A Phase I/II Study of Combination Chemotherapy with Gemcitabine and 5-Fluorouracil for Advanced Pancreatic Cancer

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Background: In an effort to improve efficacy of single-agent gemcitabine in pancreatic cancer, several studies have examined the effects of 5-FU combined with gemcitabine. However, no studies to date have been performed in Japanese patients. We thus conducted a phase I/II study of gemcitabine and infusional 5-FU in Japanese patients to determine a recommended dosage for this combination and clarify efficacy and toxicity.

Methods: Phase I evaluated the frequency of dose limiting toxicity of two 5-FU dosages (400 and 500 mg/m²/day) infused continuously over 5 days combined with gemcitabine 1000 mg/m²·3 every 4 weeks. Results from phase I determined the recommended dosage to be examined in phase II for effect on survival period, clinical benefit response (CBR), tumor response and safety.

Results: A total of 34 chemo-naive patients were entered into the study. All had a Karnofsky performance of >50 points and distant metastases. Dose limiting toxicities in phase I determined the recommended 5-FU dosage at 400 mg/m²/day. Grade 3–4 hematological toxicities (neutropenia, leukopenia and thrombocytopenia) were the most common severe toxicities. For the 28 patients administered the recommended dosage, 1-year survival rate was 14.3%, median survival time 7.1 months and progression free survival 3.2 months. Seven patients achieved a 25% overall response rate and three showed 27.3% improvement in CBR.

Conclusion: Although a meaningful survival benefit over single-agent gemcitabine was not demonstrated, 5-FU 400 mg/m²/day infused continuously over 5 days in combination with gemcitabine 1000 mg/m²·3 every 4 weeks appeared to be a moderately effective palliative treatment with low toxicity in Japanese patients with metastatic pancreatic cancer.

Key words: pancreatic cancer – phase I/II study – chemotherapy – gemcitabine – 5-FU

INTRODUCTION

Pancreatic cancer is a virulent disease with an extremely poor prognosis. Of all the treatment modalities for pancreatic cancer, only surgical resection offers the opportunity for a cure. However, because of local extension and/or metastatic disease, only a small minority of pancreatic cancer patients are candidates for curative resection. Moreover, even for these selected patients, prognosis remains unsatisfactory because of the postoperative recurrence, indicating that surgery alone has only limited value in the treatment of pancreatic cancer. Accordingly, to improve the overall survival of patients with pancreatic cancer, there is an urgent need to develop an effective non-surgical treatment for this disease.

Previously a randomized controlled study demonstrated that gemcitabine, a nucleoside analogue, was effective in palliating symptoms and prolonging survival in patients with advanced pancreatic cancer (1). In the present study, gemcitabine showed a statistically significant advantage in both clinical benefit response (CBR) (23.8% versus 4.8%, P = 0.0022) and median survival (5.65 versus 4.41 months, P = 0.0025) compared with weekly bolus 5-fluorouracil (5-FU). Although single-agent gemcitabine has been accepted worldwide as the first-line therapy for advanced pancreatic cancer, there is substantial room for improvement in chemotherapy for pancreatic cancer because single-agent gemcitabine provides only limited benefit with a median survival of 4–6 months (1–3).

One approach has been to look for possible agents to use in combination with gemcitabine. A promising candidate has been the fluoropyrimidine, 5-FU, a key chemotherapeutic agent for pancreatic cancer before introduction of gemcitabine. Initially two in vitro studies in HT-29 colon cancer cells...
using fluoropyrimidines in combination with gemcitabine suggested at least additive activity (4,5). Several phase II trials of gemcitabine combined with bolus 5-FU were then conducted, all of which showed promising results (6–9). Based on these findings the Eastern Cooperative Oncology Group (ECOG) conducted a phase III trial to compare gemcitabine plus bolus 5-FU with gemcitabine alone in patients with advanced pancreatic cancer (10). Although the overall survival in the combination arm tended to be superior to that in the gemcitabine alone arm, it was not possible to show a statistically significant difference. Since bolus 5-FU was adopted in this trial, we considered that administering infusional 5-FU might increase the efficacy of the regimen because (i) infusional 5-FU had previously demonstrated a superior antitumor effect to bolus 5-FU in colon cancer (11) and (ii) the effectiveness of infusional 5-FU in the combination with gemcitabine had not been elucidated in pancreatic cancer. Furthermore, since little information is available on the combination of gemcitabine and infusional 5-FU in Japanese patients, we decided to conduct a phase I/II study to determine the recommended dosage of this combination and to clarify its efficacy and toxicity in patients with metastatic pancreatic cancer.

PATIENTS AND METHODS

ELIGIBILITY CRITERIA

The present study included patients with a histological or cytological diagnosis of distant metastatic pancreatic adenocarcinoma not amenable to curative surgical resection or radiation therapy. Patients were required to have no history of chemotherapy, radiation therapy, curative resection or any other therapy for cancer; be between 20 and 74 years of age with a Karnofsky Performance Status (KPS) of 50 or higher; and have an estimated life expectancy of at least 3 months. Indicators of major organ functions were also required to be at normal levels: hemoglobin ≥ 9.5 g/dL, WBC ≥ 4000/mm³, neutrophils ≥ 2000/mm³, platelets ≥ 100 000/mm³, alanine transaminase and aspartate transaminase levels [ALT (GPT), AST (GOT)] ≤ 2.5 times upper normal limit (UNL) (or ≤ 5 times UNL in patients with obstructive jaundice or liver metastasis), total bilirubin ≤ 2 times UNL, serum creatinine ≤ UNL and PaO₂ ≥ 70 torr. Written informed consent was obtained from all patients in the study.

Patients were excluded from the study if they had pulmonary fibrosis, interstitial pneumonia, heart failure or difficult to control arrhythmia, refractory diabetes mellitus, hypercalcemia (serum Ca ≥ 11.5 mg/dL) or active infection. Other exclusion criteria included pregnant or lactating females, or females of childbearing age not using effective contraception, severe drug hypersensitivity, brain metastases, obvious neuropathy or mental disorders, active concomitant malignancy, other serious medical conditions or patients who received any investigational drug within 30 days before enrollment.

STUDY DESIGN

This was a phase I/II study performed in two steps. The objective of Step 1 (phase I) was to evaluate the frequency of dose limiting toxicity (DLT) and then use this to determine which of the three possible 5-FU dosages (400, 500, 600 mg/m²/day) would be recommended for continuous 24 h infusion over 5 days in combination with gemcitabine at its approved dosage (1000 mg/m²/day). In Step 2 (phase II), this recommended 5-FU dosage was then administered in combination with gemcitabine at its approved dosage to evaluate the effect of this combination therapy on survival period. Effects on CBR, objective tumor response and the frequency and severity of adverse events were investigated as secondary objectives in Step 2. CBR, objective tumor response and survival period were also examined in those patients from Step 1 who were administered the recommended dosage.

STUDY TREATMENT

**STEP 1 (PHASE I)**

Gemcitabine (Eli Lilly and Company; Indianapolis, IN; USA) at a dose of 1000 mg/m² was administered as an intravenous 30-min infusion on days 1, 8 and 15 every 28 days. Continuous 24-h infusion of 5-FU (Kyowa Hakko Kogyo Co., Ltd., Tokyo, Japan) began immediately after completion of gemcitabine administration on Day 1 and continued for 5 days (Days 1–5). This 28 day period constituted one administration course.

Three possible dosage levels of 5-FU (Level 0: 400 mg/m²/day, Level 1: 500 mg/m²/day, Level 2: 600 mg/m²/day) were assigned for Step 1. The first patient to enter the study began at Level 1. At least three patients were treated at this level and observed for DLT (see below for definition). If three or more patients experienced DLT at Level 1, the 5-FU dosage was reduced to 400 mg/m²/day (Level 0) in the next three to six patients. Otherwise, patients were assigned to either Level 1 or 2 until at least three, but not more than six, patients had been assigned to two sequential levels. The dosage of 5-FU was considered tolerable according to the general method used for phase I trials of anticancer agents, i.e. DLT frequency not higher than 50%.

Treatment was discontinued if there was clear evidence of disease progression or unacceptable toxicity. Another administration course could be initiated if laboratory values met specifically defined criteria (WBC ≥ 4000/mm³, neutrophils ≥ 2000/mm³, platelets ≥ 100 000/mm³, total bilirubin ≤ 2 times UNL, serum creatinine ≤ UNL, diarrhea ≤ Grade 1, mucosal disorders ≤ Grade 1). The next administration course could be delayed up to 8 weeks. Patients who experienced possible DLT received 800 mg/m² of gemcitabine in subsequent courses, although no dose adjustment was allowed during the same course. When patients experienced adverse effects such as Grade 3 diarrhea, Grade 3 mucosal disorders, Grade 3 hand-foot syndrome, serum transaminase of 10 times UNL, Grade 3 hepatic toxicity, or a total bilirubin level of 5.0 times UNL in patients with
obstructive jaundice or liver metastasis, the 5-FU dosage could be reduced to a lower dosage level in subsequent courses or 5-FU could be omitted in subsequent courses when the lowest dosage (400 mg/m²/day) of 5-FU was given. When patients had leukocytopenia (<2000/mm³) or thrombocytopenia (70,000/mm³) on day 7–8 or day 14–15, gemcitabine administration was omitted on that day and postponed to the next scheduled treatment day (12).

**Step 2 (Phase II)**

Step 2 began once the recommended dosage was determined in Step 1. Administration proceeded with the recommended dosage using the same dosing schedule as in Step 1.

**Study Assessments**

The objectives of Step 1 were to evaluate DLT frequency and to determine a recommended 5-FU dosage to be used with the standard dosage of gemcitabine in Step 2. The criteria of DLT included Grade 4 leukocytopenia or neutropenia, Grade 3 or higher neutropenia accompanied by fever (≥38°C) or infection (clinically or biologically confirmed), thrombocytopenia (<25,000/mm³) or transfusion given to patient, Grade 3 non-hematological toxicity (except nausea/vomiting, anorexia, fatigue, hyperglycemia), AST and ALT > 10 times UNL, total bilirubin > 5 times UNL (patients with obstructive jaundice or liver metastasis) or gemcitabine administration omitted twice in succession. The primary endpoint of Step 2 was to evaluate the 1-year survival rate with the recommended dosage since statistically significant improvement was not recognized in objective tumor response (5% versus 0%), but was observed in survival period in a randomized phase III study comparing gemcitabine and 5-FU (1). The secondary endpoint was to evaluate CBR and objective tumor response, as well as the frequency and severity of adverse events.

CBR was evaluated by KPS and pain, as described elsewhere (13–15). KPS was recorded weekly by the physician. Pain was evaluated by measuring changes from baseline in pain intensity and morphine consumption (analgesic use other than morphine was converted to an equivalent morphine dosage). Each patient recorded pain intensity on a pain assessment card everyday. Patients who met at least one of the following criteria were defined as eligible for evaluation of CBR: (i) baseline KPS of 50–70 points, (ii) baseline pain intensity ≥ 20 (out of 100) as measured by the pain assessment card, (iii) baseline morphine consumption ≥ 10 mg/day.

Objective tumor response was assessed every 4 weeks. In the present study, the sizes of metastatic lesions were measured to evaluate tumor response, although pancreatic masses were not considered to be measurable because of the difficulty of accurately determining pancreatic tumor size with current imaging technology (16).

The Japan Society for Cancer Therapy criteria, which are fundamentally similar to the World Health Organization criteria and NCI Common Toxicity Criteria, were used to evaluate tumor responses and adverse events (17,18). The duration of tumor response was calculated from the first day of treatment. Duration of survival was also calculated from the first day of treatment using the Kaplan–Meier method.

**Statistical Analysis**

The sample size for the recommended dosage was determined as follows. The 1-year survival rate of existing treatments was assumed to be 5% in view of the 1-year survival rate observed in the Ueno et al. (19) study. To demonstrate that the true 1-year survival rate of the recommended dosage exceeded 5% at a one-sided significance level of 10% with a power of 80% when a normal approximation test was used, the sample size for the recommended dosage needed to be at least 28 patients.

**RESULTS**

**Patients and Treatments**

Of the 36 patients who registered for the present study, 34 patients were administered the study drugs: 12 patients completed Step 1 (phase I) and an additional 22 patients completed Step 2 (phase II). Table 1 shows the baseline characteristics for patients in Step 1 (Level 1: 6 patients and Level 0: 6 patients), Step 2 and the total number of patients (20) who received the recommended 5-FU dosage in combination with standard gemcitabine (Level 0). There were 20 males and 8 females (median age: 59) who completed at least one administration course at Level 0. All patients showed a good KPS of ≥80 points. The major metastatic lesions for patients who received the recommended dosage were liver (21 patients: 75.0%), lymph node (6 patients: 21.4%) and lung (5 patients: 17.9%).

In Step 1 the dosing criteria, as defined by observed DLT events, assigned patients to the starting (Level 1: 6 patients) and lower (Level 0: 6 patients) dosage levels. No patients were administered the study drugs at Level 2. The recommended dosage (Level 0) was determined by the DLT frequency observed for each level: Level 1 (3/6 patients), Level 0 (2/6 patients).

At Level 1 (Step 1), a total of 22 administration courses were given with a median of three courses for each patient. A total of 89 administration courses were administered at Level 0 (Steps 1 and 2) with a median of two courses for each patient. At the recommended dosage level (Level 0), 23 (8.7%) of 265 scheduled gemcitabine administrations and 1 (0.2%) of 445 scheduled 5-FU administrations were omitted. The dosage was reduced for two (0.8%) gemcitabine administrations, but no dosage reductions of 5-FU were needed. The actual weekly mean dosages administered were 653.4 mg/m² (87.1% of planned dosage) for gemcitabine and 478.7 mg/m² (95.7% of planned dosage) for 5-FU.
The reasons for treatment discontinuation in Steps 1 and 2 were disease progression (27 patients), Grade 3 hepatic dysfunction (2 patients), Grade 3 appetite loss and Grade 3 infection (1 patient), patient refusal due to Grade 3 gastric ulcer (1 patient), Grade 4 stomatitis (1 patient), patient refusal to be admitted to hospital (1 patient) and patient refusal to follow the study protocol (1 patient). All patients who discontinued the treatment due to adverse events recovered from these toxicities after treatment discontinuation.

TOXICITY

All patients in Steps 1 and 2 were evaluated for toxicity. DLT in Step 1 was observed in three out of six patients at Level 1 and in two out of six patients at Level 0. At Level 1, neutropenia (Grade 4) occurred in two patients, and a combination of stomatitis (Grade 4), esophagitis (Grade 4) and increased gamma-glutamyltransferase (Grade 3) in one patient. Less severe DLT events were observed at Level 0: one patient had a gastric ulcer hemorrhage (Grade 3) and one patient a combination of infection (Grade 3) and neutropenia (Grade 3).

Table 2 summarizes the toxicities of all patients (20) who received the recommended dosage (Level 0). This combination therapy at the recommended dosage was generally well tolerated and no treatment-related toxic deaths were reported. Hematological toxicities, notably neutropenia and leukopenia, were the most common severe toxicities. The main Grade 3–4 hematological toxicities were neutropenia (53.6%), leukopenia (25.0%) and thrombocytopenia (10.7%). Hepatic dysfunction (elevated alanine aminotransferase: 17.9%), anorexia (7.2%) and nausea (25.0%) were also commonly observed as Grade 3–4 toxicities. However, the above reactions were all predictable since they are known to be associated with gemcitabine and/or 5-FU, and were well managed during the study.

Efficacy

Table 3 summarizes efficacy at the recommended dosage. Of the 28 patients who were administered the recommended dosage, 26 had died by completion of the study follow-up period. Four of these were classified as early deaths, which were defined as deaths within 91 days after beginning the first administration or within 29 days after the last administration, but all deaths were due to disease progression and not related to treatment. The 1-year survival rate was 14.3% [95% Confidence Interval (CI): 1.3–27.2%], median survival time 7.1 months (95% CI: 6.1–8.6 months) and progression free survival 3.2 months (95% CI: 1.7–4.6 months: Figure 1). All of the 28 patients administered the recommended dosage were evaluable for tumor response; of these, 7 patients achieved a partial response for an overall response rate of 25.0% (95% CI: 10.7–44.9%). The median duration of the response was 4.8 months (range, 1.9–6.3 months), and
10 patients (35.7%) had stable disease and 10 patients (35.7%) had progressive disease. Tumor response was not determined in one patient due to a serious adverse event (hepatic dysfunction), which made it necessary for this patient to discontinue the study early.

Three of the 11 patients who met the CBR analysis criteria showed improvement in CBR for an overall improvement rate of 27.3% (95% CI: 6.0–61.0%). In all 3 patients, KPS was unchanged but pain intensity was reduced. Of the remaining eight patients, CBR was unchanged in three patients and aggravated in five patients.

DISCUSSION

Despite worldwide agreement about the role of gemcitabine as a first-line agent in advanced pancreatic cancer, therapies that can achieve more significant survival advantage are needed because the prognosis of patients with this disease remains very poor. Several phase II clinical trials combining gemcitabine with 5-FU have been performed using different sequences and schedules of administration (6–9,20–31). A review of the various combination regimens of gemcitabine and 5-FU used in these studies for the treatment of advanced pancreatic cancer found them to be well tolerated (32), although adding weekly intravenous bolus 5-FU to weekly gemcitabine did not confer a significant survival benefit in a randomized trial (10). This finding may be related to the power of the study or the mode of administration of 5-FU rather than to a lack of activity of 5-FU, and it may be possible that giving continuous infusional 5-FU would increase the efficacy of the regimen sufficiently to reach both clinical and statistical significance.

The primary objective of this trial was to find a recommended dosage of infusional 5-FU for use in combination with gemcitabine and to evaluate its efficacy and toxicity in Japanese patients with metastatic pancreatic cancer. Based on the results of our trial (Step 1), we found the recommended dosage to be 5-day continuous infusional 5-FU at 400 mg/m²/day (Level 0). DLT findings seen in three of the six patients given 5-FU at 500 mg/m²/day (Level 1) ruled this out as a recommended dosage. Neutropenia, which was observed as DLT in two patients at Level 1, was common in this combination. However, stomatitis and esophagitis in the remaining one patient, both of which were considered DLT and were also consistent with the toxicity profiles of 5-FU, might have been aggravated by Sjogren syndrome in this patient.

In 28 patients at the recommended dosage level, the most common toxicities were myelosuppression, liver dysfunction, appetite loss and nausea, all of which are well known as toxicities of these two agents. Four patients discontinued the treatment due to Grade 4 appetite loss, Grade 3 infection, and Grade 3 hepatic dysfunction, although most of these adverse reactions were transient and the overall toxicity profile in this regimen was acceptable. There appears to be no cumulative toxicity.

At the recommended dosage level, there was a 25% objective response rate with a 1-year survival rate of 14.3% and a median survival of 7.1 months. With respect to CBR, 3 of 11 evaluable patients (27.3%) showed a quality of life improvement. Compared with other reports of single-agent studies of gemcitabine or 5-FU, these results imply an additional benefit for the use of this scheme. Although the activity of this regimen seems to be consistent with results reported from previous studies that used infusional 5-FU in combination regimens (20–31), most of these have been associated with only a modest increase in response rate and/or survival. However, a definitive judgment of the superiority of this
combinations are difficult because the majority of the data, including our results, represent only phase I or II trial outcomes.

Recently, Costanzo et al. (33) randomized patients with advanced pancreatic cancer to infusional 5-FU plus gemcitabine versus gemcitabine alone in a randomized phase II study. The results did not support better activity of the combination over gemcitabine alone. The overall response rate was 8% for gemcitabine alone and 11% for the combination, and the median survival time was 31 weeks and 30 weeks, respectively. Riess et al. (34) conducted a phase III study to compare the combination of gemcitabine and 5-FU administered as a continuous 24-h infusion, modulated by folic acid, with gemcitabine monotherapy. This study also failed to demonstrate any benefit of the combination in terms of overall survival or time to tumor progression despite a manageable safety profile.

The concept of continuous 5-FU administration is evolving with the introduction of oral fluoropyrimidines. Herrmann et al. (35) compared the combination of gemcitabine plus capecitabine with gemcitabine alone in a randomized phase III study. However, no differences were observed with regard to response rate, progression free survival or overall survival. Recently, Cunningham reported a statistically significant survival benefit of capecitabine and gemcitabine combination over gemcitabine, although the role of fluoropyrimidines in the combination with gemcitabine remains controversial because the difference in the median survival time was only 1.4 months (36).

In conclusion, the regimen in the present study appears to be a moderately effective palliative treatment with a low toxicity profile for Japanese patients with metastatic pancreatic cancer. Since randomized trials failed to demonstrate a meaningful survival benefit for combinations of gemcitabine with fluoropyrimidine, including bolus 5-FU, infusional 5-FU and oral fluoropyrimidines such as capecitabine, caution should be taken before planning phase III studies until more promising regimens have been confirmed in phase II studies.

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References


