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ORIGINAL ARTICLE

Efficacy of infusional 5-fluorouracil, doxorubicin, and mitomycin-C (iFAM) in the treatment of patients with gemcitabine-pretreated pancreatic cancer and analysis of prognostic factors in a salvage setting

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Abstract
Purpose In gemcitabine-pretreated pancreatic cancer, salvage chemotherapy has not been established, and the prognostic factors are not completely known. The purpose of this study was to determine the efficacy and safety of infusional 5-fluorouracil (5-FU), doxorubicin, and mitomycin-C (iFAM) in patients with gemcitabine-pretreated pancreatic cancer and to elucidate the prognostic factors.
Methods Study eligibility was as follows: (1) 18–75 years of age; (2) relapse within 6 months after adjuvant gemcitabine-based chemotherapy (GBC) or previously treated with palliative GBC; and (3) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2. iFAM consisted of a 5-FU (800 mg/m^2) infusion over 10 h on days 1–5, doxorubicin (30 mg/m^2) on day 1, and mitomycin-C (8 mg/m^2) on day 1 every 4 weeks.
Results Sixty patients were enrolled. The responses to iFAM included a partial response in 6 patients (10.0%) and stable disease in 8 patients (13.3%). The median progression-free survival (PFS) and overall survival (OS) were 2.4 months (95% confidence interval [CI], 2.0–2.8 months) and 6.1 months (95% CI, 4.2–8.0 months), respectively. The 6- and 12-month survival rates were 50.4 and 26.4%, respectively. Grade 3/4 hematologic toxicities included neutropenia (3.3%) and thrombocytopenia (3.3%). The ECOG PS was a significant prognostic factor for PFS ($P < 0.001$) and OS ($P = 0.022$). An elevated CA 19-9 at the time of initiating iFAM ($P = 0.011$) was a poor prognostic factor for OS.
Conclusions iFAM is an effective and well-tolerated in patients with gemcitabine-pretreated pancreatic cancer, even patients with an ECOG PS of 2. ECOG PS and CA 19-9 were shown to be significant prognostic factors in this salvage setting.

Keywords Pancreatic cancer · Gemcitabine-pretreated · 5-fluorouracil · Doxorubicin · Mitomycin-C · Prognostic factors

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Introduction

Pancreatic cancer is relatively rare and accounts for approximately 3% of all cancer diagnoses; however, pancreatic cancer is the 4th leading cause of cancer death in the United States [1]. The incidence of pancreatic cancer is 2.6% and the 9th most frequent cancer in Korea; however, pancreatic cancer, which is responsible for approximately 5.6% of all cancer-related deaths, is the 5th leading cause of cancer deaths in Korea. Although a small proportion of patients with pancreatic cancer are candidates for surgery, the only curative treatment option, the 5-year overall survival (OS) rate in patients who undergo pancreatectomy is only 10–25% [2, 3]. In patients with locally advanced

unresectable or metastatic disease, gemcitabine is now established as a standard first-line choice for the treatment of advanced pancreatic cancer; however, objective responses occur in <10% of patients, and OS is generally approximately 6 months [4].

Therefore, a number of clinical studies have been undertaken in an attempt to enhance the efficacy of frontline chemotherapy. Gemcitabine-based combination regimens have been associated with promising activity in phase II studies [5–7]. In general, when subsequently compared with gemcitabine alone in randomized trials, treatment with gemcitabine doublet, except for gemcitabine and erlotinib, has failed to show clinically meaningful improvements in OS and toxicities [8]. Unfortunately, the incremental survival advantage conferred with the addition of erlotinib has been very small (6.24 vs. 5.91 months; $P = 0.025$). Although efforts to improve gemcitabine as frontline therapy have been ongoing for years, relatively few studies have investigated those patients in whom tumors were initially resistant to gemcitabine, or became refractory after an initial response to gemcitabine-based chemotherapy (GBC), primarily owing to the poor prognosis and the limited life expectancy in patients with gemcitabine-refractory pancreatic cancer [9–13]. A salvage chemotherapy regimen to treat patients with gemicitabine-refractory pancreatic cancer is imperative with the increasing proportion of patients who would be ready to receive second-line therapy maintaining a sufficient performance status (PS) even after rapid failure to gemicitabine. The combination regimens of several agents, such as capecitabine, oxaliplatin, irinotecan, and erlotinib, have been studied in a salvage setting [9–11, 13]. However, there is currently no established salvage therapy in patients with gemcitabine-pretreated pancreatic cancer.

Before gemcitabine was adopted as a standard regimen for patients with advanced pancreatic cancer, 5-fluorouracil (5-FU) was the most frequently used cytotoxic agent. In fact, 5-FU-based combination chemotherapy has been reported to be superior to best supportive care alone in patients with pancreatic cancer [14, 15]. Palmer et al. [14] showed that patients receiving 5-FU, doxorubicin, and mitomycin-C (MMC) have survival advantage (33 vs. 15 weeks). Similarly, Glimelius et al. [15] reported longer survival with 5-FU and leucovorin, with or without etoposide, compared with best supportive care (6 vs. 2.5 months). Of 5-FU-based combination regimens, the combination of 5-FU, doxorubicin, and MMC (FAM) has been shown to be an effective chemotherapy regimen with feasible toxicities in patients with pancreatic cancer. The response rate to FAM is approximately 30%, and the median survival period of responding patients and all patients is 12 and 6 months, respectively [16]. Despite superiority over best supportive care in some studies, a randomized trial failed to demonstrate that FAM has an advantage over single-agent 5-FU [17].

With respect to the pharmacokinetic features of 5-FU, as a bolus of 5-FU rapidly degrades due to the short half-life, a bolus administration of 5-FU has been shown to be inferior to a continuous infusion of 5-FU for antitumor effects and safety in patients with colorectal cancer [18, 19]. Therefore, we planned to administer 5-FU at a dose of 800 mg/m^2/day over a 10-h infusion. We hypothesized that if a combination regimen consisting of infusional 5-FU, doxorubicin and MMC (iFAM) was administrated, this regimen would have a synergistic effect in patients with advanced pancreatic cancer.

There are few published studies which have investigated the efficacy and tolerability of iFAM in patients with advanced pancreatic cancer, especially gemcitabine-pretreated patients. In addition, previous studies have identified the prognostic factors in first-line setting (PS, serum albumin levels, or carbohydrate antigen 19-9 [CA 19-9]) [20, 21], but there are few data that have evaluated prognostic factors in a salvage setting.

Our study was designed to determine the efficacy and safety of iFAM in patients with gemcitabine-pretreated pancreatic cancer and to evaluate the prognostic factors in a salvage setting.

Patients and methods

Patient population

The study population consisted of patients with histologically confirmed, locally advanced or metastatic pancreatic adenocarcinoma. Patients who relapsed during adjuvant GBC or within 6 months of adjuvant GBC (including adjuvant GBC combined with radiation therapy) or developed progressive disease (PD) while receiving palliative GBC were enrolled in this study. Eligibility criteria also included an Eastern Cooperative Oncology Group (ECOG) PS of 0–2, age between 18 and 75 years, measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST), adequate bone marrow function (leukocyte count $\geq$4,000/ul, absolute neutrophil count $\geq$1,500/ul, and platelet count $\geq$100,000/ul), adequate renal and hepatic function (creatinine $\leq$1.5 mg/dl, bilirubin $\leq$1.5 mg/dl, and serum transaminase $\leq$3 times the upper normal limit or 5 times the upper normal limit for patients with liver metastasis).

Patients were excluded if they had histologic findings indicating a condition other than adenocarcinoma, brain metastasis, and a history of other malignancies, with the exception of excised cervical or basal skin/squamous cell carcinoma. All patients were required to provide written informed consent.

Treatment dose and schedule

The iFAM regimen consisted of a 10-h infusion of 5-FU (800 mg/m^2 on days 1–5), doxorubicin (30 mg/m^2 on day 1), and MMC (8 mg/m^2 on day 1). The treatment course was given every 4 weeks. This regimen was an outpatient procedure. The 5-FU infusion was possible via programmable ambulatory pumps; thus, it was an ambulatory regimen. Some patients received the infusion in a day hospital. All patients received serotonin antagonists and dexamethasone as an antiemetic regimen during the entire treatment. If a patient responded to therapy, treatment was continued until there was evidence of disease progression, the appearance of unacceptable toxicity, or patient refusal.

Before each course of treatment, assessment of hematologic and non-hematologic toxicities was performed using the National Cancer Institute Common Terminology Criteria (NCI-CTC) toxicity scale. Dose modifications and treatment delays were based on observed drug-related toxicity. At the start of subsequent courses of treatment, drug doses could be reduced by 25% if grade 3–4 hematologic toxicity or any grade 3 non-hematologic toxicity occurred. Treatment could be delayed for up to 2 weeks until adverse effects resolved or at least improved to grade 1.

Response and toxicity evaluation

A computed tomography (CT) scan of the abdomen and pelvis, as well as the serum CA 19-9 level, was routinely obtained after every second course of chemotherapy or if disease progression was clinically suspected. Evaluation of the tumor response was performed according to RECIST criteria.

Patients were assessed with complete blood counts, liver function profiles, and serum electrolyte and creatinine levels while receiving treatment. A history was obtained, and a physical examination was performed prior to each course of chemotherapy. According to the NCI-CTC toxicity scale, hematologic and non-hematologic toxicities were carefully evaluated, as well as late toxicities, if any.

Dose intensity (mg/m^2/wk) was calculated as the total cumulative dose divided by the duration of treatment. Relative dose intensity was calculated by dividing the dose intensity by the planned dose intensity and expressed as a percentage.

Statistical analysis

The objective of this study was to evaluate the activity and safety of iFAM in patients with pancreatic cancer progressing after GBC. The primary end point of this study was to determine the OS rate at 6 months. Because there are no established survival data for patients who have failed GBC for pancreatic cancer, survival data from a published phase II study in a similar clinical setting was used. Based on prior phase II trials, patients who failed prior chemotherapy had a 6-month survival rate of 30–40% and a median survival of 3–6 months. Fifty-eight patients would be sufficient to discriminate between a 6-month survival rate of 35% (H0) and 46% (H1) with 75% power (1-sided alpha error, 0.05). To calculate the patient number, we used the Fleming single-stage design and statistical tools of Cancer Research and Biostatistics (http://www.crab.org).

The secondary objectives of the study were to assess progression-free survival (PFS), OS, and toxicity. PFS was defined as the time from the first dose of iFAM to the date of documented progression or death from any cause. OS was defined as the time from study entry until death from any cause. PFS and OS were analyzed according to the Kaplan–Meyer method. Multivariate analysis was based on a Cox proportional hazards model to identify independent prognostic factors for PFS and OS. All tests were two-sided, and a P value < 0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS (version 12.0; SPSS, Chicago, IL, USA).

Ethics of study

This study was approved by the Institutional Review Board. (IRB No: H-1007-144-324).

Results

Patient characteristics

Between February 2003 and August 2009, 60 patients were enrolled in this study at the Seoul National University Hospital in Seoul, Korea. The patient characteristics are summarized in Table 1. The median age of the patients was 57.3 years (range, 35.4–74.1 years); 43 patients (71.7%) were men. As anticipated in more than a second-line study, nearly all of the patients were symptomatic from their disease. Only 2 patients (3.3%) had an ECOG PS of 0; 38 (63.4%) and 20 patients (33.3%) had a PS of 1 and 2, respectively. Of 29 patients (48.3%) who had undergone surgery, 27 (45.0%) had curative surgery and 24 received post-operative adjuvant therapy, which consisted of a gemcitabine-containing regimen (20 patients) and 5-FU (4 patients). Of the 20 patients receiving a gemcitabine-containing regimen, 18 patients (30.0%) relapsed during adjuvant GBC or within 6 months after adjuvant GBC. Forty-six patients (76.7%) received prior GBC for metastatic or relapsed disease, 5 patients (8.3%) of whom

Table 1 Patient characteristics

Characteristics	No. of patients (%)
Case	60
Median age, years (range)	57.3 (35.4–74.1)
Men (%)	43 (71.7)
ECOG PS	
0–1	40 (66.7)
2	20 (33.3)
Metastatic site[a]	
Liver	37 (61.6)
Peritoneum	14 (23.3)
Lung	10 (16.7)
Lymph node	10 (16.7)
Others	5 (8.3)
Operation	
Yes	29 (48.3)
No	31 (51.3)
Relapse during adjuvant GBC or within 6 months	18 (30.0)
Number of prior palliative chemotherapy	
1	41 (68.3)
≥2	5 (8.3)
Best response to previous chemotherapy	
Complete response	1 (1.7)
Partial response	13 (20.0)
Stable disease	21 (35.0)
Progressive disease	11 (20.0)
Median CA 19-9, U/ml	712

ECOG Eastern Cooperative Oncology Group, *PS* performance status, *GBC* gemcitabine-based chemotherapy

[a] The number of metastatic sites exceeds that of subjects, due to patients with multiple metastases

received >2 chemotherapeutic lines. The best response rates to previous GBC were 1.7, 20.0, and 35.0% in patients with a complete response (CR), partial response (PR), and stable disease (SD), respectively. Thirty-six patients had disease progression during prior chemotherapy, and 10 patients had disease progression during a chemotherapy-off period as SD or PR to previous GBC.

The most common metastatic site was the liver (61.6%); other metastatic sites included the peritoneum, lungs, and lymph nodes in descending order. The median CA 19-9 level at the time of initiating iFAM was 712 U/ml (range, 1–1,130,000 U/ml). At the time of data analysis, 45 patients (75%) were deceased and 15 patients were alive.

Treatment delivery

One hundred and eighty-five treatment cycles were completed. The median number of cycles per patient was 2 (range, 1–11). One patient underwent only one cycle of iFAM, because of a poor PS. The other patients continued iFAM until disease progression. The dose intensities for each drug, expressed as mg/m^2/week, (relative dose intensity) were as follows: 5-FU infusion, 857 (85.7%); doxorubicin, 6.42 (85.6%); and MMC, 1.72 (85.8%). Initial dose reductions were required in 20 of 60 patients (33.3%) because of an initial PS of 2. During treatment with iFAM, dose reductions due to chemotherapy-induced toxicity and decreased PS were conducted in 6 and 3 patients, respectively.

Treatment efficacy

The treatment patterns and results are listed in Table 2. Six of 60 patients had a PR to iFAM with an overall response rate (ORR) of 10.0% (95% confidence interval [CI], 2.4–17.6%) and 8 patients (13.3%) had SD. The disease control rate was 23.3% (95% CI, 12.6–34.0%) The median duration of follow-up was 5.7 months (range, 0.6–64.3 months). The median PFS was 2.4 months (95% CI, 2.0–2.8 months; Fig. 1a), and the median OS was 6.1 months (95% CI, 4.2–8.0 months; Fig. 1a). The 6-month survival rate was 50.4%, and the 1-year OS was 26.4%. All deaths were attributable to disease progression. Analyzing the treatment patterns after disease progression with iFAM, 29 patients (48.3%) had supportive care alone and 26 patients (43.4%) received further salvage chemotherapy.

Toxicity

Hematologic and non-hematologic toxicities are shown in Table 3. Hematologic toxicity was generally mild. Grade 1–2 anemia was most common, occurring in 10 patients (16.7%). There was no grade 3–4 anemia. One grade 4 toxicity was reported (febrile neutropenia). Grade 3

Table 2 Treatment outcomes

Treatment outcomes	
Median cycles (range)	2 (1–10)
Best response to iFAM[a], *n* (%)	
Partial response	6 (10.0)
Stable disease	8 (13.3)
Progressive disease	45 (75.0)
Not evaluated	1 (1.7)
Overall response rate (95% CI)	10.0% (2.4–17.6)
Disease control rate (95% CI)	23.3% (12.6–34.0)

CI confidence interval

[a] iFAM indicates infusional 5-fluorouracil, doxorubicin, and mitomycin-C

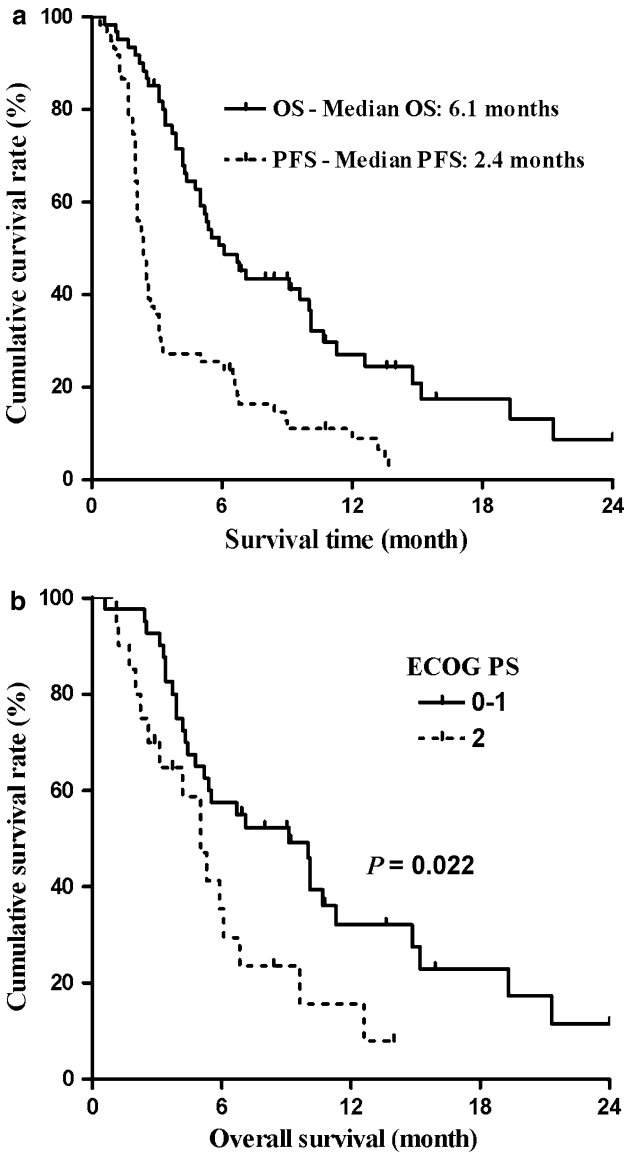

Fig. 1 Kaplan–Meier curves for progression-free and overall survival are shown after infusional 5-fluorouracil, doxorubicin, and mitomycin-C in the treatment of patients with gemcitabine-pretreated pancreatic cancer (**a**) and for overall survival stratified by ECOG PS (**b**). *ECOG* Eastern Cooperative Oncology Group, *PS* performance status

hematologic toxicities were observed in 3 of 60 patients (5.0%), consisting of neutropenia (1.7%) and thrombocytopenia (3.3%). Grade 1–2 neutropenia and thrombocytopenia occurred in 13.3 and 15.0% of patients, respectively. Grade 3 non-hematologic toxicity (mucositis) occurred in 2 patients (3.3%). Twenty-five patients (41.7%) had grade 1–2 alopecia. Other common toxicities included nausea/vomiting and diarrhea. The total number of grade 3–4 toxicities recorded was 7 (11.7%). Overall, the regimen was well tolerated. There were no treatment-related deaths.

Table 3 Treatment-related toxicities

Toxicity[a]	Grade 1–2, *n* (%)	Grade 3–4, *n* (%)
Hematologic toxicity		
Neutropenia	8 (13.3)	2 (3.3)
Anemia	10 (16.7)	0
Thrombocytopenia	9 (15.0)	2 (3.3)
Non-hematologic toxicity		
Nausea/vomiting	7 (11.6)	0
Mucositis	13 (21.6)	2 (3.3)
Diarrhea	7 (11.6)	0
Alopecia	25 (41.7)	0

[a] Toxicity was graded using the National Cancer Institute Common Toxicity Criteria

Prognostic factors

Based on a univariate analysis of survival outcomes according to the clinical variables (age, gender, ECOG PS, CA 19-9, relapse, extent of disease, and response to previous GBC), ECOG PS (0–1 vs. 2) was a significant prognostic factor for PFS ($P < 0.001$) and OS ($P = 0.022$; Fig. 1b). Also, an elevated CA 19-9 level at the time of initiating iFAM ($P = 0.011$) was a poor prognostic factor for OS (Table 4). Based on multivariate analysis for OS, ECOG PS ($P = 0.011$) and CA 19-9 ($P = 0.021$) were significantly associated with OS.

Discussion

The present study demonstrated that iFAM has considerable antitumor activity and manageable toxicities in patients with gemcitabine-pretreated pancreatic cancer. The objective response rate associated with iFAM was 10%, and the PFS and OS were 2.4 and 6.1 months, respectively. Also, the 6- and 12-month survival rates were 50.4 and 26.4%, respectively. The hematologic and non-hematologic toxicities observed were tolerable, even in patients with a PS of 2.

The median OS with best supportive care in pancreatic cancer patients who have failed GBC is approximately 2.8 months [22]. According to one study involving 99 patients who had been enrolled in prospective phase II and III studies and treated with first-line GBC for pancreatic cancer, 47 (47%) received second-line systemic chemotherapy [23]. Of 52 patients who did not receive second-line systemic chemotherapy, 20 (20%) declined second-line treatment. Thirty-two patients (32%) were unable to undergo any additional chemotherapy, because of a poor PS. Another randomized strategic phase III trial (FFCD 0301) reported

Table 4 Analysis of prognostic parameters for survival

	No. of patients (%)	Median PFS (95% CI)	Hazard ratio (95% CI)	*P* value (PFS)	Median OS (95% CI)	Hazard ratio (95% CI)	*P* value (OS)
Age							
<60	35 (58.3)	2.4 (2.0–2.8)	0.851 (0.490–1.478)	0.557	5.9 (4.2–7.6)	0.993 (0.540–1.824)	0.981
≥60	25 (41.7)	2.4 (1.9–2.9)			6.1 (2.1–10.1)		
Sex							
M	43 (71.7)	2.4 (2.0–2.8)	1.175 (0.660–2.091)	0.573	6.8 (2.1–11.5)	0.980 (0.501–1.914)	0.952
F	17 (28.3)	2.4 (1.9–2.9)			5.5 (4.6–6.4)		
CA 19-9[a]							
≤700	28 (46.7)	2.5 (2.3–2.7)	0.644 (0.373–1.114)	0.104	9.6 (3.6–15.6)	0.442 (0.231–0.846)	0.011
>700	29 (48.3)	2.0 (1.8–2.2)			4.4 (3.1–5.7)		
Serum albumin							
<3.9	27 (45.0)	2.1 (1.6–2.6)	1.319 (0.776–2.243)	0.294	5.2 (3.9–6.5)	1.637 (0.903–2.967)	0.099
≥3.9	33 (55.0)	2.5 (2.1–2.9)			9.1 (3.6–14.6)		
ECOG PS							
0–1	40 (66.7)	2.9 (2.3–3.5)	3.072 (1.652–5.711)	<0.001	9.1 (5.7–12.5)	2.068 (1.095–3.904)	0.022
2	20 (33.3)	2.0 (1.7–2.3)			5.0 (3.6–6.4)		
Relapse							
No	33 (55.0)	2.3 (1.8–2.8)	0.871 (0.508–1.495)	0.608	5.0 (3.4–6.6)	0.587 (0.320–1.074)	0.079
Yes	27 (45.0)	2.4 (2.2–2.6)			9.6 (5.1–14.1)		
Liver metastasis							
No	23 (38.3)	2.5 (1.8–3.2)	1.684 (0.966–2.937)	0.057	10.1 (4.9–15.3)	1.611 (0.872–2.973)	0.123
Yes	37 (61.7)	2.1 (2.0–2.2)			5.3 (3.7–6.9)		
Extent of disease							
Local	10 (16.7)	2.5 (0.0–9.2)	1.887 (0.903–3.943)	0.080	3.7 (0.0–12.8)	1.155 (0.524–2.546)	0.720
Distant	50 (83.3)	2.4 (2.1–2.7)			6.1 (4.4–7.8)		
Response of previous chemotherapy							
PD	11 (18.3)	2.1 (1.9–2.3)	0.853 (0.442–1.644)	0.957	3.9 (2.1–5.7)	0.597 (0.276–1.288)	0.181
PR + SD	35 (58.3)	2.4 (1.8–3.0)			6.7 (4.1–9.3)		

PFS progression-free survival, *OS* overall survival, *CI* confidence interval, *ECOG* Eastern Cooperative Oncology Group, *PS* performance status, *PR* partial response, *SD* stable disease, *PD* progressive disease

[a] CA 19-9 and albumin were divided by median value

that a high percentage of patients (61%) were able to receive a second-line chemotherapy [24].

After GBC failure, a large number of patients have a PS which is sufficiently tolerable to endure further treatment, but there is no universally accepted standard salvage chemotherapy in gemcitabine-refractory patients. Moreover, because gemcitabine as adjuvant therapy is known to be effective, many patients who have undergone curative resection receive gemcitabine in an adjuvant setting. A few studies have attempted to evaluate other chemotherapeutic options for gemcitabine-pretreated pancreatic cancer patients [9–11, 13, 25–27]. Several regimens, such as oxaliplatin/capecitabine, oxaliplatin/leucovorin/5-FU, gemcitabine/oxaliplatin, irinotecan/oxaliplatin, raltitrexed/oxaliplatin, and capecitabine/erlotinib, have been tested in gemcitabine-pretreated patients and shown ORRs of 10–24%, and a median OS of 5.2–6.5 months [9–11, 13, 25–27]. A significant improvement in OS was found in a randomized phase III trial with oxaliplatin combined with a 5-FU regimen as the second line of treatment, compared with the best supportive care [28]. Based on these phase II and phase III studies, oxaliplatin- and 5-FU-based regimens are good candidates for salvage therapy in patients with gemcitabine-pretreated pancreatic cancer.

FAM, a combination regimen of 5-FU, doxorubicin, and MMC was originally used for the treatment of advanced gastric cancer [29]. Subsequently, the efficacy of FAM has been demonstrated in other gastrointestinal tract cancers, especially pancreatic cancer [16]. 5-FU has been extensively studied since the 1950s, and ORRs vary widely from 7 to 20%. To date, 5-FU and its derivatives (capecitabine and S-1) have been utilized as components of salvage regimens in patients with pancreatic cancer. The activity of 5-FU is now known to be schedule-dependent. According

to a meta-analysis of 6 randomized trials, it has been reported that a continuous infusion of 5-FU is superior to a bolus administration of 5-FU with respect to antitumor activity and survival in patients with advanced colorectal cancer [18]. In addition, hematologic toxicity, especially neutropenia, appears to be significantly less frequent in patients receiving the infusion schedule [19].

Previous data have suggested that MMC as a single agent may have a similar efficacy to 5-FU [30, 31], and there is evidence for a synergistic effect in vitro between 5-FU and MMC [32]. Based on these findings, a multicenter, prospective randomized study was conducted to compare 5-FU alone with 5-FU plus MMC in patients with advanced pancreatic cancer [31]. The ORR was 8.4% for patients treated with 5-FU alone compared with 17.6% for 5-FU plus MMC ($P = 0.04$). In the current study, despite no significant survival advantage, 5-FU plus MMC had a superior response rate in comparison with 5-FU alone in patients with advanced pancreatic cancer. Also, doxorubicin as single-agent chemotherapy was tested by the Gastrointestinal Tumor Study Group and yielded a PR in 2 of 15 previously untreated patients (13%). The median OS of patients who received doxorubicin as initial treatment was 3 months [33]. Also, the EORTC Gastrointestinal Group showed that epirubicin, another anthracycline derivative, is an active drug in metastatic pancreatic cancer. In the current study, the ORR and disease control rate in evaluable patients were 24 and 50%, respectively, and the median OS was 5 months [34]. Therefore, anthracyclines, such as doxorubicin and epirubicin, are moderately active and can be used in patients with pancreatic cancer.

Our iFAM regimen in which 5-FU was administered via a prolonged infusion over 10 h showed acceptable antitumor activity and safety. The 6-month survival and response rates were comparable to previous phase II studies [10, 11]. Because the duration of OS and disease control rate were 6.1 months and 23.3%, respectively, our outcomes were not inferior to previous studies, even if a direct comparison between our study and other studies is difficult [9–11, 13, 25–28].

The toxicity associated with our regimen was quite acceptable and manageable, although 33.3% of the study population had an ECOG PS of 2. With the exception of one episode of febrile neutropenia, no other toxic events led to an interruption in treatment. Acute hematologic toxicity was limited, consisting mainly of grade 3 thrombocytopenia and neutropenia, and alopecia was the most common with respect to non-hematologic toxicity. There was no serious cardiac toxicity or treatment-related mortality. Although a subgroup of patients in our study with a PS of 2 usually received an initial dose reduction of 25%, the present study showed that iFAM could be administered with caution and was tolerable in this population.

After failure of first-line treatment with GBC, rapid progression, declining PS, and increased symptom burden can render patients unsuitable to receive further treatment. It is important to find the clinical factors that may help select patients with advanced pancreatic cancer who will most likely benefit from second-line therapy, but there are no validated prediction markers. With respect to prognostic factors in patients with gemcitabine-refractory pancreatic cancer, previous studies have reported that PS, previous response to first-line therapy, recurrence after pancreatectomy, peritoneal dissemination, C-reactive protein level, serum albumin level, and liver metastasis are significantly associated with prognosis [10, 23, 35–37]. However, in current study, the serum albumin level and liver metastasis were not significantly associated with PFS and OS. In the present study, a poor PS was identified as an adverse prognostic factor for PFS and OS. PS is recognized as a prognostic value in metastatic pancreatic cancer after first-line chemotherapy, as well as an important prognostic factor in other malignancies [35, 37]. Also, an elevation in CA 19-9 was recognized as a prognostic factor for OS in the current study. The cut-off value of CA 19-9 was set at a median value based on other studies [38, 39]. In several reports involving a small number of patients receiving chemotherapy for advanced pancreatic cancer, there was a correlation between the duration of patient survival and the decline in the CA 19-9 level; the baseline CA 19-9 level was an independent prognostic factor for OS [38–40]. Although a 2006 expert panel on tumor markers in gastrointestinal cancer convened by the American Society of Clinical Oncology concluded that the data are insufficient to recommend the use of serum CA 19-9 levels alone for monitoring response to treatment [41], measurement of CA 19-9 is recommended at the start of treatment and also has prognostic value for survival. Those prognostic factors which were not significant in our study, such as extent of disease and relapse, may have been prone to a Type II error. However, our study included the 60 patients in a second-line homogenous regimen. Indeed, this is not a small number in this setting. Thus, another single-regimen phase II study would not further reduce the type II error than our study. For further validation of these prognostic factors further, a meta-analysis may be helpful.

Although our study showed significant outcomes for efficacy and safety of iFAM as a salvage regimen and prognostic factors in gemcitabine-pretreated pancreatic cancer, our study had several limitations. First, there was the lack of assessment of clinical benefit or quality of life. Second, the sample size calculation was based on univariate analysis and not COX regression. Thus, the study may be underpowered. Third, because of a lack of a control group in this study, we could not make a direct comparison. Sixty patients undergoing second-line palliative setting of

pancreatic cancer is not small, but relatively large. Research resources, such as the patient pool, investigators, agents used, and money, are limited. More informative results which impact on patient management can be driven by a more sophisticated study design. Consideration of a randomized phase II design has some strength compared to single-arm phase II design.

The age limit was set at 75 years, which is not really acceptable in the current era. However, the age distribution in our study population was as follows: 3 patients (5%), 31–40 years; 11 patients (18.3%), 41–50 years; 21 patients (35%), 51–60 years; 19 patients (31.7%), 61–70 years; and 6 patients (10%), 71–75 years. The patients' ages in previous studies generally ranged from 30 to 75 years, and the median age was similar to that of our study. A study on elderly patients or including elderly patients should be considered.

In spite of the aforementioned limitations, our study results are clinically meaningful. Recent clinical trials have mainly utilized new cytotoxic and biological agents, which are very expensive and experimental. In contrast, classic cytotoxic drugs consisting of the iFAM regimen are less attractive, but our study demonstrated that these agents, which are very affordable and available, have similar efficacy and manageable toxicity profiles in patients with gemcitabine-pretreated pancreatic cancer.

The cost-effectiveness in chemotherapeutical regimens is important. However, there are few studies that have evaluated pharmacoeconomic issues associated with the salvage chemotherapy in patients with gemcitabine-pretreated pancreatic cancer. Furthermore, pharmacoeconomic data in one country could not be applied to another country because pharmacoeconomic analysis includes a society's acceptance of burden as well as the price and efficacy of drugs. We suggest that a further investigation regarding the cost-effectiveness of the salvage chemotherapy in patients with gemcitabine-pretreated pancreatic cancer is needed in the future.

The features of our study are as follow. First, in spite of less attractive agents, these classic cytotoxic drugs were studied on a relatively large scale in patients with gemcitabine-pretreated pancreatic cancer. Second, PS is a well-known prognostic factor. Study population in many studies was intended for patients with ECOG PS of 0–1 or included only a small portion of patients with PS of 2. However, our study population consisting of a considerable number of patients with a PS of 2 showed that iFAM was effective and safe, even in patients with an ECOG PS of 2.

In conclusion, gemcitabine-based combination regimens are associated with improvement in OS and clinical benefits when used as first-line therapy for patients with advanced pancreatic cancer; however, the management of gemcitabine-pretreated pancreatic cancer remains to be determined. Our study demonstrated that a classic regimen consisting of a continuous infusion of 5-FU, doxorubicin, and MMC has moderate activity in the salvage setting and can be safely administered, even for patients with an ECOG PS of 2. Therefore, iFAM may represent a reasonable treatment option for patients with advanced pancreatic cancer who experience treatment failure with GBC. Oral 5-FU derivatives, such as capecitabine or S-1, can be expected to have similar efficacy as a prolonged infusion of 5-FU. Instead of an infusion of 5-FU, these oral agents need to be further studied in patients with gemcitabine-refractory pancreatic cancer. Considering the clinical results thus far, oxaliplatin- or 5-FU-based chemotherapy can be a suitable salvage regimen for the control arm of a future randomized clinical trial. Also, the ECOG PS and CA 19-9 are significant prognostic factors for OS in this salvage setting. In the future, the need to determine prognostic and predictive factors is essential to identify the best therapy for all patients. New therapy will require a prospective selection of patients based on these factors. In the setting of second-line therapy, a further trial should be planned and conducted.

Conflict of interest None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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