Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.8736-21
Intern Med 61: 2255-2261, 2022
http://internmed.jp

【 ORIGINAL ARTICLE 】

Clinical Outcomes of S-1 Monotherapy and Modified FOLFIRINOX Therapy after Gemcitabine plus Nab-paclitaxel Therapy in Unresectable Pancreatic Cancer

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Abstract:

Objective S-1 and modified FOLFIRINOX (mFFX) were often used as the second-line chemotherapies after failure of gemcitabine plus nab-paclitaxel (GnP) in unresectable pancreatic cancer (UPC) until nanoliposomal irinotecan plus 5-fluorouracil/leucovorin therapy was approved as an alternative in Japan in 2020. However, the clinical outcomes of S-1 and mFFX after GnP have scarcely been reported. Therefore, we retrospectively studied them.

Methods We extracted the clinical data of 86 patients with UPC who received second-line chemotherapy after GnP between 2015 and 2020. Among the patients who had a good organ functions and no massive ascites, 41 patients treated with S-1 and 21 treated with mFFX were enrolled.

Results Compared to S-1, mFFX tended to be used for younger patients with a good general condition (median age, 63 vs. 71 years, $p<0.01$; and performance status 0, 67% vs. 37%, $p<0.05$). The median progression-free and overall survival were similar between the S-1 (3.7 and 7.2 months, respectively) and mFFX (3.3 and 7.4 months, respectively) groups. The response rate in patients with measurable lesions was 4% (n=1/23) in the S-1 group and 17% (n=2/12) in the mFFX group. The incidence of grade 3 or 4 adverse events was 20% in the S-1 group and 57% (neutrophil count decreased in 43%) in the mFFX group ($p<0.01$).

Conclusion S-1 and mFFX were both acceptable second-line chemotherapies after GnP therapy for UPC, although attention should be paid to myelosuppression during mFFX treatment. Further studies involving nanoliposomal irinotecan plus 5-fluorouracil/leucovorin therapy are necessary to facilitate the selection of the optimal regimen for each patient.

Key words: pancreatic cancer, second-line chemotherapy, S-1, modified FOLFIRINOX, gemcitabine plus nab-paclitaxel

(Intern Med 61: 2255-2261, 2022)
(DOI: 10.2169/internalmedicine.8736-21)

Introduction

Pancreatic cancer is often diagnosed at a late stage, when it is already unresectable, locally advanced, or metastatic and thus has a very poor prognosis (1, 2). As first-line chemotherapy for patients with unresectable advanced or metastatic pancreatic cancer (UPC), gemcitabine plus nab-paclitaxel therapy (GnP) and 5-fluorouracil (5-FU)/leucovorin+irinotecan+oxaliplatin (FOLFIRINOX) therapy pro-

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Received for publication September 27, 2021; Accepted for publication November 28, 2021
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longed the survival compared to gemcitabine monotherapy (3, 4). The median progression-free survival (PFS) and overall survival (OS) were reportedly 5.5 and 8.5 months for GnP therapy and 6.4 and 11.1 months for FOLFIRINOX therapy, respectively. However, FOLFIRINOX therapy had a high incidence of severe toxicities, such as grade 3 or 4 neutropenia (77.8%) and febrile neutropenia (22.2%), in a Japanese phase II study (5). Therefore, modified FOLFIRINOX (mFFX) therapy was developed, in which the initial dose of irinotecan was reduced from 180 mg/m^2 to 150 mg/m^2, and the 5-FU bolus administration was omitted. Promising efficacy (median PFS 5.5 months; median OS 11.2 months) with good tolerability was obtained in a domestic phase II study of mFFX therapy (6). Thus, mFFX therapy is now widely used in clinical practice in Japan.

No standard regimen for second-line chemotherapy was established until recently, when the survival benefit of nanoliposomal irinotecan plus 5-FU/leucovorin (nal-IFL) over 5-FU/leucovorin alone was demonstrated (7). Patients moving to second-line chemotherapy tend to have a poor general condition and are thus often forced to make a difficult decision concerning which regimen to receive next. Before the approval of the nal-IFL regimen, patients had two choices following the discontinuation of first-line chemotherapy with GnP: S-1 or mFFX. It is clinically important to understand the efficacy and safety of these regimens, as the appropriate choice of second-line chemotherapy regimens is a complicated problem.

In the present study, we retrospectively investigated the current treatment results of S-1 and mFFX therapies as second-line chemotherapy for UPC after failed GnP therapy.

Materials and Methods

Patients

Patients with UPC who discontinued GnP therapy as the first-line chemotherapy and were moved to second-line chemotherapy with S-1 or mFFX were searched for in the electric chart system of National Hospital Organization Shikoku Cancer Center and Ehime University Hospital, from January 2015 to December 2020, and clinical data were extracted. Patients with early recurrence during or within six months of S-1 adjuvant chemotherapy were excluded. This was a retrospective study with no clear criteria concerning the choice of second-line chemotherapy; therefore, the decision was based on patients' wishes or the judgment of the attending physician. Patients with histologically or cytologically proven pancreatic adenocarcinoma or clinically diagnosed pancreatic adenocarcinoma with available data on tumor markers, computed tomography (CT) and magnetic resonance imaging scans, and their preserved organ function as well as an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2, evaluable lesions on CT scans, and no massive ascites (extending throughout the abdominal cavity) were considered eligible for the evaluation of efficacy and safety, and their clinical outcomes were subsequently analyzed.

Chemotherapy

S-1 was administered orally at 40 mg/50 mg/60 mg twice daily, on days 1-28, every 6 weeks, depending on the body surface area. For mFFX therapy, oxaliplatin 85 mg/m^2 (2 hours), irinotecan 150 mg/m^2 (1.5 hours), l-leucovorin 200 mg/m^2 (2 hours), and 5-FU 2,400 mg/m^2 (46 hours) were administered intravenously every 2 weeks. Depending on the adverse events (AEs), the dose was reduced or withdrawn appropriately by the attending physician. The relative dose intensity (RDI) of S-1, oxaliplatin, irinotecan, and 5-FU was calculated as the ratio of the actually administered dose to the standard dose during the treatment. The third-line chemotherapies in each group were investigated.

Evaluations

The baseline characteristics, including the age, sex, ECOG PS, locally advanced/metastatic/recurrent tumors, primary tumor site, number of metastatic organs, metastatic organ site, PFS (time from the start of treatment to progression) of the first-line GnP therapy, uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) gene polymorphism, laboratory blood data [C-reactive protein (CRP), lactate dehydrogenase (LDH), albumin, carcinoembryonic antigen (CEA), and cancer antigen 19-9 (CA19-9)], and biliary drainage findings, were collected.

Efficacy evaluations of the second-line chemotherapy included the PFS (time from the start of treatment to progression or death), OS (time from the start of treatment to death), response rate, and disease control rate based on the Response Evaluation Criteria in Solid Tumors version 1.1. Tumors were evaluated every 8±2 weeks on CT. Safety was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Statistical analyses

Differences in continuous and categorical data were evaluated using Wilcoxon's rank-sum test and Fisher's exact test, respectively. The Kaplan-Meier method was used to estimate the survival. All statistical analyses were performed using the JMP version 15.2.0 software program (SAS International, Cary, USA). p values were calculated using a two-sided test, and significance was set at $p<0.05$.

Statement of ethics

Consent to participate in this study was obtained using an opt-out method in accordance with the ethical principles of the Declaration of Helsinki. This study was approved by the ethics review committee of each hospital.

Results

During the study period, a total of 135 patients with UPC (87 patients in National Hospital Organization Shikoku Can-

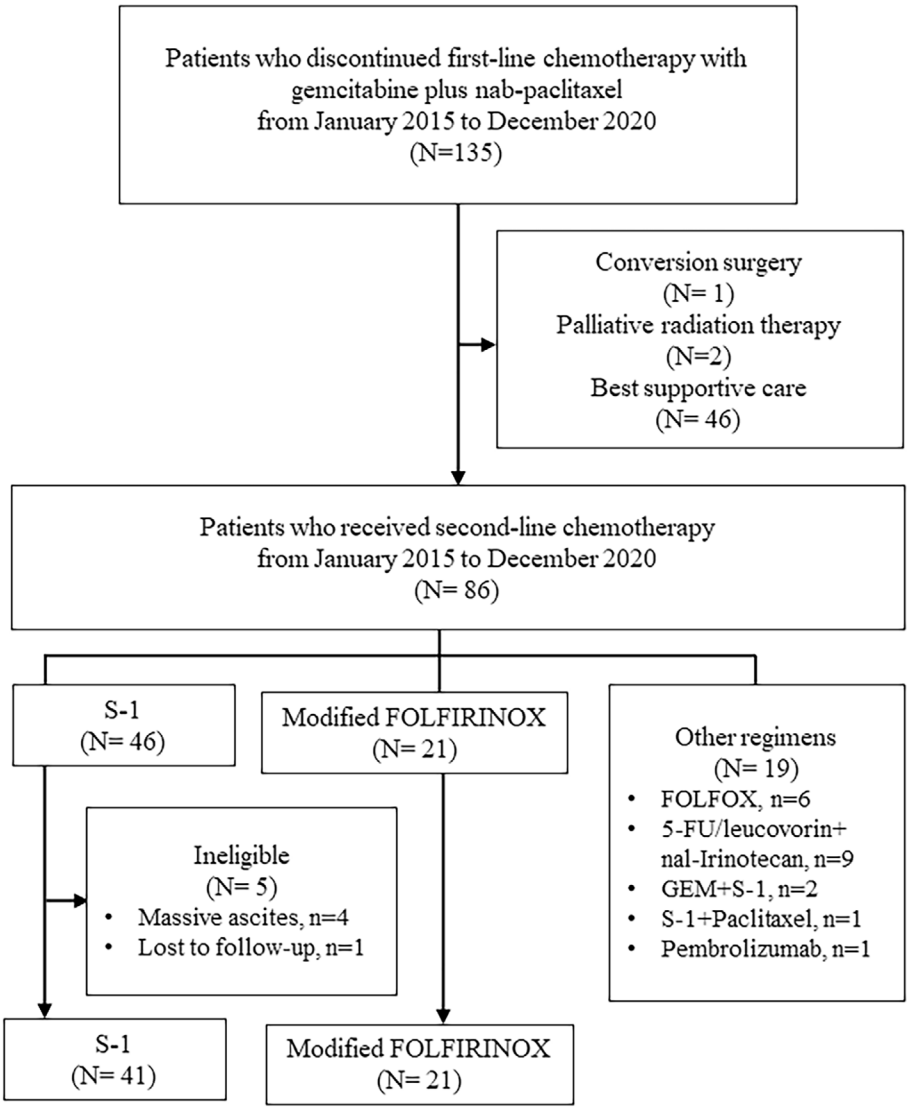

Figure 1. Consort diagram and patient extract flow. FOLFIRINOX: 5-fluorouracil/leucovorin+oxaliplatin+irinotecan, FOLFOX: 5-fluorouracil/leucovorin+oxaliplatin, GEM: gemcitabine

cer Center, and 48 patients in Ehime University Hospital) discontinued first-line GnP therapy, and 86 (64%) patients were moved to second-line chemotherapy (Fig. 1). Forty-six (34%) and 21 (16%) patients received second-line S-1 and mFFX therapy, respectively. Excluding patients with massive ascites (n=4) and those lost to follow-up (n=1), 41 patients with S-1 and 21 patients with mFFX were eligible for analyses. The choice of chemotherapy was left to each patient and the attending physician. The main reasons for the choice of chemotherapy were being elderly or with a poor general condition (n=23, 56%) and the patient's wish (n=7, 17%) in the S-1 group, and being young or with a good general condition (n=8, 38%) and the patient's wish (n=6, 29%) in the mFFX group. In the mFFX group, the UGT1A1 was wild type in 12 patients (57%), 6* 28* single heterozygotes in 7 patients (33%), and 6* 28* double heterozygotes in 1 patient (5%). The genotype was not tested in one patient.

Table 1 shows the patients' background characteristics in each group. Compared to S-1, mFFX tended to be used in younger patients (63 years vs. 71 years, $p<0.01$) and those with a good general condition (PS 0, 67% vs. 37%, $p<0.05$). There were no significant differences between the two groups in terms of the sex, locally advanced/metastatic or recurrent tumor, tumor location, biliary drainage, metastatic organ site, PFS of first-line GnP therapy, or laboratory data. Nine patients in the S-1 group and two in the mFFX group discontinued GnP due to intolerance, and all others discontinued it due to progressive disease. Two patients (5%) in the S-1 group newly received biliary drainage during the treatment.

The median length of follow-up for all 62 patients was 7.2 (range,1.5-32) months. Fifty-nine patients (95%) showed disease progression, and 50 (81%) died. Fig. 2 shows the Kaplan-Meier curves of the PFS and OS in the S-1 (A) and mFFX (B) groups. The median PFS was 3.7 [95% confidence interval (CI) 1.7-6.4] months in the S-1 group and 3.3 (95% CI 1.8-5.1) months in the mFFX group. The median OS was 7.2 (95% CI 5.6-10.4) months in the S-1 group and 7.4 (95% CI 3.8-11.9) months in the mFFX group. Patients

Table 1. Patients' Backgrounds.

	S-1 n=41	Modified FOLFIRINOX n=21	p*
Age, median year (range)	71 (54-81)	63 (37-75)	<0.01
Sex			0.41
Male	17 (41%)	11 (52%)	
Female	24 (59%)	10 (48%)	
ECOG performance status			<0.05
0	15 (37%)	14 (67%)	
1	21 (51%)	7 (33%)	
2	5 (12%)	0	
Tumor status			0.38
Locally advanced	3 (7%)	3 (14%)	
Metastasis or recurrence	38 (93%)	18 (86%)	
Primary tumor location			0.36
Head	20 (49%)	6 (29%)	
Body	12 (29%)	10 (48%)	
Tail	9 (22%)	5 (24%)	
Biliary drainage			
Yes	10 (24%)	5 (24%)	1.00
Number of metastatic organs			0.19
1	24 (63%)	8 (44%)	
2 or more	14 (37%)	10 (56%)	
Metastatic site			
Liver	17 (41%)	9 (43%)	0.92
Lung	3 (7%)	1 (5%)	0.70
Peritoneum	15 (37%)	6 (29%)	0.53
PFS of gemcitabine+nab-paclitaxel			
Median months (range)	6.5 (0.9-29)	6.7 (1.8-16)	0.96
Laboratory data			
CRP, median mg/dL (range)	0.21 (0.01-5.98)	0.48 (0.01-11.33)	0.62
Albumin, median g/dL (range)	3.6 (1.6-4.3)	3.8 (3.1-4.6)	0.11
CEA, median ng/mL (range)	6.1 (2.1-1,518)	7.8 (0.8-92)	0.91
CA19-9, median ng/mL (range)	389 (1-143,687)	346 (12-10,324)	0.78

FOLFIRINOX: 5-fluorouracil/leucovorin+oxaliplatin+irinotecan, ECOG: Eastern Cooperative Oncology Group, CRP: C-reactive protein, CEA: carcinoembryonic antigen, CA19-9: cancer antigen 19-9

*Fisher's exact test, Chi-square test or Wilcoxon rank-sum test

with PS 2 (n=5) were observed only in the S-1 group (Table 1). When these patients were excluded, the median PFS and OS of the S-1 group were 4.2 (95% CI 3.3-6.5) and 8.4 (95% CI 6.2-12.1) months, respectively.

The response rate in patients with measurable lesions was 4% (n=1/23) in the S-1 group and 17% (n=2/12) in the mFFX group. The disease control rate was 48% (n=11/23) in the S-1 group and 50% (n=6/12) in the mFFX group. The median RDIs were 83% (range 19-100%) in S-1, 80% (range 29-102%) in oxaliplatin, 86% (range 23-100%) in irinotecan, and 95% (range 30-100%) in 5-FU.

The proportions of patients who received third-line chemotherapy were 27% (n=11) in the S-1 group and 33% (n=7) in the mFFX group. The third-line chemotherapy regimens in the S-1 group were mFFX (n=5), nal-IFL (n=2), 5-fluorouracil/leucovorin+oxaliplatin, irinotecan (n=1), GnP (n=1), and investigational drug (n=1), while those in the mFFX group were S-1 (n=3), nal-IFL (n=2), GnP (n=1), and gemcitabine plus erlotinib (n=1).

Table 2 shows the AEs in both groups. The incidence of grade 3 or 4 AEs was 20% in the S-1 group and 57% in the mFFX group (p<0.01). Neutropenia and anemia of grade 3 or 4 occurred in 5% in the S-1 group. The incidences of grade 3 or 4 leukopenia, neutropenia, and anemia were 14%, 43% and 19% in the mFFX group, respectively. There were no patients with grade 3 peripheral sensory neuropathy, febrile neutropenia, or treatment-related death. Two (5%) and two (10%) patients discontinued S-1 and mFFX treatment, respectively, due to bothering symptoms, such as edema, skin rash, and fatigue in the S-1 group and fatigue and anemia in the mFFX group.

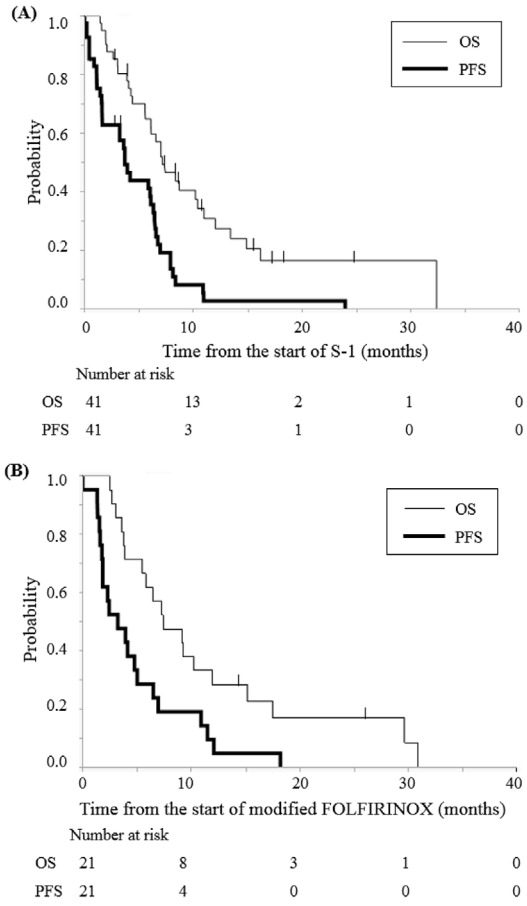

Figure 2. Kaplan-Meier curves of patients in the S-1 group (A) and the modified FOLFIRINOX group (B). The median progression-free and overall survival were 3.7 and 7.2 months in the S-1 group and 3.3 and 7.4 months in the mFFX groups, respectively. PFS: progression-free survival, OS: overall survival

Discussion

Although S-1 and mFFX therapies are often used as second-line therapy after GnP therapy, there are only a few reports on their treatment results (8, 9). In this retrospective study, we demonstrated that both therapies provided a median PFS of over three months and a median OS of over six months with primarily only mild to moderate toxicities. The results are summarized in Table 3. In the NAPOLI-1 study that showed survival benefit of nal-IFL in metastatic pancreatic cancer, the median PFS and OS were reported to be 3.1 and 6.1 months, respectively (7). Our results were comparable to those of other studies and acceptable in clinical practice, although careful attention should be paid to cross-study comparisons with different patient backgrounds.

Some of the patients' baseline characteristics after GnP therapy differed widely in our study between the S-1 and mFFX groups. mFFX therapy tended to be selected in young patients with a good PS. In contrast, S-1 therapy tended to be selected for elderly, vulnerable patients with a PS of 1 or 2. The treatment choice was suggested based primarily on a patient's general condition according to the chart description. As a result, the patient background was worse in the S-1 group than in the mFFX group, making it difficult to compare the treatment results between the two groups. However, fully understanding the actual clinical data is important in order to both present and discuss the various treatment options with both the patients and their families.

Recently, the efficacy and safety of second-line S-1 therapy for gemcitabine-refractory UPC were published in a large phase III study comparing S-1 plus leucovorin in Japan and Korea (10). The median PFS and OS of the S-1 arm were reported as 2.8 and 7.6 months, respectively. There were no grade 3 or 4 AEs in more than 10% of patients, and the treatment discontinuation rate due to AEs was 9.6%. Similar to this report, the clinical results of second-line S-1 therapy have been consistent among different studies (11, 12), and our results were also similar to these. Although there were many elderly and vulnerable patients in the S-1 group, the RDI, disease control rate, and proportion of patients receiving the third-line chemotherapy were similar to those of the mFFX groups. Applying appropriate medication to their conditions and ensuring disease control might have contributed to the survival in not only the mFFX group but also the S-1 group.

Although published data on second-line mFFX after GnP are limited, a relatively large retrospective study was reported (9). The efficacy results of this study were similar to those of our study (Table 3). Febrile neutropenia, which is frequently observed during FOLFIRINOX treatment, was reported in 5.8% of the patients in the previous study and 0% in our study. Cumulative peripheral neuropathy is a well-known and common AE of paclitaxel and oxaliplatin. This overlap toxicity occurring as a result of sequential treatment with GnP to mFFX is a concern when deciding on mFFX treatment. In fact, grade 3 neuropathy of mFFX was reported in 10.6% of patients in a previous study (9), while no grade 3 neuropathy was observed in our study. These discrepancies might be due to the short treatment period and small sample size of our study. Overall, these results suggest that mFFX can be used safely when patients are properly selected, even in a second-line chemotherapy setting after GnP therapy. However, mFFX therapy is associated with more severe AEs than S-1 therapy, which should be taken into consideration by treating physicians.

In the present study, the incidence of severe AEs (≥Grade 3) was significantly higher in the mFFX group than in the S-1 group. Since there is a concern that these toxicities may be intolerable for elderly patients and patients with a poor general condition, we consider S-1 monotherapy to be a useful alternative treatment for such patients. Whether or not the treatment selection method is truly optimal and beneficial for patients with UPC should be clarified in the future. In addition, nal-IFL as a second-line chemotherapy was approved for medical insurance in Japan in March 2020. However, clinical data for Japanese patients are still insufficient,

Table 2. Adverse Events.

	S-1		Modified FOLFIRINOX	
	All grades n (%)	≥Grade 3 n (%)	All grades n (%)	≥Grade 3 n (%)
Hematological toxicity				
Leukopenia	5 (12)	0	7 (33)	3 (14)
Neutropenia	11 (27)	2 (5)	12 (57)	9 (43)
Anemia	12 (29)	2 (5)	11 (52)	4 (19)
Thrombopenia	6 (15)	0	6 (29)	0
Non-hematological toxicity				
Nausea	6 (15)	0	10 (48)	0
Anorexia	16 (39)	1 (2)	12 (57)	1 (5)
Constipation	5 (12)	0	3 (14)	0
Diarrhea	8 (20)	1 (2)	4 (19)	0
Fatigue	13 (32)	2 (5)	15 (71)	1 (5)
Dysgeusia	5 (12)	0	0	0
Skin hyperpigmentation	3 (7)	0	0	0
Rash	3 (7)	1 (2)	0	0
AST/ALT increased	5 (12)	0	6 (29)	2 (10)
Biliary tract infection	1 (2)	1 (2)	0	0
Peripheral sensory neuropathy	1 (2)	0	13 (62)	0
Allergic reaction	0	0	2 (10)	1 (5)
Pulmonary embolism	0	0	1 (5)	1 (5)
Infection	1 (2)	1 (2)	1 (5)	1 (5)
Fever	1 (2)	0	1 (5)	0
Mucositis oral	4 (10)	0	0	0
Total ≥grade 3 adverse events	-	8 (20)*	-	12 (57)*

FOLFIRINOX: 5-fluorouracil/leucovorin+oxaliplatin+irinotecan, AST: aspartate transaminase, ALT: alanine transferase

*Fisher's exact test, $p<0.01$

Table 3. Summary of Reports on Second-line Chemotherapy after Gemcitabine Plus Nab-paclitaxel.

	S-1		Modified FOLFIRINOX	
	ref.8 (n=14)	Our study (n=41)	ref.9 (n=104)	Our study (n=21)
Efficacy results				
Progression-free survival (median months)	2.8	3.7	3.9	3.3
Overall survival (median months)	12.3	7.2	7.0	7.4
Response rate	0%	4%	10.6%	17%
Disease control rate	57.1%	48%	56.7%	50%
Safety results				
Adverse events ≥Grade 3				
Any	NR	20%	54.8%	57%
Neutropenia	0%	5%	42.3%	43%
Febrile neutropenia	0%	0%	5.8%	0%
Anorexia	0%	2%	1.0%	5%
Fatigue	0%	5%	0%	5%
Peripheral neuropathy	NR	0%	10.6%	0%

FOLFIRINOX: 5-fluorouracil/leucovorin+oxaliplatin+irinotecan, NR: not reported

and S-1 and mFFX therapies are still viable options. The positioning of each treatment is an emerging issue.

This study has several limitations such as its retrospective design and small sample size, which may have caused a bias in the results. There was a marked difference in the patient backgrounds between the S-1 and mFFX groups, so we

were unable to compare them directly. In addition, nal-IFL therapy was not included because of the lack of sufficient mature data, and its clinical significance in practice could not be estimated. In many cases of second-line chemotherapy, the general condition of patients with UPC is not very good, necessitating the consideration of various factors concerning treatment for the patient's benefit based on actual clinical experience and a timely interpretation of published results. To overcome these limitations and resolve these issues, randomized controlled studies with patient quality-of-life analyses are needed.

Conclusion

The outcomes of second-line S-1 or mFFX therapy after GnP therapy were unsatisfactory but acceptable in terms of the therapeutic effect and safety in clinical practice under appropriate application of treatments and careful monitoring of toxicities. Further studies including nal-IFL therapy are necessary to select the optimal regimen for each patient.

Author's disclosure of potential Conflicts of Interest (COI).
Tomohiro Nishina: Honoraria, Taiho Pharmaceutical. Ichinosuke Hyodo: Honoraria, Ono, Chugai, Taiho, Asahi-Kasei and Daiichi-Sankyo.

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