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Gemcitabine Plus Nab-Paclitaxel as Second-Line Chemotherapy following FOLFIRINOX in Patients with Unresectable Pancreatic Cancer: A Single-Institution, Retrospective Analysis

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Keywords

Pancreatic cancer · Gemcitabine · Nab-paclitaxel · FOLFIRINOX · Second-line treatment

Abstract

Introduction: Patients with advanced pancreatic cancer have a poor prognosis. FOLFIRINOX (FFX) and gemcitabine plus nab-paclitaxel (GnP) have been established as first-line treatment, but they have not been confirmed as second-line treatment after FFX. The aim of this study was to evaluate the safety and efficacy of GnP as second-line therapy after FFX in patients with unresectable pancreatic cancer. ***Methods:*** Twenty-five patients with unresectable pancreatic cancer were enrolled. The patients were treated with GnP after FFX between September 2015 and September 2019. Tumor response, progression-free survival (PFS), overall survival (OS), and incidence of adverse events were evaluated. ***Results:*** The response rate, disease control rate, median PFS, and median OS were 12%, 96%, 5.3 months, and 15.6 months, respectively. The common grade 3 or 4 adverse events were neutropenia (76%) and anemia (16%). ***Conclusions:*** GnP after FOLFIRINOX is expected to be one of the second-line recommendations for patients with unresectable pancreatic cancer.

Introduction

Pancreatic cancer is still one of the most lethal cancers. In Japan, pancreatic cancer is the fourth leading cause of cancer-related deaths, with >35,000 deaths in 2018 [1]. The 5-year survival rate was reported to be 5–10% [2]. Chemotherapy of advanced pancreatic cancer has improved in this last decade.

For first-line treatment, FOLFIRINOX (fluorouracil, folinic acid, irinotecan, and oxaliplatin) (FFX) and gemcitabine plus nab-paclitaxel (GnP) regimens have been established as the standard chemotherapy in patients with metastatic pancreatic cancer with good performance status (PS). In 2011, in the ACCORD-11 phase III trial, FFX demonstrated significantly longer overall survival (OS) than gemcitabine (GEM); the median OS was 11.1 months in the FFX arm and 6.8 months in the GEM arm (hazard ratio [HR]: 0.57, 95% confidence interval [CI]: 0.45–0.73, $p < 0.001$) [3]. In addition, in 2013, the MPACT phase III trial showed significantly longer OS with GnP than with GEM. The median OS was 8.5 months in the GnP arm and 6.7 months in the GEM arm (HR: 0.72, 95% CI: 0.62–0.83, $p < 0.001$) [4]. In most studies, the authors concluded that GnP had a better safety profile than FFX.

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The incidences of grade 3/4 neutropenia and febrile neutropenia were higher in FFX than in GnP [5]. A prospective study comparing FFX and GnP has not been performed, so it is still unclear which of the 2 regimens should be used as the first choice.

Various studies have been conducted on the second-line treatment after GEM-based therapy of pancreatic cancer. The CONKO-003 study showed that oxaliplatin and folinic acid and fluorouracil (OFF) significantly prolonged progression-free survival (PFS) and OS compared to folinic acid and fluorouracil (FF) [6]. Median OS was 5.9 months in the OFF arm and 3.3 months in the FF arm. However, the phase 3 randomized PANCREOX study, comparing mFOLFOX6 therapy with FF therapy, did not show any benefit of oxaliplatin add-on. In the phase 3 randomized NAPOLI-1 study, nanoliposomal irinotecan plus fluorouracil and folinic acid (nal-IRI + FF) extends the prognosis compared to FF [7]. Median OS was 6.1 months in the nal-IRI + FF arm and 4.2 months in the FF arm. Based on these results, nal-IRI + FF has been established as the second-line therapy after GnP in Japan since 2020. On the other hand, there has been no large prospective study of second-line treatment after FFX. Only a few studies of second-line GnP after FFX have been reported [8–19]. In these reports, median PFS was 2.4–6.4 months. Based on these results, in the Japanese guideline, if a fluorouracil-based regimen (e.g., FFX and S-1) is used for the first-line chemotherapy, then a GEM-based regimen (e.g., GnP or GEM) is recommended as the second-line treatment, and if a GEM-based regimen is used for the first-line chemotherapy, a fluorouracil-based regimen (e.g., FFX, nal-IRI + FF, and S-1) is recommended as the second-line treatment. Thus, there are several strategies for unresectable pancreatic cancer. In our hospital, we usually select FFX as the first-line chemotherapy rather than GnP for patients with good PS. GnP is better tolerated than FFX, so we consider that GnP can be given even if a patient's condition is deteriorating slightly after first-line FFX. Therefore, we performed a retrospective analysis to evaluate the safety and efficacy of GnP after FFX in patients with unresectable pancreatic cancer.

Materials and Methods

We conducted a retrospective review of all patients with unresectable (locally advanced or metastatic) pancreatic cancer who were treated at the Kagawa University Hospital between September 2015 and September 2019 with second-line GnP after FOLFIRINOX. All patients had histologically or cytologically confirmed adenocarcinoma of the pancreas. The data were retrospectively identified from the electronic medical records. This study was approved by the Institutional Review Board of Kagawa University. Clinical data collected were as follows: sex, disease status (locally advanced or metastatic), Eastern Cooperative Oncology Group performance status (ECOG PS) on the starting day of GnP, primary site of the tumor (head or body/tail of the pancreas), metastatic site and presence of ascites before GnP administration, toxicity, dose reduction and interruption of GnP, relative dose intensity of GnP, and the presence of third-line treatment. All patients received dexamethasone 6.6 mg and palonosetron 0.75 mg intravenously for 30 min as an antiemetic. Nab-paclitaxel was then injected intravenously at 125 mg/m^2 for 30 min, followed by gemcitabine injected intravenously at 1,000 mg/m^2 for 30 min, on days 1, 8, and 15. Treatment cycles were repeated every 4 weeks until disease progression or unacceptable toxicity was observed. The doses of gemcitabine and nab-paclitaxel were generally reduced in cases of grade 4 hematological toxicity and grade 3 or greater non-hematological toxicity. In cases of prolonged peripheral neuropathy, the dose of nab-paclitaxel was postponed or reduced at the discretion of the attending physician, even if it was grade 2. The radiologic response to second-line GnP was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [20]. The dates of tumor progression, death, and the last follow-up visit were captured. Kaplan-Meier curves were used to estimate PFS and OS. OS was defined as the time from the start of GnP to the date of death or last follow-up. PFS was defined as the time from the start of GnP to the date of detection of progressive disease or the patient's death. Postprogression survival (PPS) was defined as the time from the date of detection of progressive disease with second-line GnP to the date of death or the last follow-up visit. The following potential predictors of PFS were also examined: age, sex, primary site of the pancreas, ECOG PS, disease status (locally advanced or metastatic), serum carbohydrate antigen 19-9 (CA19-9) levels before GnP, presence of ascites on the starting day of GnP, and presence of grade 3 or 4 neutropenia during GnP therapy. To identify the predictors of PFS, univariate analysis and the log-rank test were used. The significance level was set at $p < 0.05$. All analyses were performed using JMP Pro 15.1 software for Windows (SAS Institute, Cary, NC, USA). Adverse events were evaluated and graded by review of chart documentation according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Results

Patients' Characteristics

Thirty-six patients received FFX as primary treatment. Thirty-one patients received subsequent treatment after discontinuation of FFX. The subsequent treatments were GnP in 25 patients (69%), surgical resection in 5 patients (14%), and nab-PTX monotherapy in 1 patient (3%) (shown in Fig. 1). Five patients could not receive second-line treatment because of worsening of PS or complications such as interstitial pneumonitis. A total of 25 patients were included in the retrospective analysis. The patients' characteristics and clinical data before GnP are

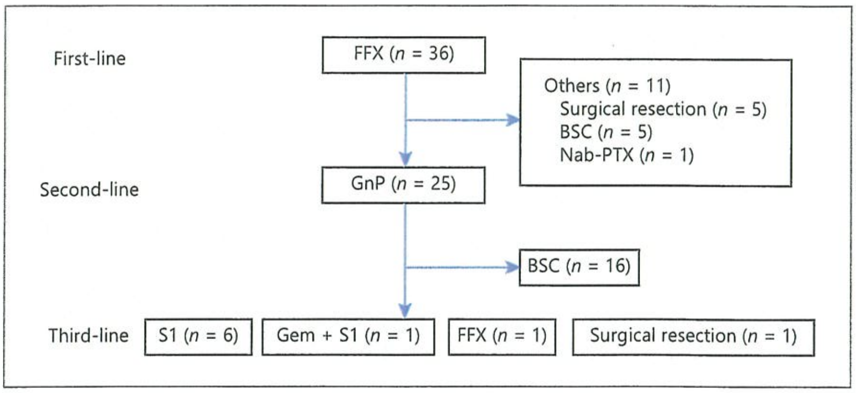

Fig. 1. Flow diagram.

Table 1. The patients' characteristics and clinical data before gemcitabine plus nab-paclitaxel therapy (*n* = 25)

Characteristics	
Age, median [range], years	69 [41–77]
Sex, *n* (%)	
Male	16 (64)
Female	9 (36)
ECOG PS, *n* (%)	
0	8 (32)
1	15 (60)
2	2 (8)
Primary site of pancreas, *n* (%)	
Head	15 (60)
Body or tail	10 (40)
Disease status, *n* (%)	
Metastatic	21 (84)
Locally advanced	4 (16)
Serum CA19-9, median [range], ng/mL	5,001 [2–143,643]
Metastatic sites, *n* (%)	
None	4 (16)
Liver	10 (40)
Lymph node	9 (36)
Lung	9 (36)
Peritoneum	5 (20)
Others	4 (16)
Presence of ascites, *n* (%)	
Absent	17 (68)
Small amount of ascites	6 (24)
Moderate amount of ascites	2 (8)
Large amount of ascites	0 (0)

ECOG PS, Eastern Cooperative Oncology Group performance status.

summarized in Table 1. The median age was 69 years (range, 41–77 years), and 16 patients (64%) were male. Twenty-one patients (84%) had metastatic disease, and 4 patients (16%) had locally advanced disease. The median follow-up time was 8.2 months (range, 1.6–33.5 months). FFX was discontinued in 22 patients, the reason being PD in 19 patients and adverse events in 3 patients.

Efficacy of GnP as a Second-Line Regimen

The median duration of GnP therapy was 3.9 months (range, 0–14.4 months). The median PFS and OS were 5.3 months (95% CI: 3.4–6.4 months, shown in Fig. 2) and 15.6 months (95% CI: 6.4–33.5 months, shown in Fig. 3), respectively. The best overall response was partial response in 3 patients (12%), stable disease in 21 patients (84%), and progressive disease in 1 patient (4%). The overall response rate (complete response + partial response) was 12%, and the disease control rate (complete response + partial response + stable disease) was 96%. GnP was discontinued in 23 patients (92%) because of progressive disease in all patients. Predictors of PFS were also examined. A high serum level of CA19-9 (>1,000 U/mL) was a predictor of poor PFS. Median PFS was 10.2 months (95% CI: 4.9–15.8) and 4.4 months (95% CI: 3.2–5.9), respectively (HR 3.98, $p = 0.02$). No other factors were identified (Table 2).

Safety

The adverse events are summarized in Table 3. The most frequent nonhematologic adverse events related to treatment were fatigue (84%), peripheral neuropathy (80%), and anorexia (76%). The most common grade 3 or 4 adverse events were neutropenia (76%) and anemia (16%). The incidence of neutropenia was very high, but febrile neutropenia occurred in only 1 patient. Grade 3 or 4 peripheral neuropathy occurred in only 1 patient (4%). There were no treatment-related deaths. Dose reduction and interruption of GnP were performed for 15 patients

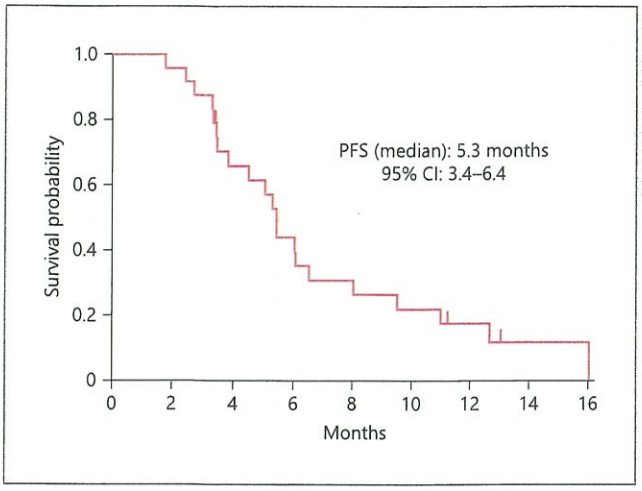

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Fig. 2. PFS curves of the 25 patients from the start of gemcitabine plus nab-paclitaxel. PFS, progression-free survival.

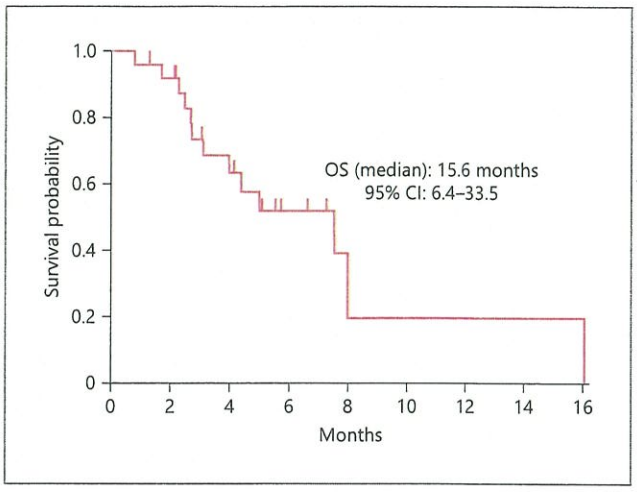

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Fig. 3. OS curves of the 25 patients from the start of gemcitabine plus nab-paclitaxel. OS, overall survival.

Table 2. Predictors of PFS

Variable	Patients, *n*	mPFS, months	HR	*p* value
Age				
<70 years	16	5.3	1	0.647
≥70 years	9	5.3	1.23	
Gender				
Male	16	5.9	1	0.097
Female	9	5.1	2.17	
Primary site of pancreas				
Body or tail	10	5.3	1	0.628
Head	15	5.2	1.25	
ECOG PS				
0–1	23	5.3	1	0.802
2	2	5.3	1.29	
Disease status				
Metastatic	21	5.3	1	0.148
Locally advanced	4	4.3	2.29	
CA19-9				
<1,000	6	10.2	1	0.020
≥1,000	19	4.4	3.98	
Presence of ascites				
Absent	17	5.9	1	0.457
Present	8	4.1	1.42	
Grade 3 or 4 neutropenia				
Absent	19	5.3	1	0.782
Present	6	4.7	1.16	

PFS, progression-free survival; HR, hazard ratio; ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 3. Adverse events ($n = 25$)

Adverse events	All grade, *n* (%)	Grade 3/4, *n* (%)
Neutropenia	22 (88)	19 (76)
Anemia	18 (72)	4 (16)
Thrombocytopenia	13 (52)	1 (4)
Febrile neutropenia	1 (4)	1 (4)
Fatigue	21 (84)	0 (0)
Peripheral neuropathy	20 (80)	1 (4)
Anorexia	19 (76)	0 (0)
Diarrhea	14 (56)	1 (4)
Constipation	13 (52)	0 (0)
Stomatitis	12 (48)	0 (0)
Nausea	10 (40)	0 (0)

(60%) and 23 patients (92%), respectively. The reasons for dose reduction and interruption were neutropenia (44%), thrombocytopenia (24%), fatigue (18%), peripheral neuropathy (6%), and others. The median relative dose intensities of GEM and nab-PTX were 70.6% and 64.9%, respectively.

Third-Line Therapy

In this study, 9 patients received third-line therapy (shown in Fig. 1). The treatments were S-1 in 6 patients (67%), GEM + S-1 in 1 patient (11%), and FFX rechallenge in 1 patient (11%). One patient (11%) underwent surgical resection, but the operation resulted in R2 resec-

Table 4. Summary of published studies of gemcitabine plus nab-paclitaxel therapy after FOLFIRINOX

Reference	Year	Study design	Patients, *n*	UICC stage	RR, %	DCR, %	Median PFS, months	Median OS, months
Salem et al. [8]	2014	Retrospective	12	III/IV	nr	nr	3.3	16.2
Portal et al. [9]	2015	Prospective	57	IV	17.5	58.0	5.1	8.8
Zhang et al. [10]	2015	Retrospective	28	III/IV	17.9	46.4	2.8	5.2
Chan et al. [11]	2016	Retrospective	40	III/IV	nr	nr	2.4	4.8
Nguyen et al. [12]	2016	Retrospective	30	III/IV	17.0	57.0	3.7	12.4
El Rassy et al. [13]	2017	Retrospective	12	IV	30.0	60.0	4.9	nr
Aung et al. [14]	2017	Retrospective	17	III/IV	nr	nr	nr	4.6
Vendrell et al. [15]	2017	Retrospective	30	III/IV	nr	nr	6.4	11.4
Zhang et al. [16]	2018	Retrospective	30	III/IV	nr	nr	3.6	5.7
Ozaka et al. [17]	2018	Retrospective	25	IV	10.5	64.0	4.3	10.4
Vogl et al. [18]	2019	Prospective	35	III/IV	9.0	62.9	3.2	13.7
Mita et al. [19]	2019	Prospective	30	III/IV	13.3	46.7	3.8	7.6
Current study		Retrospective	25	III/IV	12.0	96.0	5.3	15.6

UICC, Union for International Cancer Control; RR, response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival; nr, not reported.

tion. OS of this patient from starting GnP was 9.1 months, which did not improve the OS of the entire sample. Patients who received third-line chemotherapy had significantly longer PPS than patients who received BSC as the third-line therapy (7.1 vs. 1.9 months, $p = 0.017$). The PPS was 7.1 months (95% CI: 0.83–27.1) and 1.9 months (95% CI: 1.1–3.9), respectively (HR 5.0, $p = 0.017$).

Discussion/Conclusion

The present results suggest that GnP as the second-line therapy was an effective and feasible treatment option in patients with unresectable pancreatic cancer. Median PFS (5.3 months), median OS (15.6 months), and safety were satisfactory. No fatal adverse events and no treatment-related deaths occurred.

There has been no established standard regimen for second-line treatment of unresectable pancreatic cancer after FFX. Previous retrospective studies reported that median PFS and OS of second-line GEM after FFX were 2.0–2.5 and 3.1–5.7 months, respectively [16, 21–25]. Compared with these results, the PFS and OS in the present study were better.

Moreover, previous studies reported that median PFS and OS of second-line GnP after FFX were 2.4–6.4 and 4.6–16.2 months, respectively (Table 4) [8–19]. PFS in the present study was comparable to the previous reports, and OS in the present study was considered good. In the present study, 9 patients received third-line chemotherapy, and these patients had a good prognosis that may have contributed to the extension of the OS.

The disease control rate in this study was higher than the other studies. This may be due to the fact that this study was retrospective analysis, and patient selection may have been included. Another reason may be that we often perform CT scan 4 weeks after the initiation of GnP at our hospital, which is relatively early compared to other trials, and therefore more SD judgment was taken.

As to adverse events, there was a high incidence of grade 3/4 neutropenia (76%), but febrile neutropenia occurred in only 1 patient (4%). Grade 3/4 neutropenia in the phase III first-line GnP study occurred in 38% of patients [4]. The present study had a high incidence of grade 3/4 neutropenia. The reason for this is considered below. First, the present study targeted second-line chemotherapy. FFX had been performed as frontline treatment, so the bone marrow might have been exhausted at the time of starting GnP. Second, there is an ethnic difference. The Japanese phase I/II trial of first-line GnP reported a higher incidence of grade 3/4 neutropenia (70.6%) [26] than the phase III trial of first-line GnP therapy (38%) [4]. Moreover, in the Japanese phase II trial of first-line FFX, the incidence of neutropenia was higher (77.8%) [27] than in the phase III trial of first-line FFX therapy (45.7%) [3]. Since neutropenia occurred frequently, it may be useful to start with a low dose of GnP when using GnP in second-line therapy. However, whether low-dose GnP is effective or not has not been investigated, and future studies are needed.

Peripheral neuropathy is a common adverse event of FFX and GnP therapy, so there was concern that many patients would discontinue GnP therapy due to continuing severe peripheral neuropathy. However, in the present study, few patients developed grade 3 peripheral neuropathy. Dose reduction and interruption due to hematotoxicity may reduce peripheral neuropathy. In fact, no patient discontinued GnP therapy due to peripheral neuropathy, and long PFS was obtained in the present study. Given these results, second-line GnP appears to be a feasible treatment.

A high serum level of CA19-9 (>1,000 U/mL) was a predictor of poor PFS. CA19-9 was previously reported as a prognostic factor in patients with advanced pancreatic cancer treated with chemotherapy. Most of these studies reported that the cutoff value of CA19-9 was around 1,000 U/mL [28–30]. No other predictors could be identified.

The present study had some limitations. First, it was a retrospective, single-institution study with a small number of patients. Second, there was a potential selection bias in patients who could receive second-line treatment. However, all patients who were treated at our hospital between September 2015 and September 2019 with second-line GnP after FFX were included in this analysis.

In conclusion, the present results suggest that GnP as second-line therapy is an effective and feasible treatment option in patients with unresectable pancreatic cancer. A prospective study to verify the safety and efficacy and appropriate dosing of GnP as a second-line treatment after FFX in patients with unresectable pancreatic cancer should be performed.

Statement of Ethics

This study was approved by the Institutional Review Board of Kagawa University.

Conflict of Interest Statement

The Department of Clinical Oncology, Faculty of Medicine, Kagawa University, has previously received support to conduct research from Sanofi Corporation, Ono Pharmaceutical Co., Ltd., Pfizer Japan Inc., TAIHO Phamaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Eisai Co., Ltd., MSD Corporation, Toray Medical Co., Ltd., and Daiichi Sankyo Co., Ltd. and honoraria from Eli Lilly Japan Co., Ltd. and Bristol-Myers Squibb Corporation.

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Author Contributions

A.T., H.O., and K.H. designed the study, and H.O. and K.H. wrote the initial draft of the manuscript. H.O. contributed to analysis and interpretation of data. Y.O. and T.N. have contributed to data collection and interpretation, and all authors have contributed critically, reviewed the manuscript to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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