S-1 and Gemcitabine as an Outpatient-based Regimen in Patients with Advanced or Metastatic Pancreatic Cancer

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Objective: The standard beneficial chemotherapy proved for patients with pancreatic cancer is a regimen containing gemcitabine. Novel oral fluoropyrimidine, S-1, can be added to gemcitabine to improve the efficacy of chemotherapy and to provide better convenience for patients. We aimed to evaluate the efficacy and safety of S-1 plus gemcitabine combination chemotherapy as a first-line treatment in patients with locally advanced or metastatic pancreatic cancer.

Methods: Patients with histologically confirmed, bidimensionally measurable advanced/metastatic pancreatic cancer were eligible for the study. Chemotherapy consisted of S-1 (30 mg/m² p.o. bid from Day 1 to 14) and gemcitabine (1000 mg/m² on Days 8 and 15) every 3 weeks based on the results of a previously reported Phase I trial. Treatment was repeated until disease progression or unacceptable toxicity occurred.

Results: From January 2005 to August 2007, 22 patients were enrolled. Median age was 62 years (range, 50–73). Nineteen patients (86.3%) had metastases and of these, 11 patients (57.9%) had multiple liver metastases. The overall response rate was 27.3% (95% CI, 8.7–45.9), with a partial response in six patients, stable disease in nine (40.9%) and progressive disease in seven (31.8%). With a median follow-up of 25.4 months, the median time to progression and overall survival were 4.6 (95% CI, 2–7.2 months) and 8.5 months (95% CI, 6.8–10.1 months), respectively, and 1-year survival rate was 27.3%. S-1 plus gemcitabine was well tolerated. Grade 3/4 hematological adverse events were neutropenia (9.1/9.1%) and anemia (4.5/0%). Non-hematological adverse events were mainly gastrointestinal events. Twenty patients (91%) received chemotherapy on an outpatient basis.

Conclusions: Combination chemotherapy of S-1 plus gemcitabine appears to be active and well tolerated as first-line treatment in patients with advanced/metastatic pancreatic cancer.

Key words: S-1 – gemcitabine – pancreatic neoplasms – drug therapy, combination

INTRODUCTION

Gemcitabine has been approved as the standard of care in patients with pancreatic cancer for more than a decade, based primarily on improvement in clinical benefit response such as pain reduction, improvement in performance status and increase in body weight (1). However, the gain in survival was modest and the outcome of advanced pancreatic cancer remains dismal.

Efforts to improve the treatment results have continued. Modification of the administration schedule or dose intensification strategies has showed superiority to standard gemcitabine therapy in small clinical trials, but failed to demonstrate an increased survival in randomized comparative trials (2,3). Another approach to enhance the antitumor potential of gemcitabine is to combine the agent with other active drugs.

S-1 is an oral fluoropyrimidine derivative that combines tegafur with two modulators of 5-fluorouracil (5-FU) metabolism, 5-chloro-2,4-dihydroxypyridine and potassium oxonate. 5-chloro-2,4-dihydroxypyridine is a competitive inhibitor of dihydroxypyridine dehydrogenase and acts to...
maintain efficacious concentrations of 5-FU in the plasma and in tumor tissue (4). Potassium oxonate inhibits the phosphorylation of 5-FU in the gastrointestinal tract, reducing the serious gastrointestinal toxicity associated with the use of 5-FU (5). S-1 has demonstrated single-agent activity in advanced pancreatic cancer, with a 21–37.5% overall response rate (6,7). In addition, synergy between gemcitabine and 5-FU in tumor cell lines, including pancreatic cancer cells, has been reported. The combination of S-1 and gemcitabine has shown promising clinical activity in Phase I clinical studies in advanced pancreatic cancer patients (8,9).

In the present study, we sought to evaluate the response rate, time to progression (TTP) and safety of a combination regimen of S-1 plus gemcitabine in patients with advanced pancreatic cancer.

PATIENTS AND METHODS

Eligibility

Patients were eligible for the study if they met the following criteria: histologic or cytologic evidence of locally advanced or metastatic adenocarcinoma of the pancreas with at least one unidimensionally measurable disease (i.e. a diameter ≥1 cm, as assessed by spiral computed tomography); ECOG performance status 0, 1 or 2; adequate hematological function (absolute neutrophil count ≥1.5 × 10^9/l, platelet count ≥100 × 10^9/l, hemoglobin ≥9 g/dl), adequate renal function (serum creatinine ≤1.5 mg/dl and creatinine clearance ≥50 ml/min) and adequate hepatic function (total bilirubin ≤2 mg/dl and serum transaminase level ≤3 times the upper limit of the normal range). Adjuvant treatment with 5-FU plus radiotherapy was allowed if therapy had been administered more than 12 months before trial inclusion. Patients were ineligible if they had previously received palliative chemotherapy or radiation therapy, or had other severe medical illnesses, CNS metastasis, or another active malignancy. The study was approved by the local Ethics Committee and written informed consent was obtained before enrollment.

Study Protocol

Patients received 30 mg/m^2 oral S-1 twice daily at 12-h intervals on Days 1–14 every 3 weeks. Individual doses were rounded down to the nearest pill size less than the calculated dose, given the available formulation. Gemcitabine was administered as a 1000 mg/m^2 intravenous infusion over 30 min on Days 8 and 15 every 3 weeks. Ondansetron (8 mg or equivalent) was administered orally as premedication on the day of gemcitabine administration. Patients with evidence of response [complete response (CR) or partial response (PR)] or stable disease continued receiving treatment until there was evidence of disease progression, unacceptable toxicity or withdrawal of patient consent.

Dose Modification

If Grade 2 hematologic toxicity was observed, the gemcitabine dose was reduced by 25% on Day 8 or 15. In cases of Grade 3 toxicity, gemcitabine administration was omitted. Grade 4 hematologic adverse events necessitated delay or interruption of the administration of both drugs until they resolved to Grade 0 or 1, and the dose of gemcitabine was subsequently reduced by 25% at the discretion of the investigator. No dose modification was required for anemia because it was managed by RBC transfusion. Grades 2–4 non-hematologic adverse events necessitated delay or interruption of treatment. Treatment cycles could be delayed up to 3 weeks. Supportive and/or prophylactic care for symptoms could be administered as needed (e.g. hematopoietic growth factors for symptomatic neutropenia, but not given prophylactically; loperamide for diarrhea; and metoclopramide or 5-hydroxytryptamine-3 antagonist for nausea and vomiting).

Study Assessment

Study evaluation included toxicity assessments and measurement of hematological, renal and hepatic function weekly. Patients were evaluated with computed tomography at 6, 12 and subsequently every 9 weeks after the initiation of treatment. Response and progression were evaluated using Response Evaluation Criteria in Solid Tumors (RECIST). Blood analysis of carbohydrate antigen 19-9 (CA19-9) was performed every 3 weeks during treatment.

Statistical Analysis

Simon’s two-stage optimal design was used (10). We used an objective response rate in 25% of patients to extend the evaluation of the combination regimen of S-1 plus gemcitabine in further randomized trials. If <10% of patients showed no objective response or stable disease, this regimen would not be tested in further trials because of inefficacy. Applying an α error of 10% and a β error of 20%, the calculated total number of patients was 34. Assuming that ~10% of patients would be unevaluable, 37 patients would have to be enrolled in this study. The first test would be performed after 13 eligible patients had been enrolled. If ≥1 responses were observed, 11 more patients would need to be evaluated. Although we initially predicted that 37 patients would be enrolled by 2007, only 22 patients were enrolled by August 2007. We decided to report these preliminary results due to the low accrual rate. The duration of response, TTP and overall survival (OS) were calculated using the Kaplan–Meier method. The duration of response was defined as the interval from the onset of CR or PR until evidence of progressive disease (PD) was found. TTP was defined as the time from first dose the date of documented progression. OS was defined as the time from study entry until death from any cause. Analyses were performed using SPSS version...
12.0 (SPSS, Chicago, IL, USA) and SigmaPlot version 9.0 (Systat Software, San Jose, CA, USA).

RESULTS

PATIENTS CHARACTERISTICS

From January 2005 to August 2007, 22 patients were enrolled from two institutions. Median patient age was 62 years (range, 50–73 years), consisting of 14 males and eight females. Nineteen patients (86.3%) had metastases and, of these, 11 patients (57.9%) had multiple liver metastases (Table 1). Seventeen patients (77.3%) had increased pretreatment serum CA19-9 levels. Two patients (9%) had recurrent disease after surgical resection of primary tumors. None of the patients had received prior chemotherapy or radiotherapy.

EFFICACY

The overall response rate was 27.3% (95% CI, 8.7–45.9), with a PR in six patients, stable disease in nine patients (40.9%) and PD in seven patients (31.8%) (Table 2). Of the 17 patients with increased pretreatment CA19-9 levels, 13 patients were available for follow-up. Three patients had a CA19-9 decline of >50% after 6 weeks of chemotherapy. At the time of analysis, 21 patients were confirmed to have died, except for one who was still alive. The median TTP and OS were 4.6 months (95% CI, 2–7.2 months) and 8.5 months (95% CI, 6.8–10.1 months), respectively, and the estimated 1-year survival rate was 27.3% (Fig. 1).

TREATMENT ADMINISTRATION

A total of 123 cycles (median 4; range, 2–18 cycles) was administered to 22 patients. Five patients (22.7%) and 34 cycles (27.6%) required a dose reduction of gemcitabine on Day 8, while dose omissions of gemcitabine on Day 15 were needed in two (9%) cycles. In addition, a total of 24 cycles (19.5%) were delayed. The percentage of the maximal dose intensity for gemcitabine and S-1 over all treatment cycles was 88.6% (591 mg/m²/week) and 93.9% (18.8 mg/m²/week). Twelve (55%) of all the 22 patients did not require dose reduction and cycle delay for all cycles.

Table 1. Patients characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14</td>
<td>63.6</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td>36.4</td>
</tr>
<tr>
<td>Median age in years (range)</td>
<td>62 (50–73)</td>
<td></td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>9.1</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>90.9</td>
</tr>
<tr>
<td>Prior surgical resection of primary tumor</td>
<td>2</td>
<td>9.1</td>
</tr>
<tr>
<td>Extent of disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>3</td>
<td>13.6</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>19</td>
<td>86.4</td>
</tr>
<tr>
<td>Sites of metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>11</td>
<td>57.9</td>
</tr>
<tr>
<td>Lung</td>
<td>1</td>
<td>5.3</td>
</tr>
<tr>
<td>Liver, Lung</td>
<td>1</td>
<td>5.3</td>
</tr>
<tr>
<td>Adrenal</td>
<td>1</td>
<td>5.3</td>
</tr>
<tr>
<td>Ovary</td>
<td>1</td>
<td>5.3</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>2</td>
<td>10.5</td>
</tr>
<tr>
<td>Extra-abdominal LNs/soft tissue</td>
<td>1</td>
<td>5.3</td>
</tr>
<tr>
<td>CA19-9, U/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>17</td>
<td>77.3</td>
</tr>
<tr>
<td>Median (range)</td>
<td>250 (3–54320)</td>
<td></td>
</tr>
</tbody>
</table>

ECOG, Eastern Clinical Oncology Group; PS, performance status; LNs, lymph nodes; CA19-9, carbohydrate antigen 19-9.

Table 2. Tumor response

<table>
<thead>
<tr>
<th>Response</th>
<th>No. of patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>6</td>
<td>27.3</td>
</tr>
<tr>
<td>Stable disease</td>
<td>9</td>
<td>40.9</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>7</td>
<td>31.8</td>
</tr>
</tbody>
</table>

Figure 1. Kaplan–Meier curves for time to disease progression and overall survival (n = 22).
Non-hematologic and hematologic adverse events have indicated a significant survival benefit when combination chemotherapy has been combined with gemcitabine-based regimens (13). Therefore, new drug combination regimens are still being tried to improve the outcome of patients with pancreatic cancer. In this context, we studied gemcitabine and S-1 combination chemotherapy and have demonstrated that the hematologic and non-hematologic toxicities of this regimen were generally mild, comparable to those in patients treated with gemcitabine monotherapy (17). Although the regimen was the same, the response rate and toxicity differed in the two studies, perhaps due to the differences in dose intensities and study populations. Differences may also have been due to the small sample sizes. Larger clinical trials are required to confirm the efficacy of this regimen.

Another Phase I study of the use of gemcitabine–S-1 combination chemotherapy with a different schedule was reported by Ueno et al. (9). These investigators administrated 1000 mg/m² gemcitabine on Days 8 and 15 (8). The response rate of patients to this regimen was 27% and the median TTP was 4.6 months. The treatment was well tolerated with only 18.2% of patients having Grade 3/4 neutropenia and only 4.5% having Grade 3 anemia. Non-hematological adverse events were mainly gastrointestinal, and most patients were treated as outpatients. A previous trial found that the response rate to gemcitabine and S-1 combination therapy was 48%, median survival was 12.5 months, 54% of patients had Grade 3/4 neutropenia and non-hematologic toxicities were generally mild (17). Although the regimen was the same, the response rate and toxicity differed in the two studies, perhaps due to the differences in dose intensities and study populations. Differences may also have been due to the small sample sizes. Larger clinical trials are required to confirm the efficacy of this regimen.

Several oral 5-FU prodrugs have been investigated in various types of cancer (14). One of these, capecitabine, has been shown to be equivalent, or possibly slightly better, in efficacy to fluorouracil (14,15). Recently, the use of gemcitabine–capecitabine combination chemotherapy has demonstrated a significant survival benefit in patients with good performance status (16).

S-1 is a new oral 5-FU prodrg that was designed to enhance the efficacy and to reduce the gastrointestinal toxicity of 5-FU. Several trials have assessed the combination of gemcitabine and S-1 in patients with advanced/metastatic pancreatic cancer. Based on the results of an earlier Phase I study, we used a combination regimen consisting of 60 mg/m² of S-1 for 14 consecutive days and 1000 mg/m² gemcitabine on Days 8 and 15 (8). The response rate of patients to this regimen was 27% and the median TTP was 4.6 months. The treatment was well tolerated with only 18.2% of patients having Grade 3/4 neutropenia and only 4.5% having Grade 3 anemia. Non-hematological adverse events were mainly gastrointestinal, and most patients were treated as outpatients. A previous trial found that the response rate to gemcitabine and S-1 combination therapy was 48%, median survival was 12.5 months, 54% of patients had Grade 3/4 neutropenia and non-hematologic toxicities were generally mild (17). Although the regimen was the same, the response rate and toxicity differed in the two studies, perhaps due to the differences in dose intensities and study populations. Differences may also have been due to the small sample sizes. Larger clinical trials are required to confirm the efficacy of this regimen.

Another Phase I study of the use of gemcitabine–S-1 combination chemotherapy with a different schedule was reported by Ueno et al. (9). These investigators administrated 1000 mg/m² gemcitabine on Days 1 and 8 and 80 mg/m² S-1 from Day 1 to 14 followed by a 1-week rest. The best combination schedule to use with gemcitabine and S-1 is not known. However, it was recently reported that pretreatment with S-1 enhances the effects of gemcitabine in pancreatic cancer xenografts (18,19). Considering this result, S-1 may be used before gemcitabine treatment in a gemcitabine–S-1 combination regimen and our protocol is supported by these study results. More studies are needed to determine the best combination schedule.

Recently, capecitabine and S-1 were shown to have equivalent activity and toxicity in patients with advanced gastric cancer, although the incidence rates of hand–foot syndrome and stomatitis were higher in patients treated with capecitabine (20). Gemcitabine plus capecitabine combination chemotherapy showed a response rate of 15–25% in patients with advanced pancreatic cancer (16,21). In addition, the hematologic and non-hematologic toxicities of this regimen were generally mild, comparable to those in patients treated with gemcitabine plus S-1. The survival benefits of gemcitabine and capecitabine in Phase III trials suggest that S-1 plus gemcitabine may show encouraging results in further randomized trials (22).

### Table 3. Treatment-related adverse events: worse grade reported during treatment period

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>2 (9.1)</td>
<td>3 (13.6)</td>
<td>2 (9.1)</td>
<td>2 (9.1)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (13.6)</td>
<td>15 (68.2)</td>
<td>2 (9.1)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6 (27.3)</td>
<td>3 (13.6)</td>
<td>1 (4.5)</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Non-hematologic

- Aspartate aminotransferase: 3 (13.6), 2 (9.1), 0, 0
- Bilirubin: 1 (4.5), 1 (4.5), 0, 0
- Anorexia: 3 (13.6), 2 (9.1), 1 (4.5), 0
- Nausea and vomiting: 0, 1 (4.5), 1 (4.5), 0
- Diarrhea: 4 (18.2), 0, 0, 1 (4.5)
- Pneumonia: 0, 0, 0, 1 (4.5)
- Anemia: 3 (13.6), 15 (68.2), 2 (9.1), 0
- Neutropenia: 2 (9.1), 3 (13.6), 2 (9.1), 2 (9.1)

Patients (45%) received second-line chemotherapy after failure of first-line treatment.

**Toxicity**

All patients were assessed for toxicity. Grade 2/3 hematological adverse events were neutropenia (13.6/9.1%) and anemia (68.2/9.1%). Grade 4 neutropenia was observed in two patients (9.1%). Non-hematological adverse events were mainly gastrointestinal events (Table 3). One patient died of pneumonia that was unrelated to the toxicity of treatment. Twenty patients (91%) received chemotherapy on an outpatient basis.

**Discussion**

Erlotinib is the only drug that has been proved to provide an additional survival benefit over gemcitabine monotherapy for patients with pancreatic cancer in a prospective Phase III trial (11). However, the prolongation of survival was just 2 weeks and it may not be clinically significant (12). Therefore, new drug combination regimens are still being tried to improve the outcome of patients with pancreatic cancer. In this context, we studied gemcitabine and S-1 combination chemotherapy and have demonstrated that the addition of S-1 to gemcitabine chemotherapy is a feasible and tolerable combination regimen.

The synergistic effect of 5-FU with gemcitabine has been reported in pancreatic cancer cells and a recent meta-analysis of randomized trials of gemcitabine-based combination chemotherapy has indicated a significant survival benefit when gemcitabine was combined with fluoropyrimidine (13).
In conclusion, gemcitabine plus S-1 combination chemotherapy was a feasible and well-tolerated regimen for patients with advanced/metastatic pancreatic cancer. Additional multicenter Phase II and III studies are required to confirm these promising results.

Conflict of interest statement
None declared.

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References