Abstract. Background: The efficacy of systemic chemotherapy for peritoneal dissemination of gastric cancer remains unclear. The efficacy of weekly paclitaxel in combination with doxifluridine (5'-DFUR) in gastric cancer patients with malignant ascites was evaluated. Patients and Methods: Patients with histologically confirmed gastric cancer with ascites were eligible. The treatment consisted of paclitaxel intravenously (i.v.) administered at 80 mg/m² on days 1, 8 and 15 every 4 weeks, and doxifluridine administered orally at 533 mg/m² on days 1-5 every week. The response rate for patients with ascites was determined based on the Japanese Classification of Gastric Carcinoma. Also, the concentration of paclitaxel in the ascites was measured. Results: Twenty-four patients were investigated. The response rate (RR) was 41.7%, including complete remission (CR) and partial remission (PR) in 4 and 6 patients, respectively. The concentration of paclitaxel in the ascites was maintained between 0.01 μM and 0.05 μM until 72 hours. The median overall survival (OS) was 215 days, and 1-year survival rate was 29.2%. No severe toxicity was noted. Conclusion: Weekly paclitaxel in combination with doxifluridine is effective for gastric cancer patients with malignant ascites with an acceptable toxicity profile.

Gastric cancer, still occurring with a high incidence, is one of the leading causes of death worldwide. Metastatic gastric carcinoma is an incurable disease with a median survival of only 4 to 8 months. Previous randomized studies have shown that systemic chemotherapy can prolong survival and improve the patient’s quality of life (1-3). Gastric cancer can progress to a systemic disease through various patterns such as direct invasion or lymphatic or vascular spread. Peritoneal dissemination, i.e. peritoneal carcinomatosis, very commonly occurs in patients with advanced gastric cancer and is considered an incurable disease state (4). Malignant ascites developing in patients with terminal gastric cancer is a severe end-stage disease and poses particular problems to clinicians in providing suitable palliative care. No treatment method of peritoneal dissemination and/or
ascites associated with gastric cancer metastasis has been established, often due to the lack of measurable lesions in gastric malignant ascites, hindering assessment using the standard Response Evaluation Criteria in Solid Tumors (RECIST) (5). It is difficult to evaluate the efficacy of chemotherapy for peritoneal dissemination in the clinical trial setting as well as in clinical practice, because most disseminated tumor cells do not form a measurable mass but rather constitute a diffuse lesion and few studies have been undertaken. Clinicians have to assess the efficacy of treatment and disease status in each patient based on the integrated clinical information such as clinical imaging results, tumor markers and clinical symptoms (6).

The World Health Organization (WHO) criteria for the assessment of response to nonsurgical cancer treatment have been proven to provide a durable international standard. These criteria alone, however, are insufficient to assess the outcome of treatment of gastric cancer. The Japanese Research Society for Gastric Cancer (JRSGC) established new assessment criteria for gastric cancer, including pleural effusion/ascites (7), which were used in the present study.

Paclitaxel and doxifluridine (5'-DFUR), an intermediate metabolite of capecitabine, have distinct mechanisms of action and toxicity profiles. They have been shown to have considerable single-agent activity in the treatment of gastric cancer. A synergistic interaction between these two drugs has been suggested to be associated with the taxane-induced up-regulation of thymidine phosphorylase, which converts 5'-DFUR to 5 Fluorouracil (5-FU) (8). Recent studies have also shown that when administered weekly, paclitaxel had a modest activity with a safety profile superior to that of its tri-weekly regimen, thus suggesting that the weekly regimen is the most suitable treatment option for patients with gastric cancer treated on an out-patient basis (9, 10). Also, paclitaxel is more effective for undifferentiated gastric carcinoma.

The present study was performed in order to evaluate the efficacy and toxicity of weekly paclitaxel administration in combination with 5'-DFUR, in patients with advanced gastric cancer with malignant ascites.

**Patients and Methods**

**Patients.** Patients with histologically confirmed non-resectable or recurrent gastric cancer with malignant ascites were eligible for this study. The inclusion criteria were a performance status (PS) of 0-2; age 20 years or older; a measurable target according to the RECIST; a life expectancy exceeding 3 months; no major history of surgery, radiotherapy, or chemotherapy within 28 days before study participation; normal bone marrow, renal and liver functions as defined by a white blood cell count (WBC) of 3000/mm³ or more, Hgb of 8.0 g/dl or more, platelet (PLT) of 80,000/mm³ or more, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) of 100 IU/l or less and total bilirubin of 1.5 mg/dl or less; no significant cardiac disease as established by echocardiography and no restriction on prior regimens. All the patients gave written informed consent to participate in the study in advance, according to the institutional guidelines.

The present study was performed as a subset analysis in our phase II study (11).

**Treatment schedule.** The study treatment consisted of paclitaxel at 80 mg/m² administered via intravenous (i.v.) infusion for 60 min weekly on days 1, 8 and 15 in combination with 5'-DFUR at 533 mg/m²/day 5 days per week in a 28-day cycle (Figure 1) and was continued until disease progression (PD) or unacceptable toxicity. The recommended dose of 5'-DFUR and paclitaxel was based on the results obtained from our previous phase I study (12).

The doses of paclitaxel and 5'-DFUR were determined according to the patient’s body surface area. The practical doses of 5'-DFUR were decided based on 200-mg capsules. Paclitaxel was diluted with 250 ml of either 0.9% sodium chloride solution or 5% dextrose solution, and the final solution was administered through i.v. infusion for 1 hour. The pretreatment administered for 60 min prior to paclitaxel therapy consisted of dexamethasone at 20 mg i.v., chlorphenamine at 10 mg i.v. and either ranitidine at 50 mg i.v. or famotidine at 20 mg i.v.

**Pretreatment assessment and follow-up studies.** Collection of the patients’ medical histories, physical examinations and routine laboratory studies were performed once before treatment and weekly during treatment. Routine laboratory studies included complete blood cell counts with differential WBC counts, serum electrolytes, and blood analyses. If any toxicities were noted in association with grade 3 or 4 clinical manifestations based on the hematological or biochemical laboratory parameters, laboratory tests were repeated immediately and then performed daily until the toxicity resolved.

**Evaluation during the treatment period.** The evaluation end-point was the response rate (RR) for ascites patients, which was evaluated at every treatment cycle, based on computed tomography findings. The RR was determined according to the 13th Edition of the Japanese Classification of Gastric Carcinoma published by the Japanese Gastric Cancer Association (Table I) (7). The overall survival (OS) and the incidence of adverse events were also evaluated. Intention-to-treat (ITT) analysis was used to evaluate patients for their response to treatment, survival and toxicity.

**Toxicities.** Toxicities were graded according to the National Cancer Institute’s Common Toxicity Criteria, Ver. 3 (NCI-CTC). The following toxicities were defined as dose-limiting if they occurred during the treatment: Grade 4 leukopenia (neutropenia) persisting for longer than 4 days; Grade 4 thrombocytopenia; a fever greater than 38°C with Grade 3 or greater leukopenia; a study schedule delay of longer than 14 days and Grade 3 or greater non-hematological toxicity without nausea or alopecia.

**Paclitaxel concentrations in ascites.** The level of paclitaxel was measured in the ascites obtained from 4 out of the 24 patients. A catheter was inserted into the patient’s abdominal cavity to collect the ascites. Three ml of ascites were obtained from the catheter at 2, 4, 6, 8, 12, 24, 48, 72 hours after paclitaxel treatment. The ascites were collected in a heparinized tube, then centrifuged and the supernatant was stored at −20°C until assay. High-performance liquid chromatography was used to analyze the concentration of paclitaxel in the ascites, as previously described (13).
Results

Between April 2003 and May 2006, a total of 30 patients were enrolled in the study. Six patients were not evaluable for the therapeutic response, five failed to return to the clinic for evaluation, and one refused to receive chemotherapy. In all, 24 patients were evaluated for ascites therapeutic response and toxicities. The patient demographic characteristics are presented in Table II. Ten patients had advanced gastric cancer and 14 had recurrent gastric cancer.

Antitumor activity. The ITT analysis revealed an overall RR of 41.7% (95% CI, 21.9-61.4%), including complete remission (CR) in four patients, partial remission (PR) in 6, and no effect in 14. The median OS was 215 days and the 1-year survival rate was 29.2% (Figure 2).

Toxicity. The distribution of the NCI-CTC grades of the most common hematological and non-hematological toxicities observed through the treatment period is presented in Table III. The most common hematological toxicity was leukopenia. However, only 6 out of the 24 (25.0%) patients reported grade 3/4 leukopenia, indicating no clinical significance of the event. The most frequently observed non-hematological grade 3/4 adverse event was increased ALT in 12.5% of the patients. There was no neutropenic fever or treatment-related death.

Pharmacokinetics of paclitaxel. The concentration of paclitaxel in the collected ascites increased to a peak level after 4-8 hours of treatment, remaining almost unchanged above 0.02 μM up to 48 hours after treatment, and maintained above 0.01 μM until 72 hours after treatment (Figure 3).

Discussion

In a study (JCOG9603) of patients with unresectable advanced or recurrent gastric cancer with concurrent malignant ascites treated with methotrexate (MTX) and 5-FU administered with a time interval, ascites decreased in 13 out of 37 patients (35%), including three complete remission cases (14). Based on these findings, was a phase III study (JCOG0106) compared MTX-5-FU therapy to 5-FU continuous infusion (5-FUci) (15) and the ingestion-possible survival was found to be superior in the MTX-5-FU group, whereas no significant difference was found between the two groups in terms of the survival rate.
Table III. Toxicity profile of weekly paclitaxel and 5'-DFUR therapy (24 assessable patients).

<table>
<thead>
<tr>
<th>Toxicity*</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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</thead>
<tbody>
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<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
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<tr>
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*Common Terminology Criteria for Adverse Events v.3.0 (CTCAE).
Among the chemotherapeutic agents with a therapeutic effect on advanced gastric cancer, taxanes have been shown to be highly effective in the treatment of undifferentiated tumors and peritoneal dissemination, demonstrably better than conventional anticancer agents such as cisplatin (CDDP) (16-18). In a recent study (JCOG0407) (19), conducted in patients with peritoneal metastatic gastric cancer refractory to the primary therapy, the progression free survival was significantly better in the patients treated with paclitaxel than those receiving best available 5-FU therapy, while the one-year survival rate was comparable between the two treatment groups.

When systemic chemotherapy is provided in patients with fluid retention such as ascites or pleural effusion, the clinicians have to consider any variation in the pharmacokinetic parameters of the antitumor agents used.

An in vitro dose of 0.01 μM paclitaxel inhibited growth of human gastric carcinoma cells which were arrested mainly during the G2/M phases before apoptosis (20). However, this treatment decreased the cells at the G0/G1 phases without increasing the cells at the G2/M phases, indicating the cytotoxicity of the drug to gastric carcinoma cells at the G0/G1 phase (20). Gianni et al. (21) demonstrated that exposure of plasma to paclitaxel concentration over 0.05 μM/l led to myelosuppression and that a concentration of 0.1 μM/l was clinically relevant (22), which was consistent with findings from other studies (23-25). Other recent studies (22, 26), have also suggested that the dose range of paclitaxel that is clinically effective and can be used safely is 0.01 to 0.05 μM. The pharmacokinetic data of the present study revealed that the level of paclitaxel remained within the therapeutic range in the patients with malignant ascites from 2 until at least 72 hours following systemic administration of the drug. The peak plasma level of paclitaxel varies individually, but in most cases the drug level reached a peak immediately after administration. The efficacy of this dose was shown by the decrease of the ascites in 10 out of the 24 patients, with an overall response rate of 41.7%, including complete remission (CR) in four patients. The one-year survival rate was 29.2%, which is comparable to that from the 5-FUci group in Study JCOG0106 (15). The safety profile of the treatment was also acceptable with few grade 3/4 serious adverse events.

In order to improve the efficacy of paclitaxel treatment in patients with gastric cancer, a further study will be conducted to determine whether intraperitoneal administration of paclitaxel (27), which has already been introduced for the treatment of ovarian cancer (28), is effective for gastric cancer as well.

In conclusion, sequential paclitaxel plus 5'-DFUR therapy is effective in controlling malignant ascites in gastric cancer patients with a generally acceptable toxicity profile.

References


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