Gemcitabine and Erlotinib with or without Oxaliplatin in Previously Untreated Advanced Pancreatic Cancer: A Randomized Phase II Trial

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Purpose: Erlotinib has been the only targeted agent to show significantly improved outcomes in pancreatic adenocarcinoma when combined with gemcitabine. We aimed to evaluate whether the addition of oxaliplatin to a combination gemcitabine/erlotinib treatment conferred a clinical benefit in patients with locally advanced unresectable or metastatic pancreatic cancer.

Materials and Methods: Chemotherapy-naïve patients with locally advanced or metastatic pancreatic cancer were randomly assigned to receive GEMOX-T [gemcitabine 1000 mg/m² and oxaliplatin 50 mg/m² on day 1 (D1) and D8 plus erlotinib 100 mg daily for 3 weeks] or GT (gemcitabine 1000 mg/m² on D1 and D8 plus erlotinib 100 mg daily for 3 weeks). The primary endpoint was the overall response rate (ORR).

Results: Between 2013 and 2016, 65 patients were assigned to a treatment group (33 in the GEMOX-T arm, 32 in the GT arm). The ORR was 18.2% [95% confidence interval (CI), 8.82−27.58] in the GEMOX-T arm and 6.2% (95% CI, 0.34−12.06) in the GT arm (p=0.051). The disease control rate was significantly superior in the GEMOX-T arm compared to the GT arm (72.7% vs. 43.8%, p=0.019). After a median follow-up of 19.7 months, the median progression-free survival (PFS) was 3.9 months for the GEMOX-T arm and 1.4 months for the GT arm (p=0.033). However, this did not translate to an improvement in overall survival. The most common grade 3 or higher hematologic adverse events were neutropenia (16.9%) and anemia (13.8%).

Conclusion: The addition of oxaliplatin to a first-line gemcitabine/erlotinib regimen demonstrated higher response rates and significantly improved PFS in patients with locally advanced or metastatic pancreatic cancer.

Key Words: Pancreatic adenocarcinoma, palliative chemotherapy, gemcitabine and erlotinib, oxaliplatin

INTRODUCTION

Despite a greater understanding of molecular biology and tech-

nical advances in cancer genomics, more than 50% of pancreatic cancer patients present with metastatic disease and dismal prognosis. The 5-year survival rate of this disease is less than 10 percent.[1] Previously, gemcitabine demonstrated superiority over fluorouracil[2] in patients with locally advanced or metastatic pancreatic cancer. Thereafter, the efficacy of gemcitabine-based combination regimens has been compared to gemcitabine monotherapy in many clinical trials.[3-5] Among those studies, compared to gemcitabine alone, combination chemotherapy with oxaliplatin has shown significantly improved response rates (26.8% vs. 17.3%, respectively; p=0.04) and progression-free survival (PFS) (5.8 months vs. 3.7 months; p= 0.04),[4] although it has not improved overall survival (OS). In

2007, gemcitabine plus Tarceva (Erlotinib) (Genentech Roche, San Francisco, CA, USA) (GT) combination therapy demonstrated a statistically significant but clinically marginal advantage in terms of OS[6] compared to gemcitabine monotherapy, and it has been the only biologic agent approved by the FDA for treatment of pancreatic cancer. Therefore, there is an unmet need with erlotinib in the treatment of advanced pancreatic cancer. More recently, two phase III studies, the FOLFIRINOX[7] regimen and nab-paclitaxel in combination with gemcitabine[8] regimen (MPACT trial), showed significant survival improvements compared to gemcitabine alone, and are recommended currently as the standard therapy for metastatic pancreatic cancer patients with good performance.

Previously, we conducted a single-arm phase II study of the combination of gemcitabine and erlotinib (GT) plus oxaliplatin regimen (GEMOX-T) to evaluate efficacy and safety. The response rate was 45%, the disease control rate (DCR) was 86.2%,[9] and the median PFS and OS were 4.8 months [95% confidence interval (CI), 4.1–5.5] and 8.4 months (95% CI, 7.0–9.8), respectively. The aim of the present study was to compare the effectiveness and safety of first-line treatments using the triple combination of GEMOX-T versus the GT regimen in patients with locally advanced or metastatic pancreatic cancer.

MATERIALS AND METHODS

Study design and patient eligibility

This study was designed as a multi-center, open-label, randomized phase II study to test the efficacy of combined chemotherapy with gemcitabine/oxaliplatin plus erlotinib (GEMOX-T) versus gemcitabine/erlotinib (GT). Eligible patients were ≥18 years of age with histologically confirmed adenocarcinoma of the pancreas. All patients had locally advanced unresectable or metastatic disease, and had one or more measurable diseases. Previous neoadjuvant chemotherapy, concurrent chemoradiotherapy (CCRT), or adjuvant chemotherapy was allowed if fluorouracil was used. Local radiotherapy was allowed within the last 4 weeks preceding the start of study treatment. Other key eligibility criteria were an Eastern Cooperative Oncology Group (ECOG) performance status ≤2 and adequate bone marrow, renal, and hepatic functions. Patients with previous gemcitabine exposure were excluded. All patients were required to provide their informed consent. This study was approved by the Institutional Review Board of Soonchunhyang University Hospital (Soonchunhyang University Bucheon Hospital IRB 2013-01-020).

Treatment

Patients were randomly assigned (1:1) to receive either GT or GEMOX-T treatment. GEMOX-T consisted of gemcitabine 1000 mg/m^2 as a 100-min infusion and oxaliplatin 50 mg/m^2 as a 2-hour infusion on day 1 (D1) and D8 of a 21-day cycle with oral administration of 100 mg erlotinib daily. The GT arm was treated with gemcitabine 1000 mg/m^2 as a 100-min infusion on D1 and D8 plus oral administration of 100 mg erlotinib daily for 3 weeks. Treatment continued until disease progression, intolerable toxic effects despite supportive care and dose modifications, or withdrawal of consent. Dose modifications or delays in administration of drugs were based on the worst toxicity grade according to the protocol. Once the dose was reduced, it could not be increased again. If the dose of one drug was delayed, all drugs in the combination were delayed; and if one drug was discontinued due to toxicity, the patient could continue to receive the other drugs in the regimen at the investigator's discretion.

Efficacy assessment

Tumor assessment was performed at baseline using abdomen and pelvis computed tomography (CT) scans and chest CT scans. Tumor assessment using the same imaging studies was repeated at week 6 and every 6±2 weeks thereafter. The primary endpoint of the current study was the overall response rate (ORR), determined as complete response plus partial response (PR). Secondary endpoints were: 1) PFS, defined as the time from random assignment to progression, secondary cancer, or death from any cause; 2) OS, calculated from the time of randomization to the date of death; and 3) safety. These endpoints were measured in all registered patients (i.e., intention-to-treat population). Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and adverse events (AE) were assessed according to the National Cancer Institute criteria (CTCAE) version 4.0.

Statistics

The primary endpoint was the overall response, and at least 66 patients were required to show superiority of the GEMOX-T arm compared to the GT arm with a two-sided alpha of 0.05 and power of 0.80. The sample size for the trial was derived from the following assumption. We used a Simon 2-stage design with 80% power and 5% significance. Assuming a clinically non-significant efficacy level of 10% (i.e., a null hypothesis of 10% for the GT arm), 58 subjects were required to provide 80% power to conclude in favor of a clinically significant efficacy level for the GEMOX-T treatment, should this efficacy level be as high as 30% (i.e., a research hypothesis of 30%). For a total of 58 participants, 10 were to be accrued in each arm during stage 1 of the trial, and 19 during stage 2 of the trial. If ≥2 responses were observed during the first stage, the trial was to proceed to the second stage. A 10% ineligible or non-assessable rate was assumed, resulting in the accrual goal of a total of 66 patients (33 patients for each arm). Survival rates were estimated by the Kaplan-Meier method and compared between the two treatment groups using the log-rank test. Statistical analyses were performed using SPSS version 21 (IBM Corp., Armonk, NY, USA).

RESULTS

Patients

Between May 2013 and April 2016, 65 patients were enrolled and randomly assigned to receive either GEMOX-T or GT treatment (33 in the GEMOX-T arm, 32 in the GT arm). Patient base-

Table 1. Baseline Patient Characteristics

Characteristics	GEMOX-T Arm (n=33)	GT Arm (n=32)	p value
Age (yr)			0.110
Mean±SD	59.4±8.10	62.7±8.59	
Range	42–76	41–76	
Sex			0.531
Male	16 (48.5)	18 (56.2)	
Female	17 (51.5)	14 (43.8)	
ECOG performance status			0.760
0	4 (12.1)	3 (9.4)	
1	24 (72.7)	22 (66.8)	
2	5 (15.2)	7 (21.9)	
Disease stage			0.953
Locally advanced	6 (18.2)	6 (18.8)	
Metastatic	27 (81.8)	26 (81.2)	
Histology			
Ductal adenocarcinoma	33 (100)	32 (100)	-
Differentiation			0.728
Well	1 (3.0)	-	
Moderate	4 (12.1)	3 (9.4)	
Poor	6 (18.2)	5 (15.6)	
Unknown	22 (66.7)	24 (75.0)	
Tumor site			0.805
Head	10 (30.3)	11 (34.4)	
Body	9 (27.3)	8 (25.0)	
Tail	13 (39.4)	11 (34.4)	
Uncinate	1 (3.0)	2 (6.2)	
Previous treatment			
Surgery	4 (12.1)	5 (15.6)	0.590
Adjuvant Tx (CCRT, chemotherapy)	3 (9.1)	1 (3.1)	0.613
Smoking status			0.386
Current smoker	3 (9.1)	4 (12.5)	
Ex-smoker	2 (6.1)	5 (15.6)	
Never smoker	28 (84.8)	23 (71.9)	
CA 19-9 (U/mL)			
Median (range)	286.7 (1.8–216395)	622.7 (0.7–10000)	0.412
Elevated	27 (84.4)	22 (73.3)	0.286
CRP (mg/dL)			
Median (range)	1.125 (0.1–85.1)	0.6 (0.03–34.5)	0.782
Elevated	21 (65.6)	16 (51.6)	0.259

SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; CCRT, concurrent chemoradiotherapy; CRP, C-reactive protein.
Data are presented as n (%).

line characteristics are shown in Table 1, and were well balanced between the two groups. About 20% of the patients were diagnosed with locally advanced unresectable disease, and the rest were metastatic pancreatic cancers. All had ductal adenocarcinoma histology, nine patients (four in the GEMOX-T arm, five in the GT arm) had received surgery, and four had been treated with adjuvant chemotherapy or CCRT with 5-fluorouracil before enrollment. More than 70% of the patients in both groups showed elevated CA 19-9 level at baseline.

Efficacy

At the time of data analysis (December 2020), a total of 63 patients had disease progression (33 in the GEMOX-T arm and 30 in the GT arm). Two patients in the GT group withdrew before administration of the first dose and could not be assessed. The ORR was 18.2% for the GEMOX-T group and 6.2% for the GT group (*p*=0.051) (Table 2). In both arms, none of the patients showed complete response, and PR were observed in six patients in the GEMOX-T arm and in two patients in the GT arm. The DCR was 72.7% in the GEMOX-T arm and 43.8% in the GT arm (*p*=0.019). After a median follow-up of 19.7 months, the median PFS was 3.9 months (95% CI, 2.21−5.59) for the GEMOX-T arm and 1.4 months (95% CI, 0.00−3.01) for the GT arm [hazard ratio (HR), 0.58; 95% CI, 0.35−0.97; *p*=0.033] (Fig. 1A). However, this did not translate to an improvement in OS (median OS, 6.2 months and 5.1 months in the GEMOX-T and GT arms, respectively, *p*=0.110) (Fig. 1B). The 12-month OS rate was 27% for the GEMOX-T group and 18% for the GT group.

In both the GEMOX-T and GT groups, there was a no significant trend toward OS improvement in patients who developed any grade of rash (Fig. 2A). The median PFS was significantly improved to 4.1 months in patients with any grade of rash compared to 2.7 months in patients without rash (*p*=0.030) (Fig. 2B). Among patients in the GEMOX-T arm, the median OS for patients with rash grade ≥1 was 9.0 months compared to 5.6 months in those with no rash (HR, 0.60; 95% CI, 0.33−1.09). The median PFS for patients with rash grade ≥1 was 4.5 months compared to 3.0 months for those with no rash (*p*=0.053). No significant difference in PFS or OS was observed in the GT group

Table 2. Best Objective Response

Response	GEMOX-T Arm (n=33)	GT Arm (n=32)	p value
CR	-	-	
PR	6 (18.2)	2 (6.2)	
SD	18 (54.5)	12 (37.5)	
PD	9 (27.3)	14 (43.8)	
NE	-	4 (12.5)	
Overall response rate	6 (18.2)	2 (6.2)	0.051
Disease control rate	24 (72.7)	14 (43.8)	0.019

CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
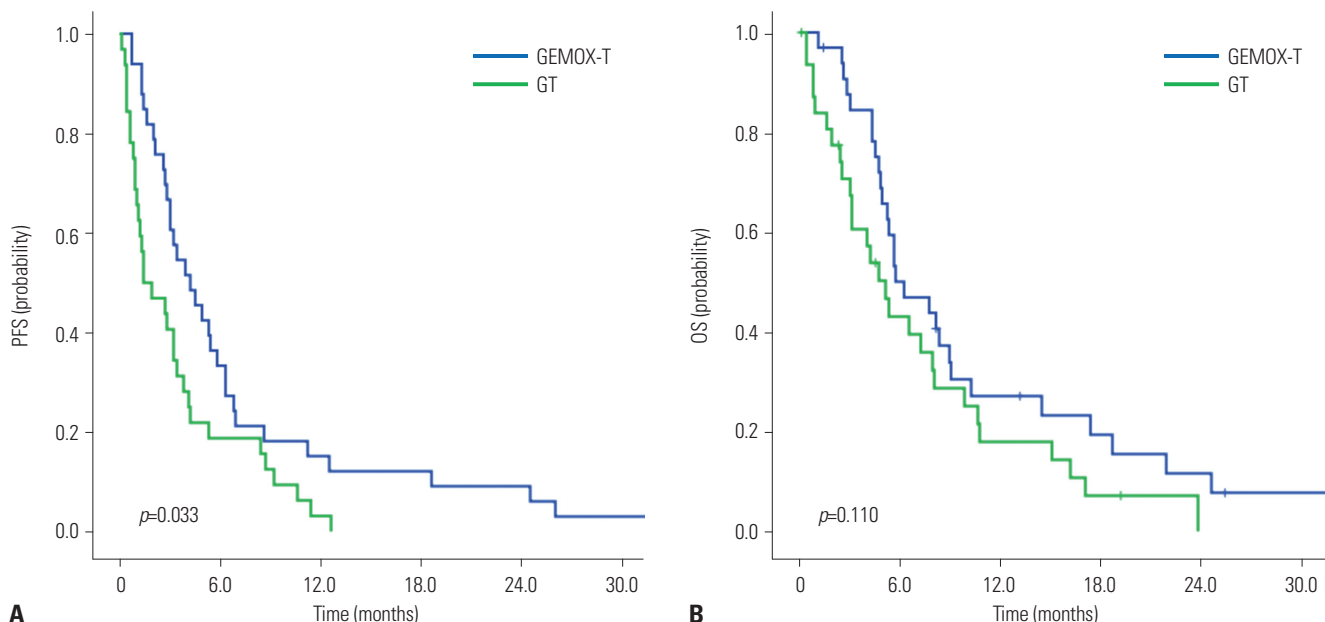Data are presented as n (%).

Fig. 1. Kaplan-Meier survival curves by treatment arm and corresponding *p*-values. (A) Progression-free survival (PFS). (B) Overall survival (OS).
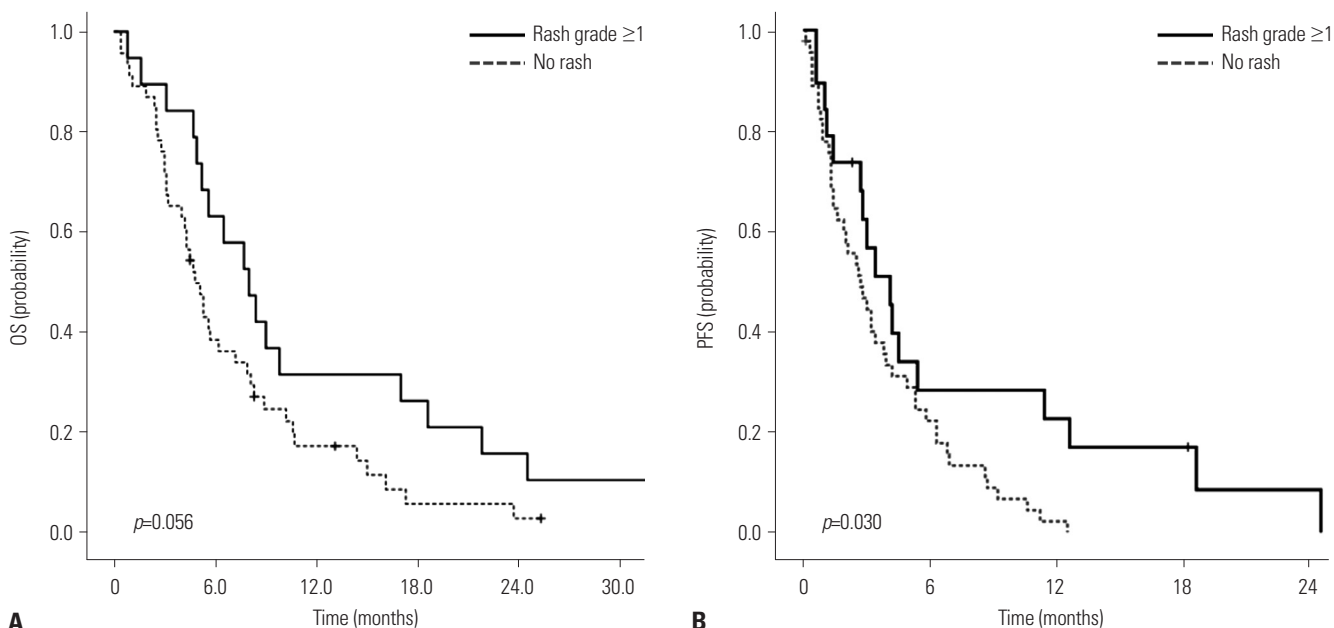

Fig. 2. Survival analysis by presence and absence of any grade of rash. (A) Overall survival (OS). (B) Progression-free survival (PFS).

by the presence or absence of rash.

The results of univariable analysis of baseline characteristics as prognostic survival factors are shown in Table 3. Significant factors for OS improvement were locally advanced disease, low serum CA 19-9 level, low C-reactive protein (CRP) concentration, and no history of smoking (*p*<0.05). A baseline CRP above the median value (0.92 mg/L) was an independent prognostic factor for poor OS in multivariate analysis (HR, 2.07; 95% CI, 1.16−3.69; *p*=0.014).

Subgroup analyses for PFS and OS are shown in Fig. 3. The GEMOX-T group demonstrated better OS than the GT group

among patients with peritoneal metastasis (HR, 0.20; 95% CI, 0.05−0.79; *p*=0.02) as well as among patients with high baseline CRP concentration (HR, 0.46; 95% CI, 0.22−0.96; *p*=0.04). The GEMOX-T group also showed better PFS than the GT group in three distinct patient subgroups: good ECOG performance status (0 or 1), initial metastatic disease, and high CRP.

Safety

All patients were monitored for AE, and 96.9% (63/65) of them experienced an AE during the study period. A summary of toxicity profiles is presented in Table 4. Neutropenia and

thrombocytopenia hematologic AE grade ≥3 occurred more frequently in the GEMOX-T group compared to the GT group. Febrile neutropenia developed in one patient in each treatment group. Other common grade 3–4 AEs were nausea/vomiting (27.3% in the GEMOX-T vs. 6.2% in the GT group), diarrhea (18.2% vs. 3.1%), rash (0% vs. 12.5%), and Aspartate Aminotransferase/Alanine Aminotransferase (AST/ALT) elevation (3.0% vs. 12.5%). Rash of grade 2 or greater severity occurred

Table 3. Univariate Analysis of Prognostic Variables

	PFS			OS		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Treatment group						
GEMOX-T vs. GT	1.72	1.03–2.97	0.037	1.54	0.89–2.65	0.122
Age (<65 yr vs. ≥65 yr)	1.24	0.72–2.13	0.437	1.46	0.84–2.57	0.184
ECOG PS						
0 or 1 vs. 2	1.47	0.77–2.80	0.240	1.40	0.69–2.81	0.342
Sex						
Female vs. male	1.13	0.68–1.87	0.633	1.17	0.68–2.00	0.570
Disease stage						
Locally advanced vs. metastatic	2.42	1.21–4.85	0.013	2.18	1.07–4.43	0.032
Baseline CA 19-9						
≤434.7 vs. >434.7	1.98	1.12–3.49	0.019	1.87	1.05–3.31	0.033
Baseline CRP						
≤0.92 vs. >0.92	2.47	1.43–4.26	0.001	1.74	1.02–2.98	0.043
Smoking status						
Never vs. ex-smoker	2.35	1.04–5.34	0.040	4.66	1.97–11.06	<0.001
Never vs. current	2.08	0.93–4.68	0.075	1.60	0.67–3.79	0.287

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PS, performance status; CRP, C-reactive protein.
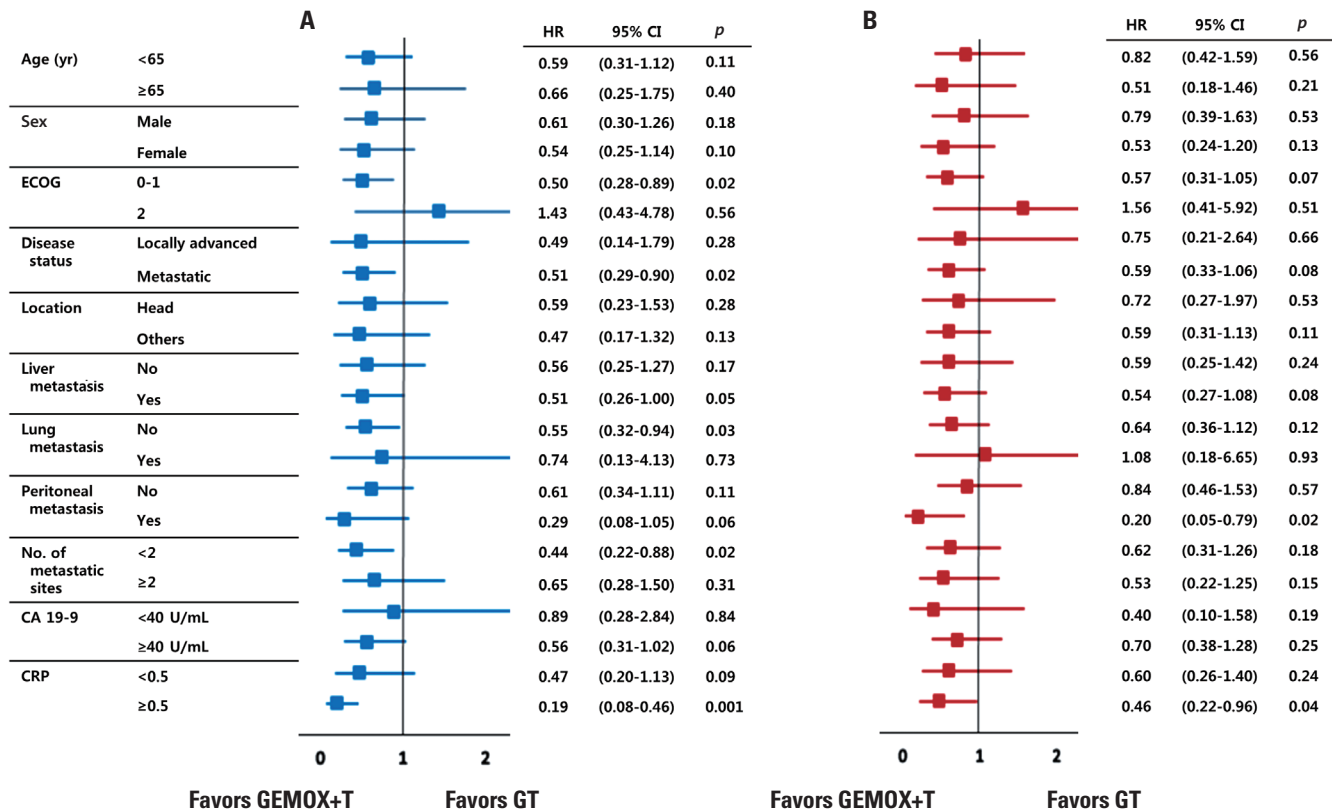

Fig. 3. Forrest plots showing the survival outcomes of patient subgroups. (A) PFS. (B) OS. PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; CRP, C-reactive protein.

Table 4. Toxicity Profiles

Toxicity	GEMOX+T (n=33) NCI-CTC grade (%)		GT (n=32) NCI-CTC grade (%)		p value for G3/4 AE
	Any grade	G3-4	Any grade	G3-4	
Hematologic					
Neutropenia	17 (51.5)	16 (48.5)	10 (31.2)	8 (25.0)	0.072
Febrile neutropenia	-	1 (3.0)	-	1 (3.1)	>0.999
Anemia	20 (60.6)	10 (30.3)	18 (56.2)	11 (34.4)	0.794
Thrombocytopenia	13 (39.4)	4 (12.1)	5 (15.6)	2 (6.2)	0.672
Non-hematologic					
Nausea/vomiting	24 (72.7)	9 (27.3)	14 (43.7)	2 (6.2)	0.044
Diarrhea	9 (27.3)	6 (18.2)	8 (25.0)	1 (3.1)	0.105
Constipation	11 (33.3)	2 (6.1)	7 (21.9)	1 (3.1)	>0.999
Mucositis	9 (27.3)	-	3 (9.4)	1 (3.1)	0.306
Peripheral neuropathy	4 (12.1)	-	-	-	0.042*
Alopecia	9 (27.3)	-	3 (9.3)	-	0.063*
Anorexia	20 (60.6)	3 (9.1)	10 (31.2)	2 (6.2)	>0.999
Rash	9 (27.3)	0 (0.0)	10 (31.2)	4 (12.5)	0.053
Fatigue	12 (36.4)	1 (3.0)	9 (28.1)	1 (3.1)	>0.999
AST/ALT elevation	5 (15.2)	1 (3.0)	8 (25.0)	4 (12.5)	0.228

NCI-CTC, National Cancer Institute-Common Toxicity Criteria; AST/ALT, Aspartate Aminotransferase/Alanine Aminotransferase; AE, adverse events.
*Any grade of peripheral neuropathy and alopecia AEs were analyzed.

in nine (27.3%) of 33 patients in the GEMOX-T group and 10 (31.2%) of 32 patients in the GT group. Peripheral neuropathy at grade 1 or 2 was observed in 12% of patients in the GEMOX-T group.

Subsequent treatment

In the GEMOX-T group, among 33 patients who eventually developed progressive disease during GEMOX-T treatment, 9 (28%) received salvage chemotherapy. One patient who showed PR with GEMOX-T received a curative distal pancreatectomy. A few months later, the disease recurred and was treated with salvage chemotherapy. The salvage chemotherapy regimens administered to the nine patients in the GEMOX-T group were TS-1 (4 patients), 5-FU/Cisplatin (5 patients), and FOLFOX (1 patient). Among 32 patients in the GT group, 7 (21%) were treated with second-line chemotherapy after progression on gemcitabine/erlotinib therapy. Two patients were treated with 5-FU/Cisplatin chemotherapy, three with TS-1 monotherapy, and the other two patients received FOLFOX regimen.

DISCUSSION

Despite the increase in targeted approaches in many cancers, such as non-small cell lung cancer, most clinical trials using targeted therapy in pancreatic cancer have failed,[10-13] even though genetically altered core pathways and regulatory processes have been revealed.[14] This might be attributed to the high molecular heterogeneity of pancreatic cancer and the high content of surrounding stromal and inflammatory components.

Erlotinib is the only targeted agent to have demonstrated a statistically significant, yet clinically marginal, survival benefit in pancreatic cancer.[6]

In the current trial, the ORR was numerically improved to 18.2% compared to the control arm; however, the study failed to meet its primary endpoint of improvement in ORR by the triplet regimen, which involves the addition of oxaliplatin to gemcitabine plus erlotinib. The efficacy of GEMOX-T in our study was comparable to that of other triplet regimens containing erlotinib,[15] which showed that combining capecitabine with gemcitabine plus erlotinib did not improve PFS compared to gemcitabine plus erlotinib in the first-line setting for metastatic pancreatic cancer.[15] Higher DCR up to 73% and a median PFS of 3.9 months in the GEMOX-T group were statistically significant improvements compared to the GT group. However, the interpretation of these results is limited since the survival results in the control GT group were not comparable to the pre-existing data.[6,16] Here, the median PFS in the GT group was only 1.4 months and the OS was 5.1 months. This might be explained by the larger number of patients with an ECOG performance status of 2 in the GT group, as well as the small number of patients who received subsequent treatment after progression of first-line therapy (21%). The unfavorable survival outcome in the GT group might have been influenced by the effects of higher baseline CA19-9. Although the proportion of patients with elevated CA19-9 level at the beginning of the study was not significantly different among the two treatment groups, the median value of CA19-9 in the GT group was more than two times higher than that of the GEMOX-T group. Since CA19-9 level is a well-known prognostic factor of pancreatic cancer, it

might reflect greater disease burden in the GT group. Visual inspection of the OS curves showed separation of the two treatment arms. However, this was not a statistically significant difference, and it might have been affected by the small sample size of this study. Initially, the sample size calculation was based on the difference of ORR. In addition, the lack of improvement in OS could be partly explained by the effect of salvage treatments.

Previously, GEMOX plus erlotinib was evaluated in advanced biliary tract cancers, and showed modest efficacy and manageable toxicity.[17] In the current study, there were no significant differences between the two groups for incidence of grade ≥3 myelosuppression and peripheral neuropathy, which might be associated with the addition of oxaliplatin to the groups. Grade 3 rash was more frequently observed in the GT group, though the difference was not significant. We found similar results to other studies that reported development of skin rash as a predictive marker of improved survival with erlotinib treatment.[6,15,18] In both groups, patients with any grade of rash showed longer survival compared to those without skin rash; however, no significant difference was observed due to the relatively small number of patients in each group. Also, baseline CA 19-9 and CRP concentrations showed prognostic importance in this study, in agreement with previous findings.[19,20]

This study had some limitations. The primary limitation was that the difference in the median value of baseline CA19-9 level might be attributed to the difference in survival outcomes in the groups. In addition, the study regimen using erlotinib was outdated compared to the current standard treatments in pancreatic cancer. The current standard treatments, such as FOLFIRINOX or gemcitabine plus nab-paclitaxel, show higher survival results in both median PFS and median OS up to over 12 months. GEMOX-T combination therapy could be considered for only a small subset of patients, such as those with higher baseline CRP or susceptibility to skin rash in response to erlotinib.

In conclusion, the addition of oxaliplatin to the gemcitabine/erlotinib doublet regimen slightly improved the response rates and PFS in treatment-naïve patients with advanced pancreatic cancer. Erlotinib-containing treatment might be beneficial for patients who develop any grade skin rash, which could be used as a predictive marker. To improve the limited efficacy of the current therapeutic approaches using combination cytotoxic chemotherapy, further research combining cytotoxic chemotherapy, small molecule inhibitors, monoclonal antibodies, or immunotherapy are warranted to prolong the survival of patients with advanced pancreatic cancers.

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