastric cancer cases are diagnosed at an unresectable stage at which the prognosis is extremely poor. Current treatment for unresectable gastric cancer is based on systemic chemotherapy with an oral fluoropyrimidine (i.e., S-1 or capecitabine) plus cisplatin. S-1 plus cisplatin is a standard treatment in Japan based on the SPIRITS trial, which demonstrated the superiority of S-1 plus cisplatin compared with S-1 alone, while capecitabine plus cisplatin has also been recognized as a standard therapy around the world (1,2).

Patients exhibit peritoneal metastasis in approximately half of all cases of unresectable gastric cancer. Peritoneal metastasis causes many serious complications, such as malignant ascites, intestinal obstruction, hydrenephrosis and obstructive jaundice. Gastric cancer patients with severe peritoneal metastasis, and particularly those with massive ascites, have been excluded from clinical trials of cisplatin-containing regimens, and patients with inadequate oral intake have been excluded from trials with oral fluoropyrimidine. For such patients, continuous infusion of fluorouracil (5-FU ci) had been used in Japan based on the results of a Japan Clinical Oncology Group (JCOG) 0106 trial, which demonstrated that methotrexate (MTX) and 5-FU sequential therapy (MTX/5-FU) were not superior to 5-FU ci in chemotherapy-naive patients with peritoneal metastasis, except in those with massive ascites (3). In a recent a Phase III trial (ISO-5FU study), a weekly bolus regimen of 5-FU/l-leucovorin (L-LV) for unresectable gastric cancer was shown to be non-inferior to S-1, which had been also proved to be non-inferior to 5-FU ci in the previous JCOG9912 trial (4–5). Therefore, bolus 5-FU/L-LV has been used as one of the treatment options for peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake in the clinical setting.

Many patients with severe peritoneal metastasis suffer from acute clinical symptoms, such as abdominal fullness, vomiting, nausea, anorexia and abdominal pain, and show rapid progression of the disease. Chemotherapy with greater therapeutic efficacy than that of 5-FU/L-LV is needed as first-line treatment to promptly improve the symptoms and quality of life of patients. 5-FU/L-LV and paclitaxel (FLTAX) are both appropriate regimens for peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake, because this regime does not require that patients be hydrated and includes no oral agents. Weekly administration of FLTAX was demonstrated to be an effective regimen in Phase I/II studies for general unresectable gastric cancer patients, except those with peritoneal disseminated gastric cancer and massive ascites or inadequate oral intake (6,7). We conducted a multicenter feasibility study of peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake. The study consisted of two phases: in the first phase, we assessed the dose-limiting toxicity (DLT) and determined the maximum tolerated dose (MTD) and recommended dose (RD), and in the second phase, the feasibility of the FLTAX regimen at the RD level was assessed in an additional group of patients.

PATIENTS AND METHODS

Eligibility Criteria

Eligibility criteria included: histologically proven gastric adenocarcinoma; unresectable advanced or recurrent disease; age range of 20–80 years; Eastern Cooperative Oncology Group performance status of 0–2; peritoneal metastasis with bowel stenosis confirmed by barium enema, ascites and/or peritoneal nodule detected by computed tomography scan; massive ascites extending throughout the entire abdominal cavity, or inadequate oral intake which is defined as receiving an intravenous drip infusion because of nutritional support or proper hydration; previously untreated disease or the disease after one prior systemic chemotherapy as follows: recurrence during adjuvant chemotherapy or within 6 months after its completion, or failure of 5-FU ci or oral fluoropyrimidine as the first-line chemotherapy; preserved organ function, including leukocyte counts ≥3000/mm³, platelet counts ≥100,000/mm³, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤100 U/l, total bilirubin ≤1.5 mg/dl and serum creatinine ≤2.0 mg/dl and provision of written informed consent.

The levels of ascites were classified as follows: massive ascites was defined as extending throughout the entire abdominal cavity; moderate ascites was defined as inconsistent with either mild or massive ascites; mild ascites was defined as localized only in the upper or lower part of the abdominal cavity; no ascites was defined as undetectable by computed tomography scanning.

Exclusion criteria included active infection, uncontrolled heart disease, uncontrolled diabetes, pulmonary fibrosis or active pneumonitis, history of hypersensitivity to alcohol, prior taxane-containing chemotherapy, massive pleural effusion, symptomatic brain metastasis, watery diarrhea, active concomitant malignancy and pregnancy or lactation.

This study was approved by the independent ethics committee for each trial center and was conducted in accordance with the Declaration of Helsinki, and local laws and regulations. This study was registered with UMIN-CTR, number 00002093.

STUDY DESIGN AND TREATMENT

This was a multicenter feasibility study conducted in 2 phases, carried out across 12 sites in Japan. The first phase consisted of a dose-escalation study to determine DLT, MTD and RD of FLTAX. The predefined dose escalation scheme in the first phase consisted of two levels as follows: Level 1, 500 mg/m² of 5-FU, 250 mg/m² of l-LV and...
60 mg/m² of paclitaxel; Level 2, 600 mg/m² of 5-FU, 250 mg/m² of l-LV and 80 mg/m² of paclitaxel.

In the first phase, six patients were enrolled per dose level. If 0–2 DLT occurred in six patients, the next six patients were enrolled at the next dose level. If three or more DLT were observed at dose level 1, the FLTAX regimen would be deemed unfeasible for peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake. In the second phase, additional patients were enrolled and were assessed together with the patients at the RD level in the first phase.

Paclitaxel was administered as a 60 min intravenous infusion followed by 5-FU as a bolus intravenous infusion. A 120 min intravenous infusion of l-LV was started at the same time as the paclitaxel infusion; all agents were administered on Days 1, 8 and 15 every 28 days. As prophylaxis for potential paclitaxel hypersensitivity reactions, 8 mg of dexamethasone, 50 mg of ranitidine and 10 mg of chlorpheniramine were administered before the infusion of paclitaxel. Protocol treatment was defined as two cycles of FLTAX. Completion of two cycles was defined as the successful administration of FLTAX in at least four out of a total of six doses during two cycles. Post-protocol treatment was not defined, but continuation of FLTAX was recommended until disease progression or unacceptable toxicity occurred.

**Dose-limiting Toxicity and RD**

A DLT was defined as any of following events observed in Cycle 1: febrile neutropenia; neutrophil counts < 500/mm³ for 5 days or longer without use of granulocyte colony-stimulating factor; platelet counts < 25 000/mm³ or requiring platelet transfusion; Grade 3 non-hematological toxicity except for glucose, electrolyte, nausea, vomiting, anorexia, constipation and fatigue; treatment delay of Cycle 2 longer than 14 days and skipping of chemotherapy on Days 8 and 15 in Cycle 1 and treatment delay of Cycle 2 due to prolonged toxicities.

**Dose Modification of FLTAX**

When adverse events, described as follows, developed in Cycle 1, the dosage at Cycle 2 was reduced by one level: neutrophil counts < 500/mm³; febrile neutropenia; infection with Grade 3 or 4 neutropenia; platelet counts < 25 000/mm³; Grade 3 or higher non-hematological toxicity except for glucose, electrolyte, nausea, vomiting, anorexia, constipation and fatigue; delay of Day 1 in Cycle 2 longer than 8 days or skipping of chemotherapy on both Days 8 and 15. Dose reduction was performed level-by-level from Level 2 to Level 0: the lowest dosage (Level 0) of 400 mg/m² of 5-FU, 200 mg/m² of l-LV and 50 mg/m² of paclitaxel, dosage of Level 1 and Level 2 is shown in Study design and treatment. Once the dosage of each drug was reduced, a regain in dosage was not permitted. If Grade 3 sensory neuropathy did not recover by the start of a subsequent cycle, treatment could be continued with 5-FU/l-LV alone. Dose adjustment was done on a per cycle basis but not within a cycle.

**Criteria for Administration on Day 8 and 15**

When adverse events, described as follows, developed on Day 8 and 15 in each cycle, administration of FLTAX was skipped: neutrophil counts < 1000/mm³, platelet counts < 75 000/mm³, AST or ALT > 150 IU/l, total bilirubin > 2.0 mg/dl, serum creatinine > 2.0 mg/dl, fever (38.0°C or higher), and physician’s decision due to Grade 2 or higher non-hematological toxicities.

**Criteria for Starting Cycle 2**

After confirming that the following criteria were met, Cycle 2 was started: neutrophil counts ≥ 3000/mm³, platelet counts ≥ 150 000/mm³, platelet counts ≥ 100 000/mm³, serum creatinine ≤ 2.0 mg/dl, total bilirubin ≤ 2.0 mg/dl, without fever (38.0°C or higher) and recovery of non-hematological toxicities appearing in Cycle 1 to Grade 1 or lower at initiation of Cycle 2. If initiation of Cycle 2 was delayed more than 4 weeks from the scheduled initiation date, the patient was withdrawn from the study.

**Study Assessments**

Physical examination and laboratory tests were checked every week during the protocol treatment, and adverse events were assessed according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0). Tumor response was evaluated for patients with measurable lesions after each cycle during protocol treatment with the Response Evaluation Criteria in Solid Tumors guidelines, version 1.0 using computed tomography of the chest, abdomen and pelvis (8). The ascites response was evaluated as follows: complete response (CR) was defined as disappearance of ascites; partial response (PR) was defined as decreasing by one or more levels, as described above; incomplete response/stable disease was defined as other than CR, PR or progressive disease (PD) and PD was defined as an increase by one or more level, or need for more frequent drainage.

Overall survival was defined from the date of registration to the date of death or to the last contact date. Progression-free survival was defined from the date of registration to the date of disease progression or death from any cause. If there was no documented disease progression and if the patient had not died, data on progression-free survival were censored on the date that the absence of progression was confirmed.

**Study Endpoints**

The primary endpoints were the RD of FLTAX based on the assessment of DLT and MTD in the first phase of the study.
and the feasibility of FLTAX in peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake based on the completion rate of two cycles in the second phase. The secondary endpoints were safety, ascites response rate, progression-free survival and overall survival.

**Statistical Analysis**

The completion rate of two cycles of FLTAX as the primary endpoint was expected to be 60% based on data from clinical trials of advanced gastric cancer patients with ascites indicating a median treatment duration of 8–10 weeks (9–11). The threshold rate of completion of two cycles was set at 30%, with an \( \alpha \) of 0.1 (one-sided) and power of 80%, and the required number of patients was 19. The target number of patients was set at 20 to allow for a sufficiently large study cohort after dropouts and exclusions. Progression-free survival and overall survival were estimated using the Kaplan–Meier method.

**Results**

**Patients**

From June 2009 to July 2010, 32 patients were registered in this study: 13 patients were enrolled in the first phase—6 at Level 1, and 7 at Level 2. One patient at Level 2 was registered but never received protocol treatment and failed to meet the administration criteria over 7 days. Twenty-five patients who received the RD (including six patients at Level 1 in the first phase) were evaluated in the second phase. By the time of registration of 15 patients in the second phase, death within 30 days after the last administration of FLTAX including post-protocol treatment occurred in six patients (three second-line patients at Level 1, two second-line patients at Level 2 and one first-line patient at Level 2). All these patients died from disease progression, except one second-line patient at Level 2 who died due to a treatment-related cause. The continuation of this study was approved by the Date and Safety Monitoring Committee after protocol amendment to limit the patients in first-line setting. Table 1 shows the baseline demographics of the patients in the first and second phases.

**MTD and RD Determination**

In the first phase, one of six patients at Level 1 had DLT of Grade 4 gastrointestinal perforation (a good response to chemotherapy resulted in perforated gastric cancer). Two of six patients at Level 2 had DLT (one had Grade 3 febrile neutropenia and another had Grade 3 infection of the central venous device without neutropenia), and there was one treatment-related death; a patient who developed pneumonia with Grade 4 neutropenia at 17 days after protocol treatment out of the DLT assessment period. Therefore, Level 2 was considered as the MTD and Level 1 was determined as the RD for the second phase of the study.

**Feasibility and Safety**

The completion rate of two cycles in the second phase was 92% [90% confidence interval (CI): 76.9–98.5]: 21 of 25 patients continued further FLTAX treatment after protocol treatment of two cycles, and the median number of cycles was 4 (range 1–11). The reasons for treatment discontinuation in the second phase were disease progression (\( n = 21 \))

<table>
<thead>
<tr>
<th>Category</th>
<th>First phase</th>
<th>Second phase</th>
<th>RD (( n = 25 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Level 1 (( n = 6 ))</td>
<td>Level 2 (( n = 6 ))</td>
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<td>49 (32–69)</td>
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<tr>
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RD, recommended dose; ECOG, Eastern Cooperative Oncology Group; PS, performance status; IVH, intravenous hyperalimentation; CDDP, cisplatin.

*The RD group (\( n = 25 \)) included six patients at Level 1 dose in the first phase.*
and unacceptable toxicity (n = 4) consisting of Grade 2 sensory neuropathy (n = 2), Grade 3 motor neuropathy (n = 1) and Grade 3 perforation of the primary site (n = 1). Thirteen patients in the second phase received subsequent chemotherapy after FLTAX treatment.

Table 2 summarizes all toxicities observed during the protocol treatment. At the RD level, major Grade 3 or 4 toxicities were neutropenia, leucopenia, fatigue and anorexia.

**Treatment Efficacy**

In the second phase, the ascites response was evaluated in 24 patients but not in 1 patient with peritoneal nodules. The overall ascites response rate was 44.0% (five patients CR, six patients PR). The ascites response rate in the 17 first-line patients in the second phase was 44.4%, and that of the 7 second-line patients was 42.9%. At a median follow-up of 8.0 months, the median progression-free survival in the second phase was 4.2 months (Fig. 1): 6.2 months in first-line patients (n = 18) and 2.9 months in second-line patients (n = 7). Median overall survival in the second phase was 8.0 months (Fig. 2): 9.5 months in first-line patients (n = 18) and 5.6 months in second-line patients (n = 7).

**DISCUSSION**

Our results suggest that FLTAX is a feasible and promising regimen for first-line treatment of peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake. The RD was determined as 500 mg/m² of 5-FU, 250 mg/m² of l-LV and 60 mg/m² of paclitaxel on Days 1, 8 and 15, every 28 days. At the RD level, the toxicity profile was acceptable and the completion rate of two cycles was
92%. Efficacy in the second phase of the study was promising; the response rate in ascites was 44%, the median progression-free survival was 4.2 months and median overall survival was 8.0 months.

Severe peritoneal metastasis causes severe clinical symptoms, such as abdominal fullness, vomiting, nausea, anorexia and abdominal pain, and it reflects rapid progression of the disease. Chemotherapy with greater therapeutic efficacy is needed as first-line treatment to promptly improve the symptoms and quality of life of patients. Furthermore, about 75% of patients with unresectable gastric cancer received second-line chemotherapy in some Phase III trials previously reported from Japan (1,5,12,13). However, only 40% of peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake, who received 5-FU-based regimen as first-line chemotherapy, received second-line chemotherapy in our retrospective study (14). These data revealed that many patients with peritoneal disseminated gastric cancer and massive ascites or inadequate oral intake must have missed the opportunity to receive second-line chemotherapy because of rapid progression at the failure of first-line chemotherapy. Therefore, the use of a powerful combination regimen as first-line treatment is a promising strategy to improve the overall prognosis.

Bolus 5-FU/LV has been widely used in clinical practice for peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake, who cannot receive standard treatment (oral fluoropyrimidines plus cisplatin) for general unresectable gastric cancer. Weekly paclitaxel was shown to significantly improve progression-free survival (hazard ratio, 0.57; 95% CI, 0.37–0.87; \( P = 0.004 \)) when used as a second-line treatment in patients with peritoneal metastasis, except those with massive ascites (15). Therefore, a combination regimen of FLTAX would be more effective for peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake because this combination regimen does not require the patient to be hydrated and includes no oral agents. FLTAX was already demonstrated to be an effective regimen in Phase I/II studies of general unresectable gastric cancer patients (6,7) and, therefore, we sought to evaluate the feasibility of FLTAX for the treatment of peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake.

The median survival time in patients with peritoneal disseminated gastric cancer and massive ascites was much longer (8.0 months) with FLTAX treatment in our study than with MTX/5-FU (5.1 months) in a previous Phase II study (9). In retrospective studies, the median survival time of peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake who received systemic chemotherapy was 4.6–5.0 months (14,16). Furthermore, the ascites response rate in this study (44%) was also higher than that of MTX/5-FU (35%) in the Phase II study described above. Such high therapeutic efficacy would improve severe clinical symptoms at the start of first-line chemotherapy, and lead more patients to receive second-line chemotherapy, thereby improving the prognosis. In fact, 77% of first-line patients at the RD level could receive second-line chemotherapy, and an overall survival time of 9.5 months was achieved in this study.

In conclusion, the FLTAX regimen of FLTAX (500/250/60 mg/m²) is feasible as a first-line treatment for peritoneal disseminated gastric cancer patients with massive ascites or inadequate oral intake. We intend to assess the FLTAX regimen relative to therapy with 5-FU/LV in a randomized trial of previously untreated patients with peritoneal disseminated gastric cancer and massive ascites or inadequate oral intake.

Acknowledgements

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Conflict of interest statement

None declared.

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