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ORIGINAL ARTICLE

A multicenter phase II study of gemcitabine and S-1 combination chemotherapy in patients with unresectable pancreatic cancer

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Abstract
Purpose To confirm the efficacy and toxicity of gemcitabine and S-1 combination chemotherapy when used as a first-line therapy in patients with unresectable pancreatic cancer.
Methods Patients with locally advanced or metastatic or recurrent pancreatic adenocarcinoma, which was histologically or cytologically proven, with at least one measurable lesion were eligible for the study. Gemcitabine at a dose of 1,000 mg/m^2 was intravenously given over 30 min on days 1 and 8, while S-1 at a dose of 40 mg/m^2 was orally given twice daily from day 1 to 14, and the cycle was repeated every 3 weeks. The objective response rate, which was assessed according to RECIST criteria, was the primary end point.
Results A total of 38 patients were enrolled between June 2006 and June 2007. The median number of treatment courses was 5.5 (range 1–22). Thirty-four patients were evaluable for response. Although no complete response was seen, partial responses were achieved in 11 patients, resulting in an overall response rate of 32% [95% confidence interval (CI) 17–48%]. The median response duration was 6.0 months (95% CI 4.6–8.3 months), the median time-to-progression was 5.4 months (95% CI 2.9–8.0 months), and the median overall survival was 8.4 months (95% CI 5.7–11.1 months). The major grade 3/4 hematologic toxicities were neutropenia (39.5%), leukopenia (15.8%), thrombocytopenia (2.6%), and anemia (7.9%). The major grade 3/4 non-hematologic toxicities included anorexia (10.5%), stomatitis (2.6%), rash (7.9%), fatigue (7.9%) and hyperbilirubinemia (5.3%).
Conclusions Gemcitabine and S-1 combination chemotherapy was effective and tolerable in patients with unresectable pancreatic cancer.

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Introduction

Pancreatic cancer is the fifth most common cause of cancer death in Korea [1] and reveals identical incidence and mortality rates around the world. The poor prognosis of pancreatic cancer has been suggested to be mainly due to diagnosis at the far-advanced stage and due to relative lack of chemosensitive chemotherapeutic agents compared with other tumors.

Since the report by Burris et al. [2], gemcitabine monotherapy has been the standard treatment in patients with unresectable advanced pancreatic cancer. In the study mentioned above, however, gemcitabine monotherapy produced an objective response rate of only 5%, a median survival of 5.7 months, and a 6-month survival rate of 46%, which is quite unsatisfactory. During the last decade, many efforts were made to improve the clinical outcomes of patients with advanced pancreatic cancer. Many phase III trials to compare gemcitabine monotherapy versus gemcitabine-based combination chemotherapies were attempted [3–9]. The partner cytotoxic agents included 5-fluorouracil, oxaliplatin, cisplatin, pemetrexed and irinotecan. Although combination therapy revealed higher response rates than gemcitabine monotherapy, randomized phase III trials of these combinations have failed to demonstrate a statistically significant improvement of survival over gemcitabine monotherapy.

Recently, a phase III trial of the National Cancer Institute (NCI) of Canada Clinical Trials Group in advanced pancreatic cancer revealed a significant prolongation of median progression-free survival (PFS) and overall survival (OS) with the combination of gemcitabine plus erlotinib compared with gemcitabine monotherapy (3.75 vs. 3.55 months, $P = 0.003$ and 6.37 vs. 5.91 months, $P = 0.025$, respectively) [10]. Even though the difference was statistically significant, the absolute benefit of OS was only 2 weeks, and cost-effectiveness should be considered for the acceptance of routine practice [11].

Another gemcitabine-based regimen, which deserves to be studied, is the gemcitabine and capecitabine combination. In one study, gemcitabine and capecitabine failed to improve OS and quality of life as compared with gemcitabine monotherapy [12, 13]. However, another phase III trial in an interim analysis, using different dosing schedules, showed that gemcitabine and capecitabine combination therapy prolonged the OS as compared with gemcitabine monotherapy [14]. Therefore, final analysis and further studies are needed for the definitive conclusion.

S-1 is a new oral fluorinated pyrimidine, which contains tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo) at a molar ratio of 1:0.4:1, based on the biochemical modulation of 5-FU [15]. Tegafur, a prodrug of 5-FU, is gradually converted to 5-FU, while rapidly catabolised by dihydropyrimidine dehydrogenase (DPD) in the liver. CDHP is a competitive inhibitor of 5-FU catabolism, being about 180 times more potent than uracil in inhibiting DPD. When combined with 5-FU, this results in the prolonged maintenance of 5-FU concentrations both in plasma and tumors. Oxo decreases the phosphorylation of 5-FU in the gastrointestinal tract by inhibiting the enzyme, pyrimidine phosphoribosyl transferase. Oxo preferentially localizes in the gut rather than in the tumor and potentially affects pyrimidine phosphoribosyl transferase, thereby selectively inhibiting the formation of 5-FU nucleotides in the gut and theoretically reducing gastrointestinal side effects [16].

S-1 has been shown to be effective in a variety of solid tumors including pancreatic cancer [17]. An early phase II study of S-1 showed promising results with 21% response rate and manageable toxicity profile in patients with metastatic pancreatic cancer [17]. Furthermore, a late phase II study of S-1 showed more favorable efficacy with 37.5% response rate in 40 patients with metastatic pancreatic cancer [18]. Since the combination of gemcitabine and 5-FU was shown to have a marked synergistic cytotoxic effect against pancreatic cancer cells [19], and the administration of oral S-1 is more convenient and simulates the effect of continuous infusion of 5-FU, the combination of gemcitabine and S-1 appeared to be quite logical and feasible. Indeed, in a phase I study of gemcitabine and S-1 combination in pancreatic cancer [20], patients received gemcitabine intravenously over 30 min on days 1 and 8, while S-1 orally twice daily from days 1 to 14. Cycles were repeated every 21 days until the progression of disease. In the above study, patients were scheduled to receive gemcitabine (mg/m^2 per week) and S-1 (mg/m^2 per day) at four dose levels: 800/60 (level 1), 1,000/60 (level 2), 1,000/70 (level 3) and 1,000/80 (level 4). Nevertheless, the maximum-tolerated dose was not reached even at the highest dose level (level 4), since only two of six patients at this level experienced DLT.

We report herein the results of a multicenter phase II trial of S-1 given in combination with gemcitabine, at the highest dose level of the previous phase I study in patients with unresectable pancreatic cancer. The objectives of this study were to determine the objective tumor response rate, OS and time-to-progression, and toxicity profile.

Patients and methods

This study was a multicenter, single arm, open-labeled phase II study. A total of seven centers participated in this study (Seoul National University Hospital, Seoul Municipal Boramae Hospital, Konkuk University Hospital, Korea University Ansan Hospital, Seoul National University

Bundang Hospital, Korea University Guro Hospital, and Korea University Anam Hospital). This study is registered in ClinicalTrials.gov as identifier: NCT00436423.

Patients

The following inclusion criteria were used for the selection of the patients, such as histologically or cytologically proven pancreatic ductal adenocarcinoma, unresectable locally advanced or metastatic or recurrent disease, at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria, no previous palliative chemotherapy or radiotherapy, age between 18 and 70 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, estimated life expectancy >3 months, adequate bone marrow status (absolute neutrophils count >1,500 per μL, platelets >100,000 per μL and hemoglobin >9 g/dL), adequate renal function [serum creatinine level <1.5 × upper limit of normal (ULN)], adequate liver function [serum bilirubin level <2 × ULN, alkaline phosphatase (ALP)] and transaminase levels <5 × ULN). Surgical unresectablility was observed during laparotomy or decided by a multidisciplinary approach team in each participating center.

The exclusion criteria were as follows, namely, recent congestive heart failure, angina, arrhythmia, acute myocardial infarction within 6 months, severe neurologic impairment or mental disorder, active infection, uncontrolled diabetes mellitus, pregnancy or lactation, women of childbearing age unless using effective contraception, brain metastasis, second primary malignancy within 5 years except skin cancer or cervix carcinoma in situ.

The study was approved by the Institutional Review Board of each institute and a written informed consent was obtained from all patients.

The pre-therapeutic work-up included a complete physical examination, ECOG PS, body weight, symptoms including pain scale, abdominal computed tomography (CT) scan, CA 19-9 assay, standard chest X-ray examination, and thoracic CT scan if required.

Treatment

Gemcitabine 1,000 mg/m^2 was intravenously given as a 30 min infusion on days 1 and 8. S-1 was orally administered twice daily from day 1 through day 14. The cycles were repeated every 21 days.

Three doses of S-1 were established according to body surface area (BSA) as follows, BSA <1.25 m^2, 80 mg/day; 1.25 m^2 ≤ BSA < 1.5 m^2, 100 mg/day; BSA ≥1.5 m^2, 120 mg/day.

Subsequent treatment cycles were started only when neutrophil count >1,500 per μL, platelet count >100,000 per μL, bilirubin <2 × ULN, transaminase <5 × ULN and serum creatinine <1.5 × ULN. Treatment was continued unless disease progression, unacceptable adverse events, or withdrawal of patient's consent.

Dose adjustments

The dose adjustment criteria were based on hematological parameters and the severity of non-hematological toxicities. If grade 2, 3 or 4 adverse events occurred, treatment was discontinued until the adverse events were resolved to grade 0–1. When drugs could not be administered due to adverse events even after 3 weeks postponement from the planned day of next administration, treatment was stopped.

If ANC <500 per μL lasting more than 7 days, neutropenic fever episode, platelet <50,000 per μL with bleeding, or platelet <25,000 per μL occurred during the previous treatment, the dose of gemcitabine and S-1 was reduced by 25%, respectively, for the following treatment.

Complete blood count was checked on day 8 of each cycle, and the dose of day 8 gemcitabine was adjusted according to these rules: if ANC >1,000 per mm^3 and platelet >75,000 per mm^3, 100% dose of day 1 gemcitabine; if 750 per μL < ANC <1,000 per μL or 50,000 per μL < platelet <75,000 per μL, 75% dose of day 1 gemcitabine; if ANC <750 per μL or platelet <50,000 per μL, omit day 8 gemcitabine. There was no intra-cycle dose adjustment of S-1. For grade 3 non-hematologic toxicities other than nausea/vomiting, patients received 75% of gemcitabine and S-1 dose. If grade 2 neurotoxicity was observed, S-1 dose was reduced by 25%. In cases of grade 3 neurotoxicity, S-1 administration was omitted. In cases of grade 4 toxicity, both drugs were stopped.

Assessment of therapeutic efficacy

The primary end point of this study was to determine the efficacy as the tumor response rate, which was defined as the sum of complete and partial responses based on the RECIST criteria. Tumor responses were assessed after every two cycles or earlier in patients with suspected progression. All responses were confirmed at least 4 weeks later. The secondary end point for efficacy included the time to progression (TTP), time to treatment failure, duration of response and OS.

The TTP was measured from the date of first treatment up to the time when progression or death with no evidence of progression was observed. The time to treatment failure was defined as the time between the start of treatment and the discontinuation of treatment because of progression of disease, death, patient's refusal to continue or unacceptable toxicity. The duration of response was measured from the date of response up to disease progression. The OS was

estimated from the date of first treatment to death or last follow-up visit.

Assessment of toxicity

Toxicity was assessed with the NCI Common Toxicity Criteria (CTC) scale (version 3.0). A complete blood count was carried out on day 8 to assess hematological toxicity, and patients underwent a complete physical examination and serum bilirubin, transaminase and creatinine assays before each treatment cycle. The patients were interviewed before each session, focusing on pain, nausea, vomiting, mucositis, diarrhea, asthenia, weight loss and neurological disorders. All patients who received at least one treatment session were considered assessable for toxicity.

Statistical analysis

The number of patients required for the study was determined according to the Simon's method. The null and alternative hypothesis response rates were 10 and 27%, respectively. The sample size of this trial was 38 patients with type I error of 5%, 84.6% power, and 15% dropout rate. Objective response, survival, and all toxicity analyses were carried out on intention-to-treat population. The results are expressed as mean ± standard deviation or as ranges, if appropriate.

Follow-up started at the outset of treatment. The censoring event for responses was the start of disease progression. The censoring event for survival was the date of death. The OS and TTP were determined using the Kaplan–Meier method. The median TTP, OS times and their associated 95% confidence intervals (CIs) were derived as described by Brookmeyer and Crowley.

Time-to-event end points were compared by log-rank testing. Response rates were analyzed by the χ^2 test. The influence of the prognostic factors, such as PS, disease extent (locally advanced vs. metastatic), CA19-9, CRP, CA19-9 response, on the primary and secondary end points was tested by proportional hazards techniques or logistic regression.

Results

Patient characteristics

From June 2006 to June 2007, 38 patients with advanced pancreatic adenocarcinoma were enrolled by seven centers, which participated in this prospective study. The baseline characteristics of patients are shown in Table 1. Six patients (16%) had locally advanced disease, 26 patients (68%) had metastatic disease, and 6 patients (16%) had recurrent disease. These six recurrent patients relapsed within 4–19 months after surgery. Of these recurred six patients, four patients received adjuvant concurrent chemoradiation

Table 1 Patient characteristics

Characteristics	No. (%)
Gender	
Male	24 (63)
Female	14 (37)
Age (years)	
Median (range)	63 (41–74)
ECOG PS	
0	4 (10)
1	28 (74)
2	6 (16)
Analgesics use	
Yes	28 (74)
No	10 (26)
Primary tumor site	
Head	13 (34)
Body	12 (32)
Tail	13 (34)
Disease extent	
Locally advanced	6 (16)
Metastatic	26 (68)
Recurrent	6 (16)
Sites of metastasis[a]	
Liver	28 (74)
Lung	2 (5)
Peritoneum	7 (18)
Lymph nodes	11 (29)
Bone	1 (3)
Spleen	1 (3)
Prior therapy	
Curative surgical resection	6 (16)
Palliative surgical resection	2 (5)
Adjuvant concurrent chemoradiation	4 (11)
CA 19-9[b] (U/ml)	
Elevation (>40 U/ml)	34 (89)
Median (range) in all 38 patients	979 (5–55,000)
Median (range) in 34 patients with CA 19-9 elevation	1,905 (40–55,000)
CRP[b,c] (mg/dL)	
Median (range)	3.60 (0.00–73.90)
Total bilirubin[b] (mg/dL)	
Median (range)	0.6 (0.2–1.3)

ECOG Eastern Cooperative Oncology Group, *PS* performance status, *CRP* C-reactive protein

[a] Sites are overlapping

[b] Levels are those at the time of treatment initiation

[c] $n = 20$

with fluoropyrimidine without gemcitabine. The recurred sites of these six patients were all distant sites: liver (three patients), lung (one patient), lung and regional lymph node (one patient), and liver and peritoneal seeding (one patient), respectively.

Two patients received palliative surgical resection before enrollment on this study. The remnant tumor site was peritoneum in two patients.

Thirty-eight patients were assessable for toxicity and 34 for the tumor response. At the time of last analysis, 29 patients had died and 1 patient was still being treated. The median follow-up time for all patients was 8.63 months (95% CI 7.98–12.00 months).

Delivered treatment

A total of 280 cycles were delivered to patients. Median cycle was 5.5 (range 1–22). The median dose intensity of gemcitabine was 626.5 mg/m^2/week, which was 93.9% of planned dose-intensity. Moreover, the median dose intensity of S-1 was 42.3 mg/m^2 per day, which was 90.0% of planned dose-intensity of protocol (Table 2). The calculation of actual or received dose intensity was done according to the method by Longo et al. [21].

In 29 patients, treatment was discontinued due to disease progression, and treatment was discontinued in one patient due to toxicity (cerebral vascular infarction). However, the causality of this adverse event was not clear. Since the hypercoagulability and presentation as thrombosis or embolism is well known in pancreatic cancer, this cerebral vascular infarction might be related to hypercoagulability associated with cancer. In addition, seven patients refused further treatment (intolerance to treatment in three patients and causes not defined in four patients). The causes of intolerance to treatment in three patients were anorexia (two patients) and fatigue (one patient).

Table 2 Duration of administration and dose intensity

Treatment variables	
Number of cycles	
Total	280
Median (range)	5.5 (1–22)
Dose intensity of gemcitabine, mg/m^2 per week (%)	
Mean	602.2 (90.3)
Median (range)	626.5 (333.3–666.7)
Dose intensity of TS-1, mg/m^2 per week (%)	
Mean	41.1 (87.4)
Median (range)	42.3 (12.1–50.8)

Table 3 Efficacy result

Efficacy endpoint	Result
Response[a], no. (%)	
Complete response	0 (0)
Partial response	11 (29)
Stable disease	15 (40)
Progressive disease	8 (21)
N/A	4 (10)
Response rate[b] (%)	32 (95% CI 17–48)
Disease control rate[a] (%)	68 (95% CI 54–83)
Duration of response (months)	6.42 (95% CI 4.57–8.27)
Clinical benefit response (CBR)[c] (%)	41 (95% CI 23–59)
CA 19-9 response after two cycles of chemotherapy[d] (%)	
25% decline	44 (95% CI 27–61)
50% decline	38 (95% CI 22–54)
75% decline	18 (95% CI 5–31)
Time to treatment failure (months)	3.73 (95% CI 1.72–5.75)
Time to progression (months)	5.43 (95% CI 2.91–7.96)
Overall survival (months)	8.40 (95% CI 5.68–11.12)

[a] n = all 38 patients (ITT population)

[b] n = 34 response-evaluable patients (PP population)

[c] n = 29 CBR evaluable patients

[d] n = 34 patients with baseline CA 19-9 elevation

Response to treatment and survival

Of the total 38 patients, response evaluation was possible in 34 patients. Disease evaluation by follow-up imaging study was not performed in four patients because treatment was stopped due to toxicity (one patient) or patient's refusal for further treatment (three patients) (Table 3).

There were 11 (29%; 95% CI 15–43%) partial responses in the intention-to-treat population (n = 38). Fifteen patients (40%) had stable disease, and therefore, the overall disease control rate was 69% (95% CI 54–83%). Progressive disease was observed in eight patients (21%). Median duration of response was 6.42 months (95% CI 4.57–8.27), and the time to treatment failure was 3.73 months (95% CI 1.72–5.75). Median TTP was 5.43 months (95% CI 2.91–7.96 months). OS was 8.40 months (95% CI 5.68–11.12 months). The Kaplan–Meier estimate of survival is shown in Fig. 1. The 1-year survival rate was 34% (95% CI 19–49%).

In terms of clinical benefit response, PS, weight change and pain were considered. PS improved in 11 (32%) of 34 patients whose initial ECOG PS was worse than zero. Weight gain was observed in 12 (32%) of the 38 patients, and analgesics requirement declined in 3 (11%) of 28 patients who received analgesics at the time of treatment

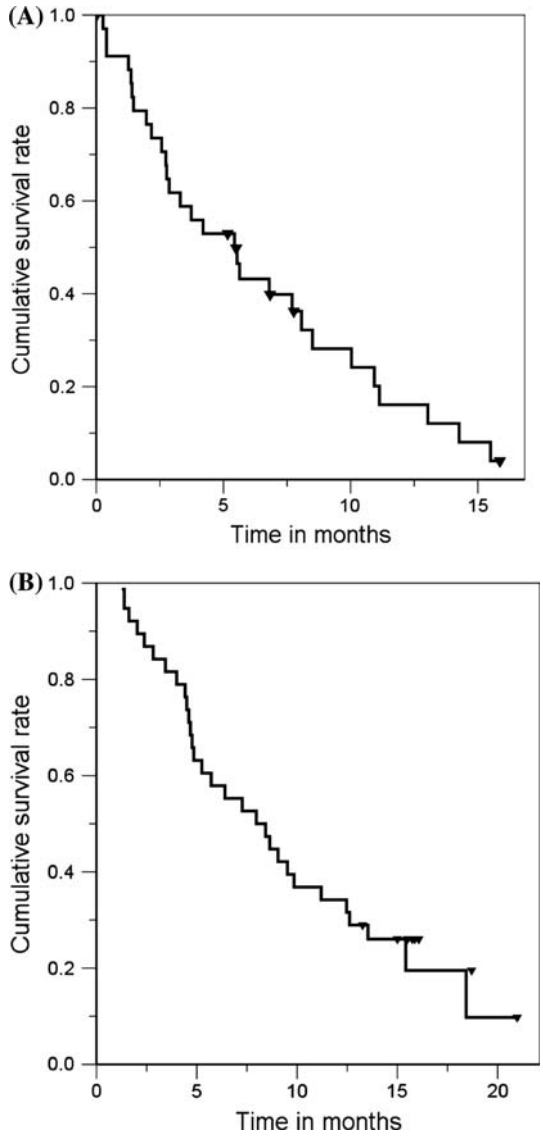

Fig. 1 Time to progression and overall survival. **a** Time to progression, **b** overall survival

initiation. Of 29 patients, 12 patients (41%) showed clinical benefit response.

Of 34 patients with baseline elevation of CA19-9, 15 patients (44%) showed 25% reduction of CA19-9, 13 patients (38%) showed 50% reduction, and 6 patients (18%) showed 75% reduction after two cycles of chemotherapy.

Univariate and multivariate analyses of prognostic factors were done for the TTP and OS (Table 4). In univariate analysis, PS, disease extent, and CA19-9 response by 25% were significant prognostic factors for TTP. In multivariate analysis, disease extent was important for TTP. CA 19-9 response by 25% was significant prognostic factor for OS in univariate analysis, but was not significant in multivariate analysis.

Toxicity

Thirty-eight patients were included in the toxicity assessment (Table 5). There were no treatment-related deaths. Grade 3/4 neutropenia occurred in 39.5% of treated patients, whereas grade 3/4 leukopenia occurred in 15.8% of patients and grade 3 febrile neutropenia occurred in three patients (7.9%). Hematologic toxicities per cycles delivered are described in Table 6.

Non-hematologic grade 3/4 toxicities were as follows: anorexia (10.5%), nausea (2.6%), stomatitis (2.6%), rash (7.9%), fatigue (7.9%), and hyperbilirubinemia (5.3%). There was one patient who gave up treatment due to multiple cerebral vascular infarction.

Discussion

For more than 10 years, the standard treatment regimen for advanced pancreatic cancer has been gemcitabine monotherapy. However, the objective response rates are low and the median OS is still unsatisfactory. Because of its limited activity, many studies have so far attempted to assess the activity of gemcitabine in combination with other cytotoxic chemotherapeutic agents or novel targeted agents.

Although the combination treatment of S-1 and gemcitabine for patients with advanced pancreatic cancer is promising, this combination has not much been investigated. In an earlier phase I study to evaluate the safety of combination therapy of gemcitabine with S-1 in patients with advanced pancreatic cancer, the maximum-tolerated dose was not reached at the highest dosing level (gemcitabine 1,000 mg/m^2 on days 1 and 8, S-1 80 mg/m^2 per day for 14 days, every 21 days) [20].

In the current study, therefore, we adopted the highest dose level of the previous phase I study for patients with unresectable pancreatic cancer. Thus we used 1,000 mg/m^2 of gemcitabine on days 1 and 8 every 21 days, while the dose of S-1 was about 80 mg/m^2 per day for 14 days and three doses of S-1 were used according to BSA (BSA <1.25 m^2, 80 mg/day: 1.25 m^2 < BSA < 1.5 m^2, 100 mg/day: BSA >1.5 m^2, 120 mg/day).

The median dose intensity of gemcitabine was 626.5 mg/m^2 per week, which was 93.9% of planned dose-intensity, while the median dose intensity of S-1 was 296.1 mg/m^2 per week, which was 90.0% of planned dose-intensity of protocol. Furthermore, the toxicity profile was generally very mild; especially, the grade 3/4 neutropenia was 39.5%. It should be mentioned that in a preliminary study, Ueno et al. [22] used the dosing schedules similar to our trial (1,000 mg/m^2 of gemcitabine on days 1 and 8, and S-1 [(BSA <1.25 m^2, 80 mg/day: 1.25 m^2 < BSA < 1.5 m^2, 100 mg/day: BSA >1.5 m^2, 120 mg/day) for 14 days,

Table 4 Prognostic factor analysis

Variables	No.	RR (%)	*P* value	mTTP (mo.)	*P* value	mOS (mo.)	*P* value
(A) Univariate analysis							
Age							
<63	19	26	1.00	3.73	0.88	9.30	0.50
≥63	19	32		5.53		8.40	
Gender							
Male	24	25	0.71	5.53	0.88	8.80	0.50
Female	14	36		2.87		7.53	
PS							
0–1	32	31	0.65	5.53	0.05	8.40	0.13
2	6	17		2.57		4.67	
Analgesics							
Yes	28	29	1.00	4.20	0.96	5.63	0.48
No	10	30		6.80		12.43	
Disease extent							
Local	6	33	1.00	15.50	0.01	16.50	0.09
Distant	32	28		4.20		7.00	
CA 19-9[a]							
< Median[b]	17	29	1.00	6.80	0.22	9.30	0.56
≥ Median[b]	17	29		4.20		5.63	
CRP[c]							
<5.0 mg/dL	11	36	1.00	10.03	0.10	9.73	0.99
≥5.0 mg/dL	9	44		5.43		8.47	
R-CA 19-9[a]							
↓25%	15	47	0.07	8.50	0.01	9.97	0.04
No	19	16		2.57		5.63	
↓50%	13	46	0.13	8.50	0.10	9.97	0.09
No	21	19		2.57		5.63	
↓75%	6	33	1.00	7.70	0.50	9.97	0.41
No	28	29		4.20		7.00	

Variables	HR for progression (95% CI)	*P* value	HR for death (95% CI)	*P* value
(B) Multivariate analysis				
PS				
0–1	–	–	–	–
2	1.94 (0.72–5.23)	0.19	1.70 (0.70–4.31)	0.26
Analgesics				
Yes	1.02 (0.43–2.46)	0.99	1.27 (0.58–2.80)	0.55
No	–	–	–	–
Disease extent				
Local	–	–	–	–
Distant	9.75 (1.29–73.68)	0.03	2.47 (0.73–8.41)	0.15
CA 19-9				
< Median	–	–	–	–
≥ Median	1.65 (0.74–3.66)	0.22	0.86 (0.33–2.24)	0.76
CRP				
<5.0 mg/dL	–	–	–	–
≥5.0 mg/dL	2.45 (0.81–7.41)	0.11	0.57 (0.19–1.76)	0.33
R-CA 19-9				
↓25%	–	–	–	–
No	2.14 (0.92–4.93)	0.07	2.00 (0.87–4.61)	0.10

RR response rate, *mTTP* median time to progression, *mOS* median overall survival, *PS* performance status, *R-CA 19-9* CA 19-9 response after two cycles of chemotherapy, *HR* hazard ratio

[a] $n = 34$ patients with baseline CA 19-9 elevation

[b] Median CRP: 1,905 U/ml

[c] $n = 20$ patients whose baseline CRP value was available

Table 5 Toxicity

Toxicity	Grade			
	1	2	3	4
Hematologic, no. (% per patient)				
Leukopenia	6 (15.8)	10 (26.3)	5 (13.2)	1 (2.6)
Neutropenia	3 (7.9)	5 (13.2)	10 (26.3)	5 (13.2)
Febrile neutropenia	–	–	3 (7.9)	0 (0.0)
Anemia	23 (60.5)	10 (26.3)	3 (7.9)	0 (0.0)
Thrombocytopenia	17 (44.7)	1 (2.6)	0 (0.0)	1 (2.6)
Non-hematologic, no. (% per patient)				
Nausea	9 (23.7)	6 (15.8)	1 (2.6)	0 (0.0)
Vomiting	8 (21.1)	4 (10.5)	0 (0.0)	0 (0.0)
Anorexia	13 (34.2)	6 (15.8)	4 (10.5)	0 (0.0)
Diarrhea	5 (13.2)	1 (2.6)	0 (0.0)	0 (0.0)
Constipation	7 (18.4)	3 (7.9)	0 (0.0)	0 (0.0)
Stomatitis	2 (5.3)	2. (5.3)	1 (2.6)	0 (0.0)
Fatigue	5 (13.2)	3 (7.9)	3 (7.9)	0 (0.0)
Rash	3 (7.9)	3 (7.9)	3 (7.9)	0 (0.0)
Pruritus/itching	8 (21.1)	4 (10.5)	1 (2.6)	0 (0.0)
Fever	6 (15.8)	5 (13.2)	0 (0.0)	0 (0.0)
Pneumonitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)
Infection without neutropenia	0 (0.0)	2 (5.3)	0 (0.0)	0 (0.0)
Pulmonary embolism	–	–	–	1 (2.6)
Cerebral vascular infarction	–	–	–	1 (2.6)
AST elevation	6 (15.8)	1 (2.6)	1 (2.6)	0 (0.0)
ALT elevation	4 (10.5)	5 (13.2)	0 (0.0)	0 (0.0)
ALP elevation	3 (7.9)	4 (10.5)	0 (0.0)	0 (0.0)
Hyperbilirubinemia	4 (10.5)	3 (7.9)	2 (5.3)	0 (0.0)

Table 6 Hematologic toxicity per cycle (n = 280)

Toxicity	Grade			
	1	2	3	4
Hematologic, no. (% per cycle)				
Leukopenia	37 (13)	28 (10)	7 (2.5)	1 (0.4)
Neutropenia	41 (14.6)	33 (11.8)	26 (9.3)	9 (3.2)
Febrile neutropenia	–	–	3 (1.1)	0 (0.0)
Anemia	164 (58.6)	36 (12.9)	4 (1.4)	0 (0.0)
Thrombocytopenia	55 (19.6)	2 (0.7)	0 (0.0)	2 (0.7)

repeated every 21 days]. In the above study of Ueno et al. [22], the objective response rate was 44.4% and disease control rate was 92.5%, while the median PFS and OS were 5.9 and 10.1 months, respectively. Even though the direct comparison between the results of Ueno et al. [22] and our present study is difficult, the efficacy results seem to be similar between them (response rate 32%, TTP 5.43 months, and OS 8.40 months). On the other hand, the incidence of grade 3/4 neutropenia was 80% and grade 3/4 thrombocytopenia was 22%, which are quite higher than our present results. In the trial of Ueno et al. [22], dose reduction was done in 30 patients among total 54 patients, and the reasons for dose reduction included myelosuppression (18 patients), rash (6), nausea (4), anorexia (4), stomatitis (3), diarrhea (2) and fatigue (2). Moreover, the treatment was discontinued because of adverse events in 22 patients (40.7% of all population) (myelosuppression in 14, fatigue, anorexia and nausea in 4, rash in 2, cerebral infarction in 1 and cholangitis in 1). In our present study, the treatment was discontinued due to toxicity in one patient (cerebral vascular infarction) and three patients refused further treatment because of intolerance to treatment. The same dosing schedule between our current trial and the trial of Ueno et al. [22] showed similar efficacy results, nevertheless, very different toxicity; especially, higher toxicity in Japanese even though they included only patients with ECOG PS 0,1 not 2. The exact reasons for these observations are not clear at present.

An another phase II study in Korea, using the same dose and schedule except higher dosage of gemcitabine (1,250 mg/m^2 on days 1 and 8), showed a response rate of

44% and OS of 7.89 months in chemo-naive patients with locally advanced or metastatic pancreatic cancer [23]. The clinical efficacy was similar to that of our present study. Although the median dose intensities actually administered in the study of Lee et al. [23] were higher than those in the present study (gemcitabine 789 vs. 626.5 mg/m^2 per week and S-1 353 vs. 296.1 mg/m^2 per week), the incidence of grade 3/4 neutropenia and grade 3/4 thrombocytopenia was similar to that of our present study (28.1 vs. 39.5%, 15.6 vs. 2.6%).

Following the phase I study using different schedule of gemcitabine and S-1 combination [24], Nakamura et al. [25] and Kim et al. [26] conducted phase II trials in patients with advanced or metastatic pancreatic cancer using gemcitabine 1,000 mg/m^2 on days 8 and 15 and S-1 60 mg/m^2 per day for 14 consecutive days of a 21-day cycle. The response rate was found to be 48 and 27.3%, and the OS was 12.5 and 8.5 months, respectively. Furthermore, grade 3/4 neutropenia was a major toxicity, which was observed in 55 and 9.1%, respectively, and Nakamura et al. [25] found that gemcitabine had to be reduced in two-thirds of patients. On the other hand, the incidence of gastrointestinal toxicity during all cycles was low in both studies and well tolerated. More studies, focused on optimal dosing schedule, of this combination therapy are warranted.

In the analysis of prognostic factors, PS, disease extent (locally advanced vs. distant), and CA19-9 response were significant for TTP in univariate analysis. However, only disease extent status was a significant factor for prediction of disease progression in multivariate analysis. It is well known that PS and disease extent are important for TTP or OS. In this study, the lack of association of OS might have been due to the small number of patients.

The early reduction of CA19-9 by more than 25% from the baseline level after the first two cycles of chemotherapy showed a tendency of importance for the prediction of treatment benefit. Since CA19-9 is emerging as a surrogate for clinical outcomes in patients with metastatic pancreatic cancer who receive chemotherapy, our present data may provide credence to this finding [27].

In conclusion, the present results demonstrated the efficacy and tolerability of gemcitabine and S-1 combination chemotherapy in patients with unresectable pancreatic cancer. Gemcitabine and S-1 combination therapy appears promising, showing higher efficacy than gemcitabine single therapy. Nowadays, besides the palliative setting, some investigators report the efficacy of gemcitabine and S-1 combination chemotherapy in a postoperative adjuvant setting [28, 29].

Therefore, further evaluation and validation of this combination chemotherapy in patients with pancreatic cancer is clearly warranted.

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Conflict of interest statement None declared.

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