World Journal of
Clinical Cases

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ABOUT COVER

Editorial board member of World Journal of Clinical Cases, Dr. Elia de Maria is Adjunct Professor of Arrhythmology Lab in the Cardiology Unit, Ramazzini Hospital in Carpi, Italy. He graduated in Medicine and Surgery from the University of Napoli in 1999, continuing on to obtain specialization in Cardiology in 2003. He also holds the distinction of High Degree Master in Electrophysiology and Cardiac Stimulation. Since 2005, he has practiced as a Permanent Consultant Cardiologist in the Italian Public Hospitals, and since 2015 as an External Contract Professor in the Faculty of Medicine and Surgery of University of Verona. His clinical and research interests encompass pharmacological therapy in acute and chronic cardiac conditions, temporary and definitive pacing, thoracentesis and pericardiocentesis, and hemodynamic monitoring. (L-Editor: Filipodia)

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

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RESPONSIBLE EDITORS FOR THIS ISSUE

Retrospective Study

Comparison of gemcitabine plus nab-paclitaxel and FOLFIRINOX in metastatic pancreatic cancer

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Institutional review board statement: The study protocol was approved by the Institutional Review Board of Pusan National University, IRB No. H-2002-023-088.

Informed consent statement: Written informed consent was waived.

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Abstract

BACKGROUND
Gemcitabine plus nab-paclitaxel (GA) and modified FOLFIRINOX (FFX) have been widely used as standard first-line treatment in pancreatic cancer. However, it is unclear which regimen is more efficacious.

AIM
To evaluate a retrospective analysis comparing the efficacy and safety of FFX and GA as first-line chemotherapeutic regimens in patients with metastatic pancreatic cancer.

METHODS
We retrospectively analyzed and compared outcomes in 101 patients who presented with pancreatic cancer and were treated with either GA (*n* = 54) or FFX (*n* = 47). Moreover, we performed subgroup analysis based on the neutrophil/lymphocyte ratio (NLR) and Eastern Cooperative Oncology Group (ECOG) performance status.

RESULTS
There were no significant differences between two groups in baseline characteristics, except for the ECOG performance status. The median progression-

free survival (PFS) (6.43 mo *vs* 4.90 mo, P = 0.058) was comparable between two groups; however, median overall survival (OS) (10.17 mo *vs* 6.93 mo, P = 0.008) was longer in patients who received GA regimen. In patients with ECOG 0 (PFS: 8.93 mo *vs* 5.43 mo, P = 0.002; OS: 16.10 mo *vs* 6.97 mo, P = 0.000) and those with NLR < 3 (PFS: 8.10 mo *vs* 6.57 mo, P = 0.008; OS: 12.87 mo *vs* 9.93 mo, P = 0.002), GA regimen showed higher efficacy.

CONCLUSION
GA regimen may be recommended to the patients with NLR < 3 or ECOG 0 status although GA and FFX showed comparable efficacy outcomes in patients with metastatic pancreatic cancer.

Key words: Metastatic pancreatic carcinoma; Chemotherapy; FOLFIRINOX; Nab-paclitaxel plus gemcitabine; Predict marker; Adverse event

Core tip: Gemcitabine plus nab-paclitaxel (GA) and modified FOLFIRINOX (FFX) have been widely used as standard first-line treatment in pancreatic cancer. However, it is unclear which regimen is more efficacious. Our retrospective study aims to explore the efficacy and safety of FFX and GA as first-line chemotherapeutic regimens in patients with metastatic pancreatic cancer. Our data showed that comparable result in both regimens. However, GA regimen have better result of median progression free survival and overall survival in patients with ECOG 0 status or neutrophil/lymphocyte ratio < 3.

INTRODUCTION

Pancreatic cancer has a poor prognosis, with a 5-year survival rate of less than 10%[1]. Most patients are diagnosed at an advanced stage, and less than one-third of the patients are suitable for surgical resection. Therefore, systemic chemotherapy is an important approach for treating patients at the metastatic stage, including patients with a locally advanced disease.

Recently, many advances have been made in chemotherapy development for pancreatic cancer. Gemcitabine plus nab-paclitaxel (GA) and modified FOLFIRINOX (FFX) therapies have been widely used as standard first-line treatments for pancreatic cancer. The FOLFIRINOX regimen, which consists of 5-fluorouracil (5-FU), leucovorin, oxaliplatin, and irinotecan, was introduced by the PRODIGE4/ACCORD11 trial[2]. In this clinical trial, FOLFIRINOX yielded superior survival rates when compared to gemcitabine monotherapy. Another randomized phase III trial, MPACT, showed that a combination of gemcitabine and nab-paclitaxel yielded a statistically significant survival benefit and response rate when compared with gemcitabine monotherapy[3]. As a result, these two regimens are recommended as the first-line therapy for metastatic pancreatic cancer[4,5]. Although there have been comparative studies on these two chemotherapy regimens, it remains unclear which of the two is more efficacious. In a pivotal trial for each regimen, FFX showed numerically better results than GA in progression-free survival (PFS) (5.5 *vs* 6.4 mo) and overall survival (OS) (8.5 *vs* 11.1 mo)[2,3]. However, in these studies' analysis, direct comparisons are difficult to make because of the different baseline characteristics of the patients, which include known prognostic factors. A study conducted among patients living in South Korea revealed that the GA regimen showed better results for peritoneal metastasis among patients aged 65 years or older or having a Charlson comorbidity index of 9 or higher[6]. However, FFX showed better results than GA in studies conducted in Europe and Canada[7,8]. A recently published meta-analysis[9] showed no major benefit of one regimen over the other. Thus, more research is needed to understand whether the

efficacies of these two regimens are similar or different depending on the situation.

In this study, we retrospectively reviewed the efficacy and safety of FFX and GA as first-line chemotherapeutic regimens in patients with metastatic pancreatic cancer and evaluated to identify the predictive markers of which chemotherapy regimens were more effective.

MATERIALS AND METHODS

Patients
We retrospectively reviewed medical records of patients with metastatic pancreatic cancer and included those who received either GA or FFX as first-line chemotherapy between January 2013 and September 2019 at Pusan National University Hospital, Busan, Korea. All patients were histologically diagnosed with ductal adenocarcinoma. This study was performed in accordance with the ethical guidelines of the Helsinki Declaration (revised in 2013), and the study protocol was approved by the Institutional Review Board of Pusan National University, IRB No. H-2002-023-088.

Treatment regimen and chemotherapy-response assessment
GA therapy consisted of a 30-min intravenous infusion of nab-paclitaxel at a dose of 125 mg/m^2, followed by gemcitabine at a dose of 1000 mg/m^2 on days 1, 8, and 15, administered every four weeks, as described in the MPACT trial[3]. FFX therapy consisted of a sequence of a 2-h intravenous infusion of oxaliplatin at 85 mg/m^2, a 90-min intravenous infusion of irinotecan at 180 mg/m^2, a 2-h infusion of leucovorin at 400 mg/m^2, an intravenous bolus of 5-FU at 400 mg/m^2, and a 46-h continuous infusion of 5-FU at 2400 mg/m^2 administered every two weeks[10]. Tumor response was assessed every 10–12 wk using computed tomography and graded according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. All patients who were available had a follow-up period of at least six months (excluding those lost during the follow-up). Patients, who were lost during the follow-up period were analyzed assuming there was a disease progression on the last visit date or death.

Outcomes and subgroup analysis
The primary outcomes of the study were the PFS and OS in patients who were treated with two regimens. Secondary outcomes were used to assess the safety and feasibility of each regimen and to identify special factors related to prognosis. We performed a Cox regression analysis to identify factors that correlated with PFS and OS. The Eastern Cooperative Oncology Group (ECOG) performance status and the neutrophil/lymphocyte ratio (NLR) were identified as significant factors at a 99% confidence level (see Supplementary 1 and 2). Thus, a subgroup analysis was performed on these factors. These factors were also used to correlate patient situation with the efficacy of each regimen. The NLR and platelet/lymphocyte ratio (PLR) were evaluated at the 1st tumor response to chemotherapy as well.

Statistical analysis
Statistical analysis was performed using SPSS software (version 22.0, IBM Corp., Armonk, NY, United States). Categorical data were expressed as frequency and percentage, with between-group differences evaluated using the chi-square test. Continuous data were expressed as mean ± SD, with between-group differences evaluated using independent Student's *t*-test. Statistical significance was determined at $P < 0.05$. For comparison, OS and PFS were assessed using Kaplan–Meier survival curves and the log-rank test. For subgroup analysis, the Cox regression test was used to test for variables affecting the PFS and OS at 99% confidence.

RESULTS

Baseline characteristics
The baseline characteristics of the 101 patients are summarized in Table 1. Unless otherwise indicated, the following data were presented with the GA group listed first, followed by the FFX group. Of the total patients, 54 were treated with GA and 47 were treated with FFX. Mean patient age (65.7 ± 7.8 *vs* 64.4 ± 8.4 years, $P = 0.445$) and the proportion of males (72.2% *vs* 66.0%, $P = 0.501$) were similar between the groups. There were no significant baseline differences between the groups except for the

Table 1 Baseline patients' characteristics, *n* (%)

Variable	GA (*n* = 54)	FOLFIRINOX (*n* = 47)	*P* value
Age (yr)	65.7 ± 7.8	64.4 ± 8.4	0.445
Male	39 (72.2)	31 (66.0)	0.501
Body weight (kg)	59.2 ± 9.5	58.5 ± 9.9	0.716
Height (m)	1.65 ± 0.08	1.63 ± 0.07	0.352
Body mass index (kg/m^2)	21.9 ± 3.1	22.0 ± 3.5	0.852
Psoas muscle area (cm^2)	8.6 ± 2.9	8.3 ± 2.1	0.639
Number of metastasis ≥ 2	48 (88.9)	35 (74.5)	0.060
Liver meta	32 (59.3)	31 (66.0)	0.493
Carcinomatosis peritonei	21 (38.9)	16 (34.0)	0.618
Lung meta	13 (24.1)	8 (17.0)	0.389
Primary tumor site			0.778
Head	25 (46.3)	25 (53.2)	
Body	14 (25.9)	8 (17.0)	
Tail	15 (27.8)	14 (29.8)	
ECOG performance status			0.018[a]
0 or 1	48 (88.9)	47 (100)	
2	6 (11.1)	0 (0)	
Diabetes	22 (40.7)	23 (48.9)	0.414
Hypertension	12 (22.2)	12 (25.5)	0.700
Laboratory findings			
White blood cell (/μL)	6465.6 ± 2743.0	9780.0 ± 16931.6	0.159
Platelet (10^3/μL)	235.9 ± 122.4	270.1 ±107.7	0.142
Neutrophil/lymphocyte ratio	3.72 ± 2.98	3.0 ± 1.87	0.167
Pletelet/lymphocyte ratio	190.2 ± 120.7	159.5 ± 71.0	0.129
C-related protein (mg/dL)	1.49 ± 2.23	1.29 ± 2.00	0.641
Albumin (g/dL)	3.92 ± 0.46	3.98 ± 0.57	0.552
Total bilirubin (mg/dL)	1.41 ± 3.06	1.42 ± 1.60	0.988
CA 19-9 (U/mL)	12881.3 ± 54407.2	1307.1 ± 2079.1	0.153

[a]$P < 0.05$, mean ± SD. GA: Gemcitabine plus nab-paclitaxel; ECOG: Eastern Cooperative Oncology Group; CA: Carbohydrate antigen.

ECOG performance status; patients with ECOG 2 status were present only in the GA group (11.1% *vs* 0%, *P* = 0.018). Patients with an ECOG 0 status were at a higher ratio in the FFX group than in the GA group (48.1% *vs* 51.9%, *P* = 0.054). In the GA group, number of metastasis ≥ 2 was more common than that of single metastasis when compared with the FFX group (number of metastasis ≥ 2: 88.9% *vs* 74.5%, *P* = 0.060). The mean NLR was slightly higher in the GA group (3.72 ± 2.98 *vs* 3.0 ± 1.87, *P* = 0.167).

Efficacy of each chemotherapy regimen

Table 2 shows the chemotherapy response data for each regimen. When comparing the best response for each regimen, the disease control rate was similar between the groups (83.3% *vs* 76.6%, *P* = 0.402). The proportion of patients who took a reduced dose of the regimen was similar (75.9% *vs* 68.1%, *P* = 0.385). However, the mean delivery dose of chemotherapy showed a significant difference between the groups (78.9 ± 16.5% *vs* 87.3 ± 11.6%, *P* = 0.005). The proportion of patients who received more than 80% of the expected dose was higher in the FFX group (44.4% *vs* 65.2%, *P* = 0.038).

Table 2 Result of chemotherapy response of each regimen, *n* (%)			
	GA (*n* = 54)	FOLFIRINOX (*n* = 47)	*P* value
Best response			0.216
PR	10 (18.5)	5 (10.6)	
SD	35 (64.8)	31 (66.0)	
PD	9 (16.7)	11 (23.4)	
DCR (PR + SD)	45 (83.3)	36 (76.6)	0.402
Dose reduction	41 (75.9)	32 (68.1)	0.385
Delivery dose (%)	78.9 ± 16.5	87.3 ± 11.6	0.005[b]
Total over 80% dose	24 (44.4)	30 (65.2)	0.038[a]
Duration of chemotherapy (mo)	2.33 (1.43-3.24)	1.63 (1.19-2.08)	0.005[b]
Progression free survival (mo)	6.43 (4.43-8.43)	4.90 (4.44-5.36)	0.058
Overall survival (mo)	10.17 (6.03-14.31)	6.93 (5.32-8.54)	0.008[b]
2nd Chemotherapy	24 (44.4)	19 (40.4)	0.687
TS-1	15 (27.8)	1 (2.1)	
Gemcitabine mono	0 (0)	12 (25.5)	
GA	0 (0)	5 (10.6)	
FOLFIRINOX	3 (5.6)	0 (0)	
Onyvide	1 (1.9)	0 (0)	
5-FU base	5 (9.3)	1 (2.1)	
2nd chemotherapy PFS (mo)	3.23 (2.55-3.91)	2.70 (1.56-3.84)	0.191

[a]$P < 0.05$,

[b]$P < 0.01$, mean ± SD; median (95%CI). GA: Gemcitabine plus nab-paclitaxel; PR: Partial response; SD: Stable disease; PD: Progression disease; DCR: Disease control rate; TS-1: Tegafur/gimeracil/oteracil; 5-FU: 5-fluorouracil; PFS: Progression-free survival.

The median duration of chemotherapy was longer in the GA group (2.33 *vs* 1.63 mo, *P* = 0.005). There was no significant difference of the median PFS between the groups (6.43 *vs* 4.90 mo, *P* = 0.058); however, median OS was longer in the GA group (10.17 *vs* 6.93 mo, *P* = 0.008) (Figure 1). Each group had a similar proportion of patients who received secondary chemotherapy (44.4% *vs* 40.4%, *P* = 0.687). In the GA group, tegafur/gimeracil/oteracil was most frequently used as secondary chemotherapy (*n* = 15, 27.8%), while in the FFX group, gemcitabine-mono was most commonly used as secondary chemotherapy (*n* = 12, 25.5%).

Subgroup analysis

Table 3 shows response comparison depending on the NLR in subgroup analysis. When comparing between NLR < 3 and NLR > 3, the patients in two groups showed significant differences in PFS and OS. The patients in the NLR < 3 group had a longer median PFS (NLR > 3 *vs* NLR < 3: 3.83 *vs* 7.60 mo, *P* = 0.000) and OS (NLR > 3 *vs* NLR < 3: 4.47 *vs* 10.87 mo, *P* = 0.001) than those in the NLR > 3 group. In the NLR < 3 group, comparing the GA and FFX regimens, median PFS (8.10 *vs* 6.57 mo, *P* = 0.008) and median OS (12.87 *vs* 9.93 mo, *P* = 0.002) showed significant difference between two groups (Figure 2). Furthermore, Figure 3 shows patient responses in the NLR and PLR groups to different chemotherapy regimens. The mean of NLR was not different before and after chemotherapy. However, PLR was different before and after chemotherapy for both regimens. Table 4 and Supplementary Table 3 shows that a decrease in the NLR and CA19-9 after chemotherapy were associated with a good prognosis. CA19-9 decreased after GA chemotherapy, but increased after FFX chemotherapy. The response of the NLR seems to have a greater influence on the prognosis rather than response of CA19-9. Patients with decreased NLR after chemotherapy were associated with high disease control rate, longer PFS, and OS when compared with patients without decreased NLR after chemotherapy. However, change in PLR was not associated with prognosis, which was only influenced by the

Table 3 Result in subgroup analysis (neutrophil/lymphocyte ratio)

	NLR ≥ 3 (*n* = 43)			NLR < 3 (*n* = 58)			*P* value
	GA (*n* = 24)	FFX (*n* = 19)	*P* value	GA (*n* = 30)	FFX (*n* = 28)	*P* value	
PFS (mo)	3.83 (3.19-4.47)			7.60 (6.51-8.69)			0.000[b]
	3.40 (2.76-4.04)	4.40 (2.65-6.15)	0.676	8.10 (5.06-11.14)	6.57 (3.38-9.76)	0.008[b]	
OS (mo)	4.47 (2.80-6.14)			10.87 (9.22-12.52)			0.001[b]
	3.87 (2.79-4.95)	5.33 (3.87-6.80)	0.648	12.87 (10.41-15.33)	9.93 (5.91-13.95)	0.002[b]	

[b]$P < 0.01$, median (95%CI). NLR: Neutrophil/lymphocyte ratio; PFS: Progression free survival; OS: Overall survival; GA: Gemcitabine plus nab-paclitaxel; FFX: FOLFIRINOX.

Table 4 Prognosis according to response of neutrophil/lymphocyte ratio

Before chemotherapy > post chemotherapy	Post chemotherapy NLR < 3*n* = 62		Post chemotherapy NLR ≥ 3*n* = 39		*P* value
	Low > Low,*n* = 47	High > Low,*n* = 15	Low > High,*n* = 11	High > High,*n* = 28	
PFS, median mo (95%CI)	7.20 (6.07-8.33)		3.47 (2.81-4.13)		0.000[b]
	7.60 (6.42-8.79)	5.63 (3.14-8.12)	5.77 (2.29-9.26)	3.33 (3.16-3.50)	0.000[b]
OS, median mo (95%CI)	10.87 (9.16-12.58)		4.47 (3.37-5.57)		0.002[b]
	11.4 (9.93-12.87)	8.00 (2.45-13.55)	7.63 (3.10-12.16)	7.40 (4.49-10.31)	0.001[b]
GA regimen	24 (51.1)	8 (53.3)	6 (54.5)	16 (57.1)	0.112
DCR	43 (91.5)	14 (93.3)	8 (72.7)	16 (57.1)	0.000[b]

[b]$P < 0.01$, median (95%CI). Low, LNR < 3; high, NLR ≥ 3; Post chemotherapy, evaluation at 1st tumor response of chemotherapy, LNR: Neutrophil/lymphocyte ratio; PFS: Progression free survival; OS: Overall survival; GA: Gemcitabine plus nab-paclitaxel; DCR: Disease control rate.
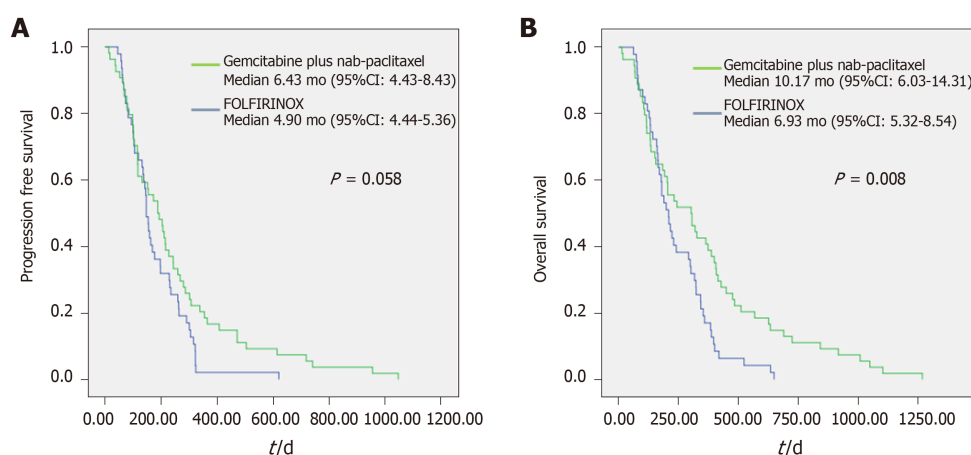
Figure 1 Progression-free survival (A) and overall survival (B) of each regimens.

PLR that was checked before chemotherapy administration (see supplementary Table 4).

Table 5 shows response comparison depending on the ECOG performance status in subgroup analysis. The patients in three groups had significant differences in median PFS (6.60 *vs* 3.90 *vs* 3.27 mo, *P* = 0.003) and OS (10.77 *vs* 6.27 *vs* 4.47 mo, *P* = 0.000). In the group with ECOG 0 status, median PFS (8.93 *vs* 5.43 mo, *P* = 0.002) and median OS (16.10 *vs* 6.97 mo, *P* = 0.000) showed significant differences (Figure 4).

Adverse events

Adverse events associated with each chemotherapy regimen are listed in Table 6. For the GA and FFX groups, thromboembolism (5.6% *vs* 19.1%, *P* = 0.035), neuropathy

Table 5 Result in subgroup analysis (Eastern Cooperative Oncology Group)

	ECOG = 0 (*n* = 52)			ECOG = 1 (*n* = 43)			ECOG = 2 (*n* = 6)			*P* value
	GA (*n* = 25)	FFX (*n* = 27)	*P* value	GA (*n* = 23)	FFX (*n* = 20)	*P* value	GA (*n* = 6)	FFX (*n* = 0)	*P* value	
PFS (mo)	6.60 (4.28-8.92)			3.90 (2.46-5.34)			3.27 (0.00-8.12)			0.003[b]
	8.93 (4.64-13.22)	5.43 (4.58-6.28)	0.002[b]	3.87 (2.03-5.71)	4.40 (1.84-6.96)	0.511	3.27 (0.00-8.12)	NA	NA	
OS (mo)	10.77 (6.26-15.28)			6.27 (4.26-8.28)			4.47 (0.00-14.00)			0.000[b]
	16.10 (10.50-21.70)	6.97 (3.53-10.41)	0.000[b]	6.10 (3.31-8.89)	6.27 (2.76-9.78)	0.674	4.47 (0.00-14.00)	NA	NA	

[b]$P < 0.01$, mean ± SD. NA: Not-availiable; ECOG: Eastern Cooperative Oncology Group; PFS: Progression free survival; OS: Overall survival; GA: Gemcitabine plus nab-paclitaxel; FFX: FOLFIRINOX.

Table 6 Adverse events of each regimen

Adverse events	GA (*n* = 54), *n* (%)	FOLFIRINOX (*n* = 47), *n* (%)	*P* value
Admission	18 (33.3)	18 (38.3)	0.608
Thromboembolism	3 (5.6)	9 (19.1)	0.035[a]
Neuropathy (Grade 1,2/3,4)	28 (51.9) (11/17)	11 (23.4) (10/1)	0.000[b]
Neutropenia (Grade 1,2/3,4)	38 (70.4) (12/26)	35 (74.5) (10/25)	0.496
Thrombocytopenia (Grade 1,2/3,4)	22 (40.7) (13/9)	17 (36.2) (6/11)	0.893
Nausea (Grade 1,2/3,4)	11 (20.4) (9/2)	22 (46.8) (18/4)	0.008[b]
Fatigue (Grade 1,2/3,4)	31 (57.4) (19/12)	26 (55.3) (17/9)	0.740
Diarrhea (Grade 1,2/3,4)	10 (18.5) (7/3)	12 (25.5) (7/5)	0.322
Colitis/pneumonia	11 (20.4) (4/7)	13 (27.7) (7/6)	0.616

[a]$P < 0.05$,
[b]$P < 0.01$. GA: Gemcitabine plus nab-paclitaxel.
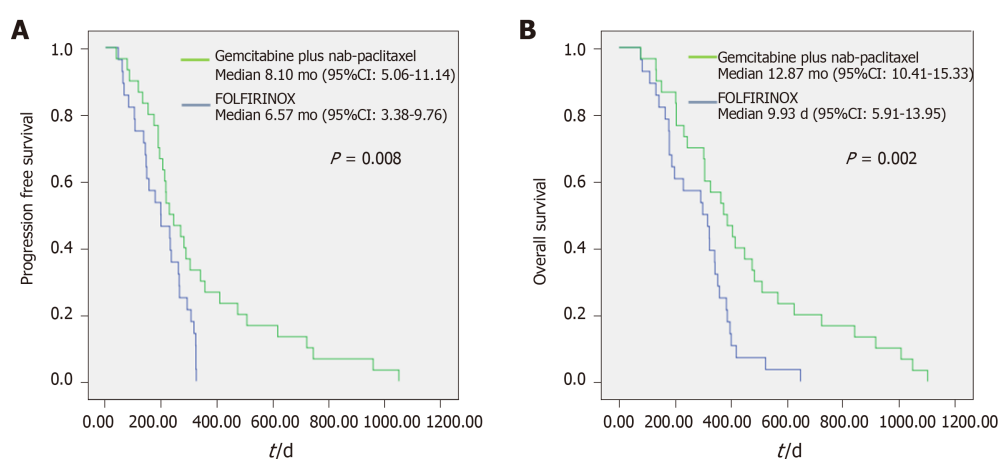
Figure 2 Progression-free survival (A) and overall survival (B) of each regimens in below 3 of neutrophil/lymphocyte ratio.

(51.9% *vs* 23.4%, *P* = 0.000), and nausea (20.4% *vs* 46.8%, *P* = 0.008) significantly differed between the groups. Neuropathy was higher in the GA group, with grade 3 or 4 having a significantly higher ratio. Nausea was higher in the FFX group, frequently with grade 1 or 2. There was no difference in admission rates for these adverse events between the groups (33.3% *vs* 38.3%, *P* = 0.608). The incidence of colitis and
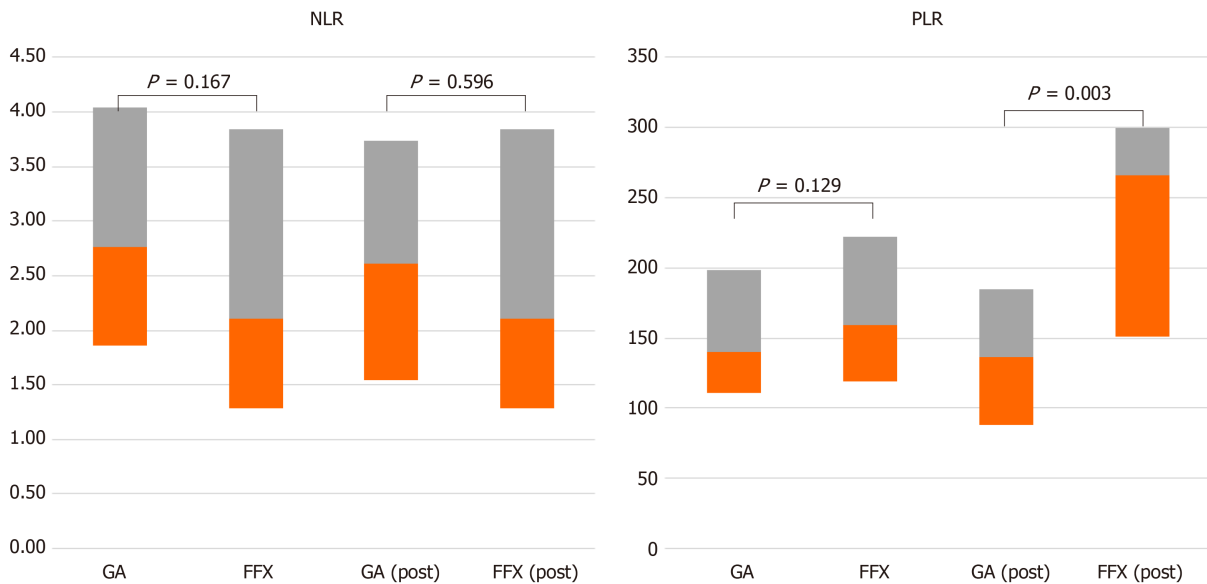
Figure 3 Response of neutrophil/lymphocyte ratio and platelet/lymphocyte ratio according to chemotherapy. NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; GA: Gemcitabine plus nab-paclitaxel; FFX: FOLFIRINOX.
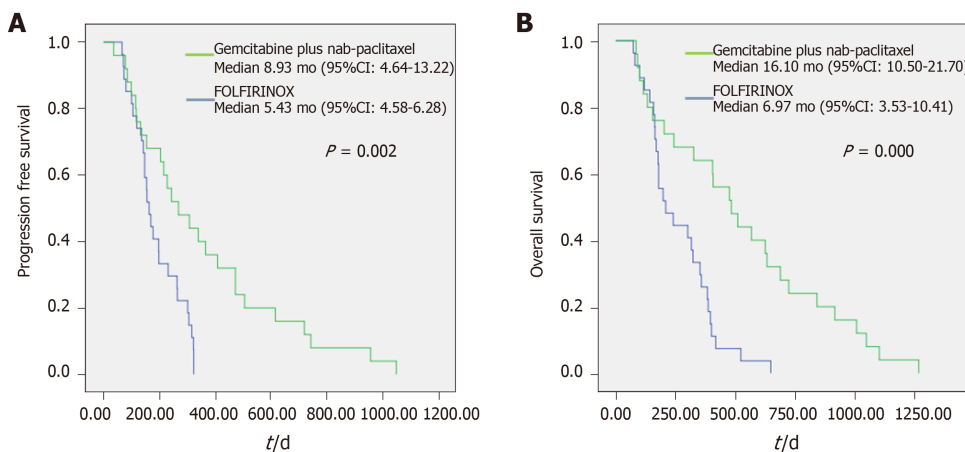
Figure 4 Progression-free survival (A) and overall survival (B) of each regimens in Eastern Cooperative Oncology Group 0 status.

pneumonia also showed no significant difference (20.4% *vs* 27.7%, $P = 0.616$).

DISCUSSION

Herein, we showed that the efficacy and safety of the GA regimen were comparable with those of the FFX regimen. NLR > 3 or ECOG status of 1 or 2 were poor prognostic factors for PFS and OS. Patients with an NLR < 3 or ECOG 0 status seemed to benefit more from GA than from FFX. Furthermore, the decrease of NLR after chemotherapy was related to a good prognosis.

Median PFS in the GA and FFX groups were 6.43 and 4.90 mo, respectively; median OS were 10.17 and 6.93 mo, respectively. The disease control rates in the GA and FFX groups were 83.3% and 72.3%, respectively. Compared with pivotal western trial studies, our study showed that the GA regimen yielded numerically better outcome (our result *vs* pivotal western trial study, PFS: 6.43 *vs* 5.5 mo; OS: 10.17 *vs* 8.5 mo) and the FFX regimen showed numerically worse result (PFS: 4.90 *vs* 6.4 mo; OS: 6.93 *vs* 11.1 mo). Objective response rates are lower (18.5% for GA and 10.6% for FFX) than those in pivotal western trial studies[2,3]. However, the disease control rate is about 80% similar to that in other studies. Compared to a European study[11] that showed a dose reduction rate of 20.5%, our study shows that of 72.3%. The low objective response rate

may be attributed to the higher dose reduction rate than that of other studies.

In a recently published meta-analysis[9] and a systematic review article[12], these two chemotherapy regimens showed similar results. However, when analyzing these studies, the difference between Asian and Western patients may have affected their responses to chemotherapy. In a study conducted among patients living in South Korea, the GA regimen showed better results for peritoneal metastasis among patients of 65 years or older, and a Charlson comorbidity index of 9 or higher[6]. Another study[13] that was published in Korea, reported comparable result for the two regimens; however, the GA group showed longer survival without statistical significance although the patients in the FFX group were approximately 10 years younger than those in the GA group. It is thought that the GA regimen may show better results in situations when the prognostic factors are similar. In another study that analyzed patients living in Japan, the GA regimen showed a higher 1-year survival rate than the FFX regimen[14]. However, studies conducted in Europe and Canada showed better results with FFX than with GA[7,8]. While this difference was not proven experimentally, it could suggest a possible trend, possibly due to genetic differences or physical conditions. In our study, the GA regimen did not prove superior in PFS over FFX; however, in special situations, the GA regimen was more efficacious than the FFX regimen.

One of such situations was an NLR < 3. The NLR is known to be an inflammatory marker and a prognostic factor in patients with cancer[15]. There are several hypotheses suggesting that a high NLR is associated with a poor prognosis in patients with pancreatic cancer. First, myeloid-derived suppressor cells (MDSC)[16,17] have been shown to inhibit the immune response of T cells and NK cells, promote cancer cell growth, and induce distant metastasis of cancer cells[16,18]. As there is no marker to discriminate between PMN-MDSC and neutrophils, an increase in the NLR is thought to be due to an increase in PMN-MDSC, which explains the association with poor prognosis in patients with malignancy. Second, cancer induces the secretion of tumor microenvironment inflammatory factors such as IL-6, IL-17, TNF-alpha, and TGF-beta, which may further induce an increased neutrophil count[19-22]. Third, cancer-related obstructive cholangitis may cause increased neutrophil count. It may be indirectly related to cancer prognosis, but inflammation will make the tumor microenvironment immunosuppressive, resulting in a poor prognosis in patients with cancer[23,24]. Our study also showed that a high NLR was associated a poor prognosis. NLR < 3 was an important prognostic factor for patients who received chemotherapy. Patients with NLR < 3 had a PFS that was four months longer and an OS that was six months longer than those in patients with NLR > 3. The GA regimen had a tendency toward a longer PFS than the FFX regimen in patients with NLR < 3. The variation of NLR after chemotherapy is associated with diseased control rate, PFS and OS. Therefore, evaluating the NLR during routine chemotherapy response assessment will be an effective tool for predicting the prognosis.

Another differential situation was the ECOG 0 status. This scale was developed to assess how a patient's disease progresses and to determine the appropriate treatment and prognosis[25]. ECOG 0 status was defined as fully active performance without any restriction. ECOG 1 was defined as being restricted in physically strenuous activity. EOCG 2 was defined as being unable to carry out any work activities, only capable of self-care. Our study revealed that the response to the two chemotherapeutic regimens was different in patients with an ECOG 0 status. The exact mechanism is unknown, but the GA regimen was more effective in patients with a better physical condition, similar to that in patients with a low NLR. FFX regimens may also be more burdensome to an Asian patient, who may have a weaker physique than that of a Western patient, as it is difficult to receive second-line chemotherapy. Therefore, the decision made for the first-line chemotherapy may be more important.

We evaluated for other prognostic factors such as PLR and CA19-9. PLR is also known as a representative inflammatory marker[26]. One study in Korea showed that PLR was a prognostic marker in metastatic pancreatic cancer. Therefore, we evaluated the prognostic value in metastatic pancreatic cancer; however, there was no significant relation with prognosis. And CA19-9 is very well known and proven as a prognostic factor in pancreatic cancer. In our study, 8 patients (7.9%) had significantly decreased after chemotherapy. They also had a good prognosis. Change in NLR after chemotherapy may significantly influence the prognosis more than the change in CA19-9.

Comparing adverse events between the GA and FFX regimens, the rate of total adverse events was similar, but some specific adverse events were different. First, thromboembolic events occurred more frequently in patients who received the FFX regimen than in those who received the GA regimen. It occurred in nearly 20% of FFX

group patients; therefore, when patients receive FFX chemotherapy, this event should be watched for carefully. Second, neuropathy more frequently occurred in patients receiving the GA regimen, especially grade 3 or 4 neuropathy. It is an irreversible condition; hence, when patients are receiving GA chemotherapy, the physician should monitor for neuropathy. If neuropathy is detected early, nab-paclitaxel should be reduced and drug administration should as conservatively as possible. Third, as nausea commonly occurred with the FFX regimen, physicians should prescribe antiemetic drugs as needed.

Our study had several limitations. First, this study had a single-center, retrospective design and enrolled a relatively low number of patients. Second, some parameters (ECOG performance status) were different between the groups in baseline characteristics. Third, disease progression could not be accurately identified in 18 patients (17.8%) for reasons such as loss during follow-up, death before the disease progressed, or the efficacy of chemotherapy maintained until the evaluation day.

CONCLUSION

In conclusion, GA and FFX showed comparable efficacy outcomes and safety profiles. Patients who had an NLR below 3 or an ECOG 0 status had a better prognosis than did the other patients. The GA regimen was more efficacious as a first-line treatment in patients who had better prognosis factors such as ECOG 0 or NLR below 3. We suggest that the patients with the LNR below 3 or ECOG 0 status should initially undergo the GA regimen. However, further studies are needed to prove which regimen works better in a wider range of situations.

ARTICLE HIGHLIGHTS

Research background
In pancreatic cancer patients, it is not well-known which chemo regimens are more effective.

Research motivation
It is hypothesized that there is a predictive markers of which chemotherapy regimens.

Research objectives
In this study, the authors aimed to determine which chemo regimen is more efficacious in metastatic pancreatic cancer patients.

Research methods
The authors performed analysis compare the patient who received gemcitabine plus nab-paclitaxel (GA) and FOLFIRINOX.

Research results
There was no significant difference in overall survival between the gemcitabine mono and combination chemotherapy groups. However, patients with Eastern Cooperative Oncology Group (ECOG) 0 or neutrophil/lymphocyte ratio (NLR) < 3 had better result when using GA regimen.

Research conclusions
GA chemotherapy may be a better option to manage metastatic pancreatic cancer with ECOG 0 or NLR < 3.

Research perspectives
There were some predictive markers of efficacy of chemotherapy regimen in metastatic pancreatic cancer.

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