Objective: The objectives of this study were to evaluate the efficacy and toxicity of combination chemotherapy with gemcitabine and cisplatin in patients with metastatic pancreatic cancer.

Methods: Patients naïve to chemotherapy who had histologically or cytologically confirmed metastatic pancreatic adenocarcinoma were entered. Gemcitabine was given at a dose of 1000 mg/m² over 30 min on days 1, 8 and 15, and cisplatin was given at a dose of 80 mg/m² over 150 min on day 1, in 28-day cycles.

Results: A total of 38 patients were enrolled in this study between August 2001 and December 2003. There were no complete responses and 10 partial responses, resulting in an overall response rate of 26% (95% CI: 13.4–43.1%). Twenty-one patients (55%) had stable disease, whereas 7 (18%) had progressive disease. The median time to progression was 4.2 months and the median overall survival was 7.5 months with a 1-year survival rate of 24%. Grade 3–4 toxicities included neutropenia in 26 patients (68%), thrombocytopenia in 19 (50%), anorexia in 15 (39%) and nausea in nine (24%). There was only one episode of neutropenic fever and there were no significant bleeding episodes or treatment-related deaths.

Conclusion: The combination of gemcitabine and cisplatin administered by this schedule produced a good response rate associated with moderate but manageable toxicities in patients with metastatic pancreatic cancer.

Key words: gemcitabine – cisplatin – phase II study – chemotherapy – pancreatic cancer

INTRODUCTION

Pancreatic cancer currently represents the fifth leading cause of cancer-related mortality in Japan, with an estimated 22,260 deaths attributable to the disease in 2004 (1). Most patients with pancreatic cancer have advanced, unresectable disease at the time of diagnosis and their prognosis is extremely poor. Since a randomized study by Burris et al. in 1997 demonstrated that gemcitabine had a survival benefit versus fluorouracil (2), gemcitabine has been accepted as the standard treatment for advanced pancreatic cancer. However, the median survival of patients with advanced pancreatic cancer treated with single-agent gemcitabine has been only about 6 months (2–4), indicating the pressing need for development of novel treatment strategies.
lung cancer and urothelial cancer based on large randomized studies (9,10). Several phase II studies of gemcitabine plus cisplatin for advanced pancreatic cancer have been published to date, most of which have shown that this combination seems to be effective, with response rates of 9–31%, and median overall survivals of 5.6–9.6 months (11–16). However, because there have been few studies of Asians receiving gemcitabine and cisplatin for treatment of pancreatic cancer, we conducted the present phase II study to evaluate the efficacy and toxicity of this combination therapy in Japanese patients with metastatic pancreatic cancer. Although various schedules for the combination of gemcitabine and cisplatin have been reported in previous studies, we administered gemcitabine at a dose of 1000 mg/m² on days 1, 8 and 15 and cisplatin at a dose of 80 mg/m² on day 1 of a 28-day cycle, based on the results of a phase I study conducted in Japanese patients with non-small-cell lung cancer (17).

PATIENTS AND METHODS

PATIENT SELECTION

Patients with histologically or cytologically proven pancreatic adenocarcinoma with at least one bidimensionally measurable metastatic lesion were eligible for the study. Other eligibility criteria included: no previous treatment for pancreatic cancer except surgery; age ≥20 and ≤74 years, Karnofsky performance status (KPS) ≥50, life expectancy ≥8 weeks, adequate bone marrow function (white blood cell count ≥4000/mm³, neutrophil count ≥2000/mm³, platelet count ≥100 000/mm³ and hemoglobin level ≥10.0 g/dl), adequate renal function (serum creatinine level ≤1.5 mg/dl and creatinine clearance ≥60 ml/min), adequate hepatic function (serum bilirubin level ≤2.0 mg/dl, serum aspartate and alanine transaminase (AST and ALT) levels ≤2.5 times upper normal limit or ≤5 times upper normal limit if liver metastases or biliary drainage were present) and adequate pulmonary function (PaO₂ ≥70 mmHg). Exclusion criteria were as follows: symptomatic pulmonary fibrosis or interstitial pneumonia, marked pleural effusion or ascites, central nervous system metastasis, active concomitant malignancy, severe mental disorder, serious complications such as active infection, active gastrointestinal ulcer, or cardiac disease and pregnant or lactating women. Written informed consent was obtained from all patients. This study was approved by the institutional review board at the National Cancer Center and conducted in accordance with the Declaration of Helsinki.

TREATMENT PLAN

This was an open-label, single-center, single-arm phase II study. The patients received gemcitabine at a dose of 1000 mg/m² intravenously over 30 min on days 1, 8 and 15, and cisplatin at a dose of 80 mg/m² just after gemcitabine administration over 150 min on day 1. The treatment cycles were repeated every 4 weeks for a maximum of six cycles unless disease progression or unacceptable toxicity occurred. If patients completed the planned six cycles of treatment without disease progression, then they received gemcitabine monotherapy until disease progression. If patients developed leukopenia of <2000/mm³, neutropenia of <1000/mm³, or thrombocytopenia of <75 000/mm³ during the cycle, gemcitabine administration was skipped. If patients developed leukopenia of <3000/mm³, neutropenia of <1500/mm³, thrombocytopenia of <100 000/mm³, total bilirubin of >2.0 mg/dl, or creatinine clearance of <50 ml/min, initiation of the next cycle was prolonged until recovery. Dose reduction of gemcitabine from 1000 to 800 mg/m² was allowed when patients experienced (i) grade 4 leukopenia or neutropenia, (ii) febrile neutropenia, (iii) grade 4 thrombocytopenia or grade 3 thrombocytopenia requiring blood transfusion, or (iv) grade 3 or greater non-hematological toxicities other than nausea, vomiting, anorexia and hyperglycemia. Patients were dropped from the study if they required more than two dose reductions, or if they were unable to start the next cycle within 4 weeks from the scheduled day.

CLINICAL ASSESSMENTS

Physical examination, complete blood cell counts, serum chemistry and urinalysis were performed at the baseline and at least once weekly after the start of treatment. All patients who received at least one dose of gemcitabine were evaluable for safety. Toxicities were graded according to the National Cancer Institute common toxicity criteria version 2.0. Tumor assessment with computed tomographic scan or magnetic resonance imaging and measurement of the tumor marker CA 19-9 was performed every 4 weeks, and tumor response was evaluated using the criteria of the Japan Society for Cancer Therapy (18), which are similar to those of the World Health Organization. Briefly, a complete response (CR) was defined as the disappearance of all clinical evidence of the tumor for a minimum of 4 weeks. A partial response (PR) was defined as a 50% or greater reduction in the sum of the products of two perpendicular diameters of all measurable lesions for 4 weeks or longer without any evidence of new lesions. No change (NC) was defined as a reduction of less than 50% or a less than 25% increase in the sum of the products of two perpendicular diameters of all lesions for a minimum of 4 weeks. Progressive disease (PD) was defined as an increase of more than 25% or in the sum of the products of two perpendicular diameters of all lesions, the appearance of any new lesion, or deterioration of clinical status that was consistent with disease progression. Primary pancreatic lesions were considered to be assessable but not measurable lesions, because it is difficult to measure the size of primary pancreatic lesions accurately. Time to tumor progression (TTP) was calculated from the date of the start of therapy until...
documented PD or death owing to any cause, whichever occurred first. For patients still alive at the time of analysis and who did not have disease progression, TTP was censored at the date of the last follow-up visit. Overall survival was calculated from the date of the start of therapy to the date of death owing to any cause. Patients alive on the date of the last follow-up visit were censored on that date. Median probability of survival and the median TTP were estimated by the Kaplan–Meier method. A total of 38 patients were scheduled for enrollment based on assumptions that the expected response rate of this regimen was 20%, the threshold rate was 5%, the $\alpha$ error was 5% (one-sided), and the $\beta$ error was 10%.

RESULTS

PATIENTS

Thirty-eight patients with metastatic pancreatic cancer were enrolled in this study between August 2001 and December 2003 at the National Cancer Center Hospital, Tokyo, Japan. All of them received at least one cycle of chemotherapy and were evaluable for toxicity and response. The patient characteristics are shown in Table 1. Before the start of the study, six patients had received surgical resection and 10 had undergone biliary drainage for obstructive jaundice. The KPS was $\geq 80$ in all patients. Twenty-eight patients had abdominal and/or back pain before treatment, and morphine had been prescribed for 18 of them.

TREATMENTS

A total of 107 cycles were administered to the 38 patients with a median of 2 cycles per patient (range 1–6). Gemcitabine was administered on day 8 and day 15 in 93 (87%) and 63 (59%) of the 107 cycles, respectively. Mean dose intensity for gemcitabine and cisplatin was 557 mg/m²/week (range 368–750) and 18.6 mg/m²/week (range 17–20), corresponding to 74 and 93% of the planned protocol dose, respectively. Gemcitabine dose reduction was required in 10 patients owing to hematological toxicity. After completion or discontinuation of the protocol study, 20 patients received subsequent chemotherapy (19 patients received gemcitabine monotherapy and one patient received fluorouracil and cisplatin combination therapy), and the remaining 18 patients received only supportive care.

RESPONSE AND SURVIVAL

There were no complete responses and 10 partial responses, giving an overall response rate of 26% (95% CI: 13.4–43.1%). NC was noted in 21 patients (55%), and PD in seven (18%). The serum CA 19-9 level was reduced to less than half in 10 of 32 patients (31%) in whom the pretreatment level of CA 19-9 had been elevated to above the upper normal limit (37 U/ml). At the time of analysis, all the patients were confirmed to have died, except for one who was lost to follow-up. The cause of death was disease progression in all cases. The median TTP was 4.2 months and the median overall survival was 7.5 months with a 1-year survival rate of 24% (Fig. 1).

TOXICITY

All 38 patients were assessed for toxicities, which are listed in Table 2. The most common toxicities were myelosuppression, especially neutropenia and thrombocytopenia. Grade 3–4 neutropenia and thrombocytopenia occurred in 68 and 50% of the patients, respectively. The neutrophil and

![Figure 1. Overall survival curve (a) and time to progression (b) for all 38 patients.](https://academic.oup.com/jjco/article-abstract/37/7/515/804300/0137515.1504.000)
platelet count nadirs typically occurred on day 15. Although most of these hematologic toxicities were transient and reversible, one patient, a 45-year-old man, required hospitalization as a result of severe myelosuppression (grade 4 neutropenia and grade 4 thrombocytopenia) accompanied by severe non-hematological toxicities (grade 4 stomatitis, grade 3 rash, grade 3 fatigue and grade 3 febrile neutropenia) in the middle of the first cycle of treatment. After intensive medical therapies including antibiotics, granulocyte colony-stimulating factor and platelet transfusion, he recovered from these toxicities. No other unexpected severe toxicities were observed during the study and there were no treatment-related deaths. Although gastrointestinal toxicities such as nausea, vomiting and anorexia were frequently observed after cisplatin administration, most of them were manageable with appropriate medical treatment (all of the study patients received cisplatin on day 1 on an inpatient basis). There were no cumulative toxicities except for renal toxicity: six patients discontinued the protocol study because their creatinine clearance decreased to 50 ml/min or less after several cycles of treatment (median 4 cycles, range 1–5), although the serum creatinine level was within 2.0 mg/dl in all patients.

### DISCUSSION

We conducted the present study to evaluate the efficacy and toxicity of gemcitabine and cisplatin combination therapy in 38 Japanese patients with metastatic pancreatic cancer. This combination therapy produced a relatively good response rate of 26%. In addition, the median TTP of 4.2 months and median overall survival of 7.5 months were better than those reported in most studies of gemcitabine monotherapy for advanced pancreatic cancer (TTP 2–3 months, overall survival about 6 months) (2–4). To date, several phase II studies of this combination for advanced pancreatic cancer have been published (Table 3) (11–16). Although those studies used various schedules of gemcitabine and cisplatin administration, most of them demonstrated promising efficacy of this combination, with a response rate of around 20% or higher and/or a median survival of >7 months.

The major toxicity of the gemcitabine and cisplatin combination is myelosuppression. In many studies of this combination, more than half of the patients were reported to suffer grade 3–4 neutropenia and/or thrombocytopenia during the study period (Table 3). Among these studies, hematological toxicity in our study was strong, with a 68% incidence of grade 3–4 neutropenia and a 50% incidence of thrombocytopenia. The schedule adopted in our study, in which cisplatin was administered as an undivided dose on day 1, might have enhanced these toxicities. Although the incidences of G3–4 neutropenia and thrombocytopenia in our study were high, most of such episodes were transient and resolved spontaneously. There was only one episode of neutropenic fever, no significant bleeding episodes and no treatment-related deaths. Furthermore, non-hematological toxicities including nausea and anorexia were manageable, and no unexpected ones occurred. Therefore, we conclude that the gemcitabine and cisplatin combination used according to our schedule is tolerable in patients with advanced pancreatic cancer. However, since the incidences of G3–4 hematological toxicity are high, caution will be required when using this regimen for patients with poor performance status.

Recently, Heinemann et al. (19) conducted a randomized phase III study comparing the gemcitabine plus cisplatin combination with gemcitabine alone. The combination regimen included gemcitabine 1000 mg/m² with cisplatin 50 mg/m² given on days 1 and 15 of a 28-day cycle. They reported that progression-free survival was improved in the combination arm (5.3 months versus 3.1 months, \( P = 0.053 \)), although overall survival showed only a non-significant tendency for improvement (7.5 months versus 6.0 months, \( P = 0.15 \)). Another randomized study performed by the Italian Group (20) also failed to demonstrate a survival benefit of combination treatment, although marked improvements in the response rate (26.4% versus 9.2%, \( P = 0.02 \)) and TTP (20 weeks versus 8 weeks, \( P = 0.048 \)) were demonstrated. Combination therapy with oxaliplatin, another platinum analog, has also failed to demonstrate a statistically

### Table 2. Treatment-related adverse events: worst grade reported during treatment period

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade (No. of patients)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>1–4 (%)</th>
<th>3–4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucopenia</td>
<td></td>
<td>10</td>
<td>11</td>
<td>13</td>
<td>4</td>
<td>100</td>
<td>45</td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td>2</td>
<td>9</td>
<td>15</td>
<td>11</td>
<td>97</td>
<td>68</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td>7</td>
<td>15</td>
<td>13</td>
<td>2</td>
<td>97</td>
<td>39</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td>10</td>
<td>8</td>
<td>18</td>
<td>1</td>
<td>97</td>
<td>50</td>
</tr>
<tr>
<td><strong>Non-hematological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>12</td>
<td>10</td>
<td>9</td>
<td></td>
<td>82</td>
<td>24</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>15</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>66</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>8</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>26</td>
<td>5</td>
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<tr>
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<td>10</td>
<td>15</td>
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<td>89</td>
<td>39</td>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
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<td>7</td>
<td>2</td>
<td></td>
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<tr>
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<td>11</td>
<td>2</td>
<td>0</td>
<td>76</td>
<td>5</td>
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<tr>
<td>Fever</td>
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<td>1</td>
<td>0</td>
<td>0</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
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<td>0</td>
<td>0</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin</td>
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<td>13</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>50</td>
<td>3</td>
</tr>
<tr>
<td>AST</td>
<td></td>
<td>8</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>45</td>
<td>8</td>
</tr>
<tr>
<td>ALT</td>
<td></td>
<td>10</td>
<td>8</td>
<td>4</td>
<td>0</td>
<td>58</td>
<td>11</td>
</tr>
<tr>
<td>Creatinine</td>
<td></td>
<td>11</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>53</td>
<td>0</td>
</tr>
</tbody>
</table>

AST, aspartate aminotransferase; ALT, alanine aminotransferase.
significant survival benefit in comparison with gemcitabine alone in two randomized phase III studies (21,22). Therefore, although many phase II studies including ours have shown promising efficacy for the gemcitabine plus platinum combination, the results of the phase III studies did not support the clinical use of this combination as a first-line therapy for advanced pancreatic cancer.

However, some recent studies have suggested potential activity of platinum-containing chemotherapy for advanced pancreatic cancer. Reni et al. (23) conducted a randomized study of a four-drug regimen including cisplatin, epirubicin, fluorouracil and gemcitabine (PEFG) in patients with advanced pancreatic cancer, and reported that patients allocated the PEFG regimen showed a small but significant improvement in overall survival: 1-year survival rate was 38.5% in the PEFG group and 21.3% in the gemcitabine group. Oettle et al. (24) performed a randomized study of second-line therapy for gemcitabine-refractory advanced pancreatic cancer and reported that the median survival time from the start of second-line therapy in the oxaliplatin/folinic acid/fluorouracil group was significantly longer than that in best supportive care group (21 weeks versus 10 weeks, P = 0.0077). Although the numbers of patients recruited in these studies were small, the results suggested that there is still room for assessing the value of platinum agents for treatment of pancreatic cancer.

In conclusion, our phase II study of gemcitabine plus cisplatin combination therapy demonstrated a good response rate of 26% in patients with metastatic pancreatic cancer with moderate toxicities. However, since all phase III studies reported so far have failed to demonstrate a survival benefit of adding platinum to gemcitabine for advanced pancreatic cancer, other strategies should be considered in further studies.

Conflict of interest statement
None declared.

**References**


