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ORIGINAL ARTICLE

Phase II study of 5-fluorouracil and paclitaxel in patients with gemcitabine-refractory pancreatic cancer

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Abstract
Purpose There is no effective salvage regimen for failed gemcitabine-based chemotherapy. This study evaluated the efficacy and toxicity of 5-fluorouracil and paclitaxel in patients with gemcitabine-refractory pancreatic cancer.
Methods Between January 2004 and December 2007, 28 patients with pancreatic cancer previously treated with gemcitabine-based chemotherapy were enrolled. 5-Fluorouracil 1,000 mg/m^2 was infused (days 1, 2, and 3) and paclitaxel 175 mg/m^2 (day 1) was administered every 4 weeks. The primary endpoint of this study was efficacy and toxicity and the secondary endpoint was time to progression and overall survival.
Results A total of 75 cycles were given, for a mean of 2.68 cycles per patient. The response could be evaluated in 20 patients. Two patients (10%) obtained a partial response, and four patients (20%) had stable disease. The median time to progression and overall survival was 2.5 and 7.6 months, respectively.

Grade 3/4 hematological toxicity included neutropenia in six patients (21.4%), anemia in one (3.6%), and thrombocytopenia in one (3.6%). One (3.6%) patient experienced grade 4 neuropathy, and two (7.2%) patients experienced grade 3 diarrhea.

Conclusion The 5-fluorouracil and paclitaxel combination treatment seems to be effective in patients with advanced pancreatic cancer that did not respond to a gemcitabine-based regimen.

Keywords Pancreatic cancer · Paclitaxel · 5-Fluorouracil · Gemcitabine

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Introduction

Pancreatic cancer is the fourth most common cause of cancer-related death in Western countries [8] and the sixth most common cause in Korea [11]. Gemcitabine is the gold-standard chemotherapy agent for advanced pancreatic cancer, although it confers only a modest progression-free survival benefit. Almost all pancreatic cancer progresses with gemcitabine-based chemotherapy. Second-line chemotherapy after gemcitabine is needed for about half of the patients, who maintain a good performance status and can tolerate another chemotherapy treatment. However, only a few phase II trials have examined second-line chemotherapy for pancreatic cancer. The survival advantage of second-line chemotherapy in pancreatic cancer has not been proven, and an optimal second-line chemotherapeutic regimen after gemcitabine failure remains to be defined. We clearly need to find better agents or more appropriate drug combinations to improve treatment efficacy and survival in gemcitabine-refractory pancreatic cancer.

Before the gemcitabine era, 5-fluorouracil (5-FU)-based chemotherapeutic regimens were the standard first-line chemotherapy treatments in advanced pancreatic cancer [5, 13, 18]. Even now, 5-FU is used as a second-line chemotherapeutic regimen in gemcitabine-refractory pancreatic cancer, conferring a modest improvement in patient survival

[14, 22]. Paclitaxel is a semi-synthetic taxane with clinical activity in solid tumors. Paclitaxel has been used as a radiosensitizer in pancreatic cancer [19, 20]. In addition, paclitaxel was reported to be an effective second-line chemotherapy in pancreatic cancer [17]. Therefore, it is reasonable to predict that a regimen of 5-FU and paclitaxel may provide some benefit for patients with gemcitabine-refractory pancreatic cancer.

This study evaluated the efficacy and toxicity of a combined 5-FU and paclitaxel regimen in patients with gemcitabine-refractory pancreatic cancer.

Patients and methods

Eligibility criteria

Patients with histologically confirmed locally advanced or metastatic pancreatic cancer who failed to respond to a gemcitabine-based regimen were eligible for enrollment in this study. The other eligibility criteria included were 18 years of age or older, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, adequate bone marrow function (absolute granulocyte count $\geq$1,500/μL, platelet count $\geq$100,000/μL), and adequate renal and hepatic function (serum creatinine level <1.5 mg/dL, serum bilirubin level <1.5 mg/dL, transaminases < twice the upper limit of normal). Patients with any of the following were excluded: non-measurable lesion; history of other malignancy; concurrent insufficiently treated disease such as heart, hepatic, or renal failure; uncontrolled infection; presence of a psychological disorder; pre-existing chemotherapeutic drugs-related toxicities; and pregnancy. This study was approved by the Institutional Review Board of Severance Hospital. We fully informed all patients about the nature and purpose of the study and all patients gave written informed consent.

Treatment schedule

5-Fluorouracil was infused at a dose of 1,000 mg/m^2 as a 24-h continuous infusion (days 1, 2, and 3) and paclitaxel 175 mg/m^2 was administered (day 1). The chemotherapy was repeated every 28 days until disease progression or unacceptable toxicity occurred. The dose of the chemotherapeutic agents was reduced by 25% in cases of World Health Organization (WHO) grade 4 febrile neutropenia, thrombocytopenia, or any WHO grade 3 organ toxicity. The chemotherapy was delayed 2 weeks in patients who did not recover from the toxicity sooner. When WHO grade 4 toxicity or recurrent grade 3 toxicity occurred despite the dose adjustment or when more than 2 weeks were needed for the recovery from toxicity, the treatment was stopped.

Response and toxicity assessments

A medical history, physical examination, complete blood cell count, biochemical profile, CA19-9, chest X-ray, and computed tomography (CT) of the abdomen were obtained before the first chemotherapy session. During treatment, a complete blood cell count and biochemical profile were obtained before and 2 weeks after chemotherapy. Patients were assessed for responses using CT at every two cycles of chemotherapy. Complete remission (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) [21]. Survival time was defined as the time from the first day of treatment until the date of death. Time to progression was defined as the time from the first day of treatment until disease progression or death. Adverse events were graded according to the WHO criteria [15]. When multiple toxicities were observed, the dose was adjusted based on the most severe toxic event. All patients completing at least one cycle of chemotherapy were evaluated for toxicity.

Statistical methods

The overall survival, time to progression, and response duration were analyzed using the Kaplan–Meier product limit method and a linear interpolation for the point estimate of the median. The statistical analyses were performed using SPSS version 11 for Windows (SPSS, Chicago, IL, USA).

Results

Between January 2004 and December 2007, 28 patients (20 males and 8 females) were enrolled in this study. The patient characteristics are shown in Table 1. The mean patient age was 59.6 years. Gemcitabine plus cisplatin was the most common regimen before the study (Table 2). Three patients had been treated with more than one regimen. The median time from initial diagnosis to paclitaxel plus 5-FU chemotherapy was 7.54 months.

A total of 75 cycles of the 5-FU and paclitaxel regimen were given, with a mean of 2.68 cycles per patient. One patient completed eight cycles of chemotherapy, and three patients completed six cycles. Seven patients underwent only one cycle of chemotherapy. One patient required a 25% dose reduction of paclitaxel owing to general weakness. The dose intensities delivered to the patients are listed in Table 3. The causes of not being able to complete the scheduled chemotherapy were disease progression (13/27, 48.1%), chemotherapy-induced toxicity (2/27, 7.4%, one of grade 4 neutropenia combined with bacterial pneumonia

Table 1 Patient characteristics

Characteristic	No. of patients (%)
Gender	
Male	20 (71.4)
Female	8 (28.6)
Age (years, mean ± standard deviation)	59.6 ± 9.6
Performance status	
0–1	13 (46.4)
2	15 (53.6)
Primary tumor site	
Head	14 (50.0)
Body and tail	14 (50.0)
Differentiation	
Well	1 (3.6)
Moderate	11 (39.3)
Poor	6 (21.4)
Unknown	10 (35.7)
Distant metastases	
None	2 (7.1)
Liver	18 (64.3)
Lung	3 (10.7)
Lymph node	6 (21.4)
Other	2 (7.1)
Elevated Carbohydrate antigen 19–9 (>37.0 U/mL)	
Yes	24 (85.7)
No	4 (14.3)
Prior surgery	
None	22 (78.6)
Curative	5 (17.9)
Palliative	1 (3.6)
Prior radiotherapy	
Yes	15 (53.6)
No	13 (46.4)

Table 2 Initial chemotherapy regimen and response

	No. of patients (%)
Initial regimen	
Gemcitabine + cisplatin	19 (67.9)
Gemcitabine only	3 (10.7)
Gemcitabine + erlotinib	1 (3.6)
Gemcitabine + TS-1	1 (3.6)
Gemcitabine + cisplatin + UFT	1 (3.6)
Two or more regimens	3 (10.7)
Best response of prior chemotherapy	
Partial response	8 (28.6)
Stable disease	5 (17.9)
Progressive disease	10 (35.7)
Adjuvant chemotherapy	5 (17.9)
Time from initial diagnosis to 5-FU + paclitaxel chemotherapy, months, median (range)	7.54 (2–69.7)

Table 3 Drug delivery and dose intensity in patients with gemcitabine-refractory pancreatic cancer treated with paclitaxel and 5-fluorouracil ($N = 28$)

Agent	Dose intensity (mg/m^2 per week)	
	Planned	Delivered median (range)
5-FU	750	728.3 (600–750)
Paclitaxel	43.75	42.5 (33.5–43.75)

Table 4 Tumor response, time to progression ($N = 20$) and overall survival ($N = 28$) in patients with gemcitabine-refractory pancreatic cancer treated with paclitaxel and 5-fluorouracil

	No. of patients (%)
Response	
Partial response	2 (10%)
Stable disease	4 (20%)
Progressive disease	14 (70%)
Disease control rate	6 (30%)
Time to progression, median (range)[a]	2.5 (1.2–20.2)
Overall survival, median (range)[a]	7.6 (1.0–31.7)

[a] From the day of the initial second-line chemotherapy

and one of grade 4 neuropathy), disease-unrelated death (2/27, 7.4%), patient refusal (1/27, 3.7%), and deterioration of general condition (9/27, 33.3%).

The response could be evaluated in 20 of 28 patients. Of the eight patients in whom it was impossible to evaluate the response, one died (1/8, 12.8%) and the general condition had deteriorated in seven (7/8, 87.5%). As shown Table 4, two patients achieved PR (10%) and four (20%) achieved SD. The disease control rate (the sum of CR, PR, and SD) was 30% in the 20 patients who could be evaluated. The median duration of time to progression from the start of paclitaxel and 5-FU was 2.5 months, and the median overall survival was 7.6 months (Fig. 1).

Toxicity could be evaluated in all 28 patients. Grade 3 anemia and grade 3/4 neutropenia were recorded in one (3.6%) and six (21.4%) cases, respectively. Grade 3/4 thrombocytopenia occurred in one (3.6%) patient (Table 5), but there was no thrombocytopenia-related bleeding. One patient required a dose reduction because of the deterioration of his general condition. In addition, this patient had to stop the chemotherapy due to pneumonia accompanied by grade 4 neutropenia. Another patient had to stop the chemotherapy because of grade 4 neuropathy. The most frequent non-hematological toxicity was gastrointestinal problems. Grade 3 nausea and vomiting occurred in two patients (7.2%), and another two (7.2%) patients experi-

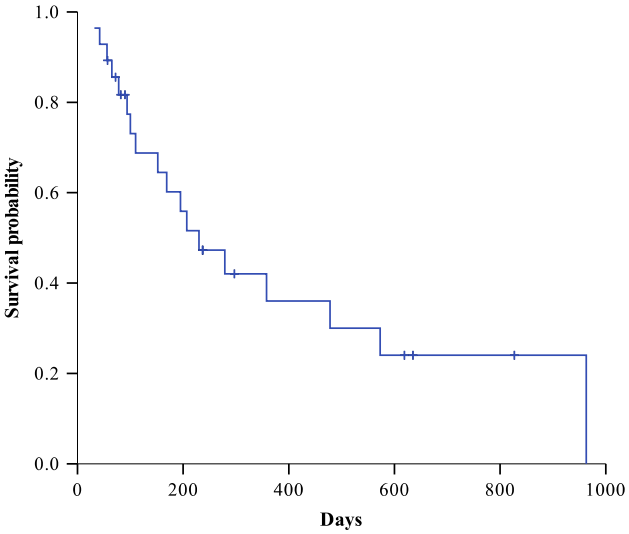

Fig. 1 Overall survival curve for the 28 pancreatic cancer patients, from the day of the initial second-line chemotherapy

Table 5 The numbers of patients who developed toxicities during chemotherapy ($N = 28$)

Toxicity parameter	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	7	3	1	0
Leukopenia	3	2	3	3
Thrombocytopenia	8	1	1	0
AST/ALT elevation	3	2	0	0
Bilirubin elevation	1	0	0	0
Nausea/vomiting	9	1	2	0
Diarrhea	3	1	2	0
Neuropathy	2	0	0	1

enced grade 3 diarrhea. There was grade 2 general asthenia in one patient.

Discussion

Gemcitabine was approved as the standard chemotherapeutic agent for advanced pancreatic cancer based on the clinical response and survival [3]. Nevertheless, the 5-year survival rate is still less than 5% because the response rate is low and chemoresistance occurs early [2]. Consequently, second-line chemotherapy is inevitable for pancreatic cancer patients. Unfortunately, no effective second-line chemotherapy has yet been established. It is difficult to prove the efficacy of new chemotherapeutic agents because pancreatic cancer progresses rapidly and the agents are very expensive. Therefore, we evaluated traditional chemotherapeutic agents as a salvage regimen for advanced pancreatic cancer in patients who were refractory to gemcitabine-based chemotherapy.

There are only a few reports on secondary chemotherapy for pancreatic cancer after failure of gemcitabine-based chemotherapy. Before the approval of gemcitabine, 5-FU was generally used as the first-line chemotherapeutic agent for pancreatic cancer patients. However, as first-line chemotherapy, 5-FU-based regimens only minimally prolong survival in advanced pancreatic cancer. [5, 13, 18]. There are only a few reports on the use of 5-FU as a second-line chemotherapeutic agent. In one report, the Folfox4 regimen was tried as second-line chemotherapy [4]. The disease control rate was 38%. In addition, Mitry et al. [16] reported that oxaliplatin chemotherapy combined with 5-FU was an effective second-line chemotherapy, with a disease control rate of 17%. Therefore, 5-FU may provide a benefit as a second-line chemotherapeutic agent in gemcitabine-refractory pancreatic cancer. The combination of gemcitabine and platinum has been reported to be effective and is frequently used as first-line chemotherapy [6]; thus, there is limited value to using 5-FU with oxaliplatin as a second-line therapy. In our study, 19 patients (67.9%) had received gemcitabine and cisplatin as the first-line regimen.

Paclitaxel interferes with spindle function to block cells at G2M, the most radiosensitive phase of the cell cycle [10]. Consequently, paclitaxel is often used as a radiosensitizer in pancreatic cancer. To our knowledge, only one phase II study has been reported for gemcitabine-refractory pancreatic cancer [17]. In that study, paclitaxel was used as a single second-line therapeutic agent, and the disease control rate was 33.3%, including one patient with CR.

Our study examined paclitaxel combined with 5-FU. This is the first report on this regime in pancreatic cancer. A chemotherapeutic regimen of 5-FU and paclitaxel, generally with the addition of folinic acid, has been studied in other gastrointestinal tract cancers, showing modest effectiveness and yielding response rates of 32–40.7% in advanced gastric cancer [1, 24]. One study reported an additive cytotoxic effect in vitro for paclitaxel followed by 5-FU, whereas sequential exposure to 5-FU followed by paclitaxel had subadditive effects [9]. Therefore, paclitaxel and 5-FU were infused sequentially every 4 weeks in our study.

In this second-line setting, a 30% disease control rate, median time to progression of 2.5 months, and overall survival of 7.6 months were achieved. In similar settings, the combination chemotherapy produced disease control rates of 25% with celecoxib plus 5-FU [14], 53.3% with oxaliplatin leucovorin plus 5-FU [22], and 37% with raltitrexed plus irinotecan [23], respectively. Epidermal growth inhibitors such as erlotinib have proven survival benefits but are not impressive as second-line treatment. The administration of capecitabine plus erlotinib and docetaxel with gefitinib in gemcitabine-refractory metastatic pancreatic cancer achieved disease control rates of 10 and 19.2% and respective median

overall survival times of 6.5 and 2.1 months [7, 12]. Our result was not inferior to those studies.

It is also important to consider the toxicity profile of the paclitaxel and 5-FU regimen. Although some patients experienced hematologic toxicity with the treatment regimen, the toxicity was generally manageable with supportive treatment. The median dose intensity exceeded 90%, and the incidence of grade 3–4 toxicity was similar to values reported for second-line chemotherapy.

In conclusion, we found that combination chemotherapy with 5-FU and paclitaxel is well tolerated and provides survival benefits in gemcitabine-refractory pancreatic cancer patients. Our result gives an additional therapeutic choice for patients with gemcitabine-refractory pancreatic cancer who maintain good performance status.

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