Weekly Paclitaxel After Failure of Gemcitabine in Pancreatic Cancer Patients with Malignant Ascites: A Retrospective Study

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Objectives: Peritoneal metastasis is one of the major sites of disease progression of pancreatic cancer. There have been few trials in the second-line setting after gemcitabine failure because patients can hardly be candidates for chemotherapy after failure in the first-line chemotherapy, especially those with malignant ascites. The safety and efficacy of weekly paclitaxel therapy was evaluated for pancreatic cancer patients with malignant ascites in this retrospective study.

Methods: The subjects of this retrospective study were 23 advanced pancreatic cancer patients with malignant ascites who received weekly paclitaxel therapy after gemcitabine failure. Paclitaxel (80 mg/m², div. for 1 h) was administered on Days 1, 8 and 15, every 4 weeks.

Results: While the disease control rate was 35%, decrease of ascites was obtained in 30% of the patients and ascites control rate was 61%. The median survival time was 101 days. Toxicities were mild, although one treatment-related death occurred.

Conclusions: Weekly paclitaxel therapy may be useful treatment option for pancreatic cancer patients with malignant ascites after gemcitabine failure.

Key words: pancreatic cancer – malignant ascites – gemcitabine resistant – paclitaxel

INTRODUCTION

Gemcitabine has remained the key drug for the treatment of advanced pancreatic cancer since the mid-1990s (1). Numerous trials conducted on thousands of patients have failed to improve the outcome compared with that obtained with gemcitabine (2). Recently, while only one large randomized phase III trial showed superiority of addition of erlotinib to gemcitabine over gemcitabine monotherapy in patients with advanced pancreatic cancer, its survival benefit was modest (3).

Several small phase II studies of various chemotherapeutic agents for advanced pancreatic patients after gemcitabine failure have been published, with response rates ranging from 0 to 24% and overall survival times ranging from 3 to 6 months (4–7). Recently, a German group reported that a 5-FU/folinic acid (FA) plus oxaliplatin regimen could prolong the survival and improve the quality of life of advanced pancreatic cancer patients after gemcitabine failure as compared with best supportive care alone (8) and 5-FU/FA (FF) (9).

At present, many of the patients who show disease progression during first-line treatment show poor general condition, especially patients who develop peritoneal carcinomatosis. Peritoneal carcinomatosis is common in advanced pancreatic cancer, and causes intestinal obstruction, massive ascites and hydronephrosis, which may manifest as abdominal pain and fullness, vomiting, constipation, malnutrition and/or renal dysfunction. Thus, patients with peritoneal carcinomatosis often have a poor quality of life and a poor prognosis. From the clinical point of view, a therapeutic option for palliative management of these complications is warranted.

Although the major treatment strategy for unresectable or metastatic pancreatic cancer is systemic chemotherapy, this conventional treatment strategy has been generally believed...
to have only a small impact on patients with peritoneal dissemination, because the drugs do not penetrate in sufficient concentrations through the peritoneum–plasma barrier to the tumor cells. Therefore, the efficacy of systemic chemotherapy against peritoneal dissemination secondary to pancreatic cancer has not been aggressively investigated.

Peritoneal carcinomatosis with malignant ascites is as common in advanced gastric cancer patients as in advanced pancreatic cancer patients. Weekly paclitaxel is recognized as one of the effective regimens for second-line chemotherapy of gastric cancer in Japan, with a reported response rate of 24% in 25 patients and rate of disappearance of ascites of 14% (3/21 patients) (10). At present, weekly paclitaxel therapy is recognized as the community standard, especially for second-line therapy, for gastric cancer patients with malignant ascites. A small study by Oettle et al. (11) demonstrated that weekly paclitaxel for pancreatic cancer in the second- or third-line setting after failure of gemcitabine also showed modest activity with a disease control rate of 42% in 14 patients. Based on these results, we considered that weekly paclitaxel may be a candidate treatment regimen to pancreatic cancer patients with malignant ascites, and this regimen was tried after obtaining the approval of the clinical practice review committee at Shizuoka Cancer Center.

We investigated the efficacy and safety of weekly paclitaxel therapy in pancreatic cancer patients with malignant ascites who had a history of failure of gemcitabine.

**PATIENTS AND METHODS**

**PATIENT SELECTION**

There were 24 patients with advanced pancreatic cancer who received weekly paclitaxel therapy after failure of gemcitabine between April 2002 and March 2008 at the Shizuoka Cancer Center. Among them, 23 patients who received weekly paclitaxel therapy were selected as the subjects of this study according to the following criteria: (i) history of failure of gemcitabine-based chemotherapy, (ii) peritoneal dissemination and/or ascites detected by abdominal CT, (iii) age >20 and <75 years, (iv) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, (v) adequate major organ functions, (vi) no other cancer and (vii) no serious complications, such as active infectious disease, serious heart disease or poorly controlled hypertension/diabetes mellitus. The reason for excluding one patient was poor performance status.

**TREATMENT METHODS**

Weekly paclitaxel therapy consisted of administration of paclitaxel (80 mg/m², div. for 1 h) on Days 1, 8 and 15, every 4 weeks. This treatment was repeated, usually on an outpatient basis, until the detection of disease progression or appearance of unacceptable toxicity. Dose reduction and the rest of the anticancer drugs were based on the judgment of the attending physicians. However, as a rule, when Grade 4 hematological or Grade 3 or more non-hematological toxicity occurred, treatment was suspended until recovery, and the dose of paclitaxel was reduced to 60 mg/m² in the subsequent administration.

**EVALUATION OF RESPONSE AND TOXICITY**

The data on the patient background characteristics, adverse events, treatment compliance, treatment response, progression-free survival (PFS) and overall survival (OS) were collected retrospectively from the medical records. Tumor response was assessed by computed tomography (CT) or ultrasonography (US) of the target lesions every 4–8 weeks after the first administration of the chemotherapy. Complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were defined according to the response evaluation criteria in solid tumors (RECIST) Ver. 1.0. The response of the ascites was evaluated by CT or US based on the following specific criteria in this study modified from those in the Japanese Classification of Gastric Carcinoma (i): decrease of ascites: apparent decrease of ascites as visualized by CT or US persisting for at least 4 weeks; (ii) no change of ascites: no apparent increase or decrease of the ascites volume as visualized by CT or US for at least 4 weeks; (iii) increase of ascites: apparent increase of ascites as visualized by CT or US. Adverse events were evaluated weekly until 4 weeks after the discontinuation of chemotherapy, according to the Common Terminology Criteria for Adverse Events (CTCAE) Ver. 3.0.

**STATISTICAL METHODS**

For analyzing the PFS and the OS, survival curves were drawn by the Kaplan–Meier method. The PFS was calculated from the date of detection of disease progression or the date of occurrence of death from any cause. PFS was censored at the date of the last visit for those patients who were alive without documented disease progression. The OS was calculated from the first day of treatment to the date of death or the date of the last follow-up visit. OS was censored at the date of the last visit for those patients whose deaths could not be confirmed. All of the analyses were performed using the StatView software program, Ver. 5.0 (SAS Institute Inc., Cary, NC, USA).

**RESULTS**

**PATIENT CHARACTERISTICS**

Table 1 shows the patient characteristics. Among the 23 patients, 13 (57%) were male and the median age was 65 years. Twelve patients (53%) had a PS of 2, and 15 patients (65%) had received two or more prior chemotherapeutic regimens. Four patients (17%) had massive ascites and required IVH.
Table 1. Patients characteristics

<table>
<thead>
<tr>
<th></th>
<th>n = 23</th>
</tr>
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<tbody>
<tr>
<td>Age, median (range)</td>
<td>65 (40–75)</td>
</tr>
<tr>
<td>Gender, male/ female</td>
<td>13/10</td>
</tr>
<tr>
<td>PS, 0/1/2</td>
<td>1/10/12</td>
</tr>
<tr>
<td>Number of metastatic organs, 1/2/3/4</td>
<td>5/10/5/3</td>
</tr>
<tr>
<td>Number of prior chemotherapy, 1/2/3</td>
<td>8/10/5</td>
</tr>
<tr>
<td>Volume of ascites, little/medium/massive</td>
<td>7/12/4</td>
</tr>
<tr>
<td>Total parenteral nutrition, No /Yes</td>
<td>19/4</td>
</tr>
<tr>
<td>CA19-9, ≤37/&gt;37</td>
<td>5/18</td>
</tr>
</tbody>
</table>

PS, performance status.

Table 2. Grade 3 or more adverse events

<table>
<thead>
<tr>
<th></th>
<th>n = 23 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Anemia</td>
<td>8 (35)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Allergy</td>
<td>1 (4)</td>
</tr>
</tbody>
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DISCUSSION

The symptoms caused by peritoneal dissemination are usually difficult to control by supportive care alone, and it is important to control peritoneal dissemination and malignant ascites for improving the patients’ quality of life in clinical practice. However, it is difficult to evaluate the efficacy of chemotherapy against peritoneal dissemination in ordinary clinical trials in which tumor shrinkage is assessed, because most disseminated tumor cells do not form a measurable mass, and no effective chemotherapy for peritoneal dissemination has been established, especially in patients with pancreatic cancer. In patients with malignant ascites, clinicians have to assess the efficacy of treatment and the disease status based on the integration of clinical information, such as that obtained by clinical imaging, tumor marker estimations and clinical symptoms. In the present study, the therapeutic efficacy was assessed based on the change in the volume of ascites as visualized by abdominal CT or US according to the criteria used in the previous study of sequential methotrexate (MTX) plus 5-FU therapy in gastric cancer patients with peritoneal dissemination (12). Using these criteria in
our study, a decrease in the volume of ascites was observed in 30% of the patients and the ascites control rate was about 60%. In a study evaluating sequential MTX plus 5-FU therapy in gastric cancer patients with peritoneal dissemination, disappearance or decrease in the volume of ascites was obtained in 35% of the patients (12). Weekly paclitaxel is recognized as one of the effective regimens for second-line chemotherapy of gastric cancer in Japan, with a reported rate of disappearance of ascites of 14% (10). While in general, it is considered that pancreatic cancer is less chemosensitive than gastric cancer, it is considered that weekly paclitaxel therapy might show similar efficacy in pancreatic cancer patients with malignant ascites to that in gastric cancer patients with malignant ascites.

In clinical trials of second-line chemotherapy for pancreatic cancer, median survival times of 2 or 3 months have been reported with best supportive care. In this study, the median survival time was nearly 4 months. Considering that the patient’s background condition in this study was worse because of malignant ascites than in the aforementioned clinical trials, it is speculated that weekly paclitaxel therapy might also yield survival prolongation. From these results, it is considered that weekly paclitaxel therapy could be useful treatment options for pancreatic cancer patients with malignant ascites.

However, the present study also shows that severe toxicity may sometimes occur in pancreatic cancer patients with malignant ascites, possibly because of the poor general condition of these patients.

Ideally, it should be evaluated in future randomized clinical trials whether these regimens might be of clinical benefit for pancreatic cancer patients with malignant ascites, especially in the second- or third-line setting after gemcitabine failure, adopting the endpoints of patient survival and quality of life. However, most advanced pancreatic cancer patients who show disease progression during first-line treatment and complicating malignant ascites are generally poor candidates for clinical trials. Under these circumstances, the present study yields valuable data for clinicians.

In conclusion, the present study suggests that weekly paclitaxel therapy may be useful treatment options in controlling malignant ascites in pancreatic cancer patients with gemcitabine failure.

Conflict of interest statement

None declared.

References