ORIGINAL ARTICLE

Efficacy and safety of modified fluorouracil/leucovorin plus irinotecan and oxaliplatin (mFOLFIRINOX) compared with S-1 as second-line chemotherapy in metastatic pancreatic cancer

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Key words
adverse event, overall survival, pancreatic adenocarcinoma, peripheral sensory neuropathy, progression-free survival.

Accepted for publication 26 April 2021.

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Declaration of conflict of interest: The authors disclose no conflicts of interest.

Abstract

Background and Aim: The optimal standard second-line chemotherapy for metastatic pancreatic cancer (MPC) remains unclear. Here, we evaluated the efficacy and safety of modified fluorouracil/leucovorin plus irinotecan and oxaliplatin (mFOLFIRINOX) compared with oral fluoropyrimidine S-1 as a second-line chemotherapy in patients with MPC.

Methods: We retrospectively reviewed 76 consecutive patients with metastatic pancreatic adenocarcinoma who underwent mFOLFIRINOX or S-1 treatment as a second-line chemotherapy after gemcitabine plus nab-paclitaxel (GnP) failure at our department between December 2014 and February 2019.

Results: Patients who underwent mFOLFIRINOX treatment exhibited significantly better objective response rates (ORRs) and progression-free survival (PFS) than S-1 (ORR, 20.0% vs 0%, P = 0.003; PFS, 3.7 vs 2.1 months, P = 0.010). Although baseline patient characteristics of age, performance status, and serum albumin levels differed significantly between the two groups, mFOLFIRINOX was identified as an independent factor of favorable PFS on multivariate analyses. Grade 3–4 neutropenia and peripheral sensory neuropathy occurred more frequently in the mFOLFIRINOX group. The median overall survival from the initiation of second-line chemotherapy was not significantly longer in the mFOLFIRINOX group than in the S1 group (8.5 vs 5.8 months, respectively; P = 0.213); however, the 8-month survival rate was significantly higher in the mFOLFIRINOX group (56.0% vs 27.5%, respectively; P = 0.030).

Conclusions: mFOLFIRINOX as a second-line regimen contributed to favorable treatment outcomes, but induced more frequent adverse events than S-1. On multivariate analyses, mFOLFIRINOX was identified as an independent factor with favorable PFS, suggesting that mFOLFIRINOX could be a promising treatment option for patients with GnP failure.

Introduction

Pancreatic cancer (PC) has become the third leading cause of cancer-related death in the United States, and the incidence of PC continues to increase.1,2 PC has a dismal prognosis, with a 5-year overall survival rate of 9%,1 and early detection of PC remains difficult.3,4 Approximately 80% of patients with PC have metastatic or locally advanced PC, and these patients primarily undergo chemotherapy.5 As a first-line chemotherapy, combination chemotherapy has become standard in advanced PC after the superiority of gemcitabine (GEM) plus nab-paclitaxel (GnP), and fluorouracil/leucovorin plus irinotecan and oxaliplatin (FOLFIRINOX) over GEM monotherapy was demonstrated in multicenter phase III studies.6,7 Although standard FOLFIRINOX has greater effectiveness, management of adverse events is difficult because of high rates of grade 3/4 neutropenia and febrile neutropenia.7,8 A modified FOLFIRINOX regimen (mFOLFIRINOX; no or decreased administration of bolus 5-fluorouracil [5-FU] plus decreased irinotecan administration) has been shown to exhibit improved safety with maintained efficacy.9,10 Although there have been no direct, prospective, randomized comparisons between the original FOLFIRINOX regimen and mFOLFIRINOX, this modified regimen is thought...
to be equivalent to the original FOLFIRINOX regimen for the palliative treatment of PC.\textsuperscript{10–12}

Second-line chemotherapy can improve the survival of patients with metastatic pancreatic cancer (MPC) after failure of first-line GEM-based chemotherapy.\textsuperscript{13–16} Although several previous phase III studies demonstrated survival benefit with their study regimens,\textsuperscript{14–16} the standard treatment remains to be established. Although mFOLFIRINOX following GnP failure could be a promising strategy because both GnP and mFOLFIRINOX have shown favorable outcomes, limited data are available regarding sequential therapy with GnP and mFOLFIRINOX.\textsuperscript{17} In Japan, S-1, an oral fluoropyrimidine, has been widely used as a second-line therapy because S-1 has antitumor activity with tolerable toxicity against GEM-refractory PC.\textsuperscript{18–21}

In this study, we aimed to examine the efficacy and safety of mFOLFIRINOX in comparison with S-1 as a second-line chemotherapy in patients with metastatic adenocarcinoma of the pancreas after GnP failure.

**Methods**

**Study design and patients.** We retrospectively reviewed the clinical data for 76 consecutive patients with pathologically proven metastatic adenocarcinoma of the pancreas who underwent chemotherapy using mFOLFIRINOX or S-1 as a second-line regimen after GnP failure at our department between December 2014 and February 2019. mFOLFIRINOX was given every 2 weeks as follows: 2 h intravenous infusion of oxaliplatin at 85 mg/m\textsuperscript{2} and 2 h intravenous infusion of l-leucovorin at 200 mg/m\textsuperscript{2}, intravenous infusion of irinotecan over 90 min at 150 mg/m\textsuperscript{2}, followed by a continuous intravenous infusion of 5-FU over 46 h at 2400 mg/m\textsuperscript{2}, with an omission of bolus 5-FU infusion. S-1 was administered orally twice a day at a dose of 40 mg/m\textsuperscript{2} for 4 weeks in a 6-week cycle. Second-line regimens were decided based on the general conditions of the patients and willingness to undergo aggressive therapy. The dosages and schedules of chemotherapeutic drugs were adjusted at the discretion of each physician according to the conditions of the patients. For each patient, data were collected regarding age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), primary tumor location, metastatic site number, lymph node involvement, biliary drainage, neutrophil-to-lymphocyte ratio (NLR), carbohydrate antigen 19-9 (CA19-9) levels, carcinoembryonic antigen (CEA) levels, UDP glucuronosyltransferase family 1 member A1 (UGT1A1) status, treatment details (chemotherapeutic regimens, treatment response, and toxicities), and survival time. Tumor responses were graded according to the Response Evaluation Criteria in Solid Tumor (RECIST) ver. 1.1.\textsuperscript{22} Hematological and non-hematological adverse events were graded according to the Common Terminology Criteria of Adverse Events version 4.0. Progression-free survival (PFS) was calculated from the administration date for the first dose of chemotherapy to the date of disease progression or any cause of death, whichever occurred first. Overall survival (OS) was calculated from the initiation of second-line chemotherapy to the date of death due to any cause. We also examined 8-month survival rates, which were set according to the median OS in previous reports on single-arm FOLFIRINOX as a second-line chemotherapy.\textsuperscript{17,23,24} Data from patients who were alive at the end of the follow-up period (December 2020) were censored. The study protocol was approved by the Institutional Review Board at Osaka International Cancer Institute (approval no. 18225-4), and the study was performed in accordance with the Declaration of Helsinki.

**Statistical analysis.** Categorical variables are described as percentages, and continuous variables are presented as the median and range. Patient characteristics, treatment outcomes, toxicities of second-line chemotherapy, and the proportion of the patients who underwent third-line chemotherapeutic regimens were compared using Chi-square and Fisher’s exact tests for categorical variables or Mann–Whitney U-test for continuous variables. Analyses of OS and PFS were performed using the Kaplan–Meier method, and differences were evaluated using log-rank tests.

Using the Cox proportional hazard model, univariate and multivariate analyses were performed to identify significant prognostic factors associated with PFS. The following 14 variables were examined: age, sex, ECOG PS, body mass index, primary tumor location, metastatic site number, lymph node involvement, biliary drainage, NLR, CA19-9, CEA, albumin, creatinine, and second-line chemotherapy regimens.

Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Factors with P values less than 0.20 in univariate analysis were entered into multivariate Cox models. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical interface for the R Commander software package for Windows (version 1.50).\textsuperscript{25} Results with P values less than 0.05 were considered significant.

**Results**

**Patient characteristics.** The characteristics of the 76 patients included in the current study are summarized in Table 1. The median age was 65.5 years (range, 43–81 years), and 35 patients (46.1\%) were men. ECOG PS was 0 in 30 patients (39.5\%), 1 in 38 patients (50.0\%), and 2 in eight patients (10.5\%). Median body mass index was 21.3 kg/m\textsuperscript{2} (range, 15.3–28.8 kg/m\textsuperscript{2}). The primary tumor sites were the pancreas head in 39 patients (51.3\%) and the pancreas body/tail in 37 patients (48.7\%). The number of metastatic sites was 1–3 in 20 patients (26.3\%) and 4 or more in 56 patients (73.7\%). Lymph node involvement was diagnosed in 23 patients (30.3\%), and biliary drainage was performed in 30 patients (39.5\%). NLR was less than 3 in 27 patients (35.5\%). The median levels of CA19-9, CEA, albumin, and creatinine were 1051 IU/mL (range, 2–100 000 IU/mL), 6.85 ng/mL (range, 1.5–1743 ng/mL), 3.55 mg/dL (range, 2.3–4.6 mg/dL), and 0.70 mg/dL (range, 0.33–1.33 mg/dL), respectively.

Table 1 also shows a comparison of patient characteristics between the mFOLFIRINOX and S1 groups. We found no significant differences in sex, body mass index, primary tumor location, metastatic site number, lymph node involvement, histological type, NLR, CA19-9, CEA, and UGT1A1 status (Table 1). By contrast, patients who underwent FOLFIRINOX were significantly younger (P < 0.001) and had significantly
better ECOG PS (P = 0.021). Moreover, serum albumin levels were significantly higher in the mFOLFIRINOX group (P = 0.006).

**Treatment outcomes.** The overall response rate (ORR) of second-line chemotherapy was 6.6% (5/76; complete response, 0; partial response, 6). ORR was significantly higher in the mFOLFIRINOX group than in the S1 group (20.0% [5/25] vs 0% [0/51]; P = 0.003). The disease control rate was not significantly different between the two groups (mFOLFIRINOX, 64.0% [16/25] vs S1, 51.0% [26/51]; P = 0.408). The median PFS of second-line chemotherapy was 2.6 months (95% CI, 1.9–3.6 months). The median PFS was significantly longer in the mFOLFIRINOX group than in the S1 group (3.7 months [95% CI, 3.0–7.2 months] vs 2.1 months [95% CI, 1.6–2.8 months]; P = 0.010; Fig. 1). Among the 68 study patients whose PS was 0–1, the median PFS was also significantly longer in the mFOLFIRINOX group than in the S1 group (3.7 months [95% CI, 3.0–7.2 months] vs 2.1 months [95% CI, 1.6–2.8 months]; P = 0.010).

Overall, 26 patients (34.2%) received third-line chemotherapy. The rate of patients who underwent third-line chemotherapy was significantly higher in the mFOLFIRINOX group than in the S-1 group (52.0% [13/25] vs 25.5% [13/51], respectively; P = 0.042; Table 2). The regimens of third-line therapy in the mFOLFIRINOX group were GEM plus S-1 in five patients, S-1 in three patients, FOLFOX in two patients, GEM in one patient, GEM plus erlotinib in one patient, and S-1 plus...
radiation for palliation of pain in one patient, whereas those in the S-1 group were mFOLFIRINOX in nine patients, GEM plus S-1 in one patient, FOLFOX in two patients, GEM in one patient, and GEM plus erlotinib in one patient.

The median OS from the initiation of second-line chemotherapy was 6.0 months (95% CI, 4.4–7.0 months). Among all patients, 74 patients (97.4%) had died at the end of the follow-up period. The median OS was not significantly longer in the mFOLFIRINOX group than in the S1 group (OS, 8.5 months [95% CI, 5.3–11.1 months] vs 5.8 months [95% CI, 3.6–6.6 months], P = 0.213; Fig. 2). The 8-month survival rate from the initiation of second-line chemotherapy was significantly higher in the mFOLFIRINOX group than in the S1 group (56.0% [14/25] vs 27.5% [14/51], respectively; P = 0.030). Among the 68 study patients whose PS was 0–1, the median OS was comparatively longer in the mFOLFIRINOX group than in the S1 group (OS, 8.5 months [95% CI, 5.3–11.1 months] vs 5.8 months [95% CI, 3.8–7.0 months], P = 0.278).

**Safety.** No treatment-related deaths occurred. The toxicity profile is summarized in Table 3. The incidence rate of neutropenia was significantly higher in the mFOLFIRINOX group than in the S1 group (all grade, 88.0% vs 3.3%, respectively [P < 0.001]; grade 3 or 4, 52.0% vs 3.9%, respectively [P < 0.001]). Febrile neutropenia occurred in two cases (8.0%) in the mFOLFIRINOX group.

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**Table 2** Treatment and outcomes of the study patients

|                                | Total (n = 76) | S1 (n = 51) | mFOLFIRINOX (n = 25) | P value |
|--------------------------------|---------------|-------------|----------------------|---------|
| Overall response rate, n (%)   | 5 (6.6)       | 0 (0)       | 5 (20.0)             | 0.003†  |
| Disease control rate, n (%)    | 42 (55.3)     | 26 (51.0)   | 16 (64.0)            | 0.408‡  |
| Third-line chemotherapy, n (%) | 26 (34.2)     | 13 (25.5)   | 13 (52.0)            | 0.042†  |

Third-line chemotherapy regimen

- mFOLFIRINOX, n (%): 9 (11.8), 9 (17.6), —
- S-1, n (%): 3 (3.9), —, 3 (12.0)
- Gemcitabine plus S-1, n (%): 6 (7.9), 1 (2.0), 5 (20.0)
- FOLFOX, n (%): 3 (3.9), 1 (2.0), 2 (8.0)
- Gemcitabine, n (%): 2 (2.6), 1 (2.0), 1 (4.0)
- Gemcitabine plus erlotinib, n (%): 2 (2.6), 1 (2.0), 1 (4.0)
- S-1 plus radiation, n (%): 1 (1.3), 0 (0), 1 (4.0)

†Fisher’s exact test.
‡Chi-square test. Statistically significant at P < 0.05.

mFOLFIRINOX, modified fluorouracil/leucovorin plus irinotecan and oxaliplatin.
stimulating factor (G-CSF) treatment was significantly higher in the mFOLFIRINOX group than in the S-1 group (28.0% [7/25] vs 0% [0/51], respectively; P < 0.001). Among the major grade 3−4 non-hematological toxicities, the rate of peripheral sensory neuropathy (PN) was significantly higher in the mFOLFIRINOX group than in the S-1 group (16.0% [4/25] vs 2.0% [1/51], respectively; P = 0.038). Among five patients who suffered from grade 3−4 PN, one patient had experienced grade 2 PN, and the other four patients had experienced grade 3 PN during GnP treatment.

**Factors associated with PFS.** Finally, we examined the predictive factors associated with PFS in patients receiving second-line chemotherapy. In univariate analysis, two variables were found to be significantly associated with PFS, that is, serum albumin levels (HR, 0.550; 95% CI, 0.343−0.882; P = 0.013) and second-line chemotherapy (HR, 0.526; 95% CI, 0.320−0.866; P = 0.012; Table 4). Multivariate analysis was performed using three variables (tumor location, serum albumin levels, and second-line chemotherapy). Second-line chemotherapy was identified as a statistically significant independent prognostic predictor (HR, 0.557; 95% CI, 0.336−0.925; P = 0.024; Table 4).

Further in the multivariate analysis using the data of the 68 study patients whose PS was 0−1, second-line chemotherapy was demonstrated as a statistically significant independent prognostic predictor (HR, 0.554; 95% CI, 0.329−0.933; P = 0.026).

**Discussion**

In previous studies in the single-arm setting, the FOLFIRINOX regimen, including mFOLFIRINOX, showed favorable treatment outcomes as a second-line chemotherapy after the failure of GEM-based chemotherapy. Multivariate analysis was performed using the data of the 68 study patients whose PS was 0−1, second-line chemotherapy was identified as an independent prognostic predictor. Collectively, mFOLFIRINOX as a second-line chemotherapy could contribute to prolonging PFS with favorable response rates.

In this study, we observed favorable OS from the initiation of second-line therapy in the mFOLFIRINOX group compared with that in the S-1 group, but did not find significant differences primarily because a few patients in the S-1 group survived for a long time (more than 2 years). By contrast, the 8-month survival rate was significantly higher in the mFOLFIRINOX group than in the S-1 group, suggesting that mFOLFIRINOX may have the potential to demonstrate significant survival benefit as a second-line chemotherapy in a larger-scale setting. Nanoliposomal irinotecan (nal-IRI) plus 5-FU/LV was not used in the current study because it was approved in Japan during the study period. Because nal-IRI plus 5-FU/LV showed superiority over 5-FU/LV as a second-line chemotherapy for patients with MPC, this combination regimen could be a standard second-line chemotherapy following GnP treatment failure. Recently, platinum-containing regimens, including FOLFIRINOX, have been increasingly used owing to their contributions to a favorable OS in patients with homologous recombination deficiency, comprising approximately 20% of patients with PC. A direct comparison between mFOLFIRINOX and nal-IRI plus 5-FU/LV as a second-line chemotherapy is necessary.

Notably, mFOLFIRINOX induced a higher rate of adverse events compared with S-1. In the mFOLFIRINOX group, grade 3−4 neutropenia was more frequently observed. G-CSF treatment was administered in 28.0% of patients in the mFOLFIRINOX group. Recent studies have demonstrated the efficacy of G-CSF not only to reduce the risk of neutropenia but also to improve the survival of patients who underwent FOLFIRINOX treatment.

**Table 3** Toxicities in patients with unresectable pancreatic cancer treated with second-line chemotherapy

|                      | S1 (n = 51) | mFOLFIRINOX (n = 25) | P value |
|----------------------|------------|----------------------|---------|
| Anemia               |            |                      |         |
| All grade (%)        | 49 (96.1)  | 24 (96.0)            | 1†      |
| Grade 3, 4 (%)       | 9 (17.6)   | 6 (24.0)             | 0.729‡  |
| Neutropenia          |            |                      |         |
| All grade (%)        | 17 (33.3)  | 22 (88.0)            | <0.001† |
| Grade 3, 4 (%)       | 2 (3.9)    | 13 (52.0)            | <0.001† |
| Thrombocytopenia     |            |                      |         |
| All grade (%)        | 19 (37.3)  | 14 (56.0)            | 0.193‡  |
| Grade 3, 4 (%)       | 0 (0)      | 1 (4.0)              | 0.329†  |
| FN                   | 0 (0)      | 2 (8.0)              | 0.105†  |
| Diarrhea             |            |                      |         |
| All grade (%)        | 10 (19.6)  | 12 (48.0)            | 0.022‡  |
| Grade 3, 4 (%)       | 0 (0)      | 1 (4.0)              | 0.329†  |
| Constipation         |            |                      |         |
| All grade (%)        | 10 (19.6)  | 11 (44.0)            | 0.050‡  |
| Grade 3, 4 (%)       | 0 (0)      | 0 (0)                | —       |
| Decreased appetite   |            |                      |         |
| All grade (%)        | 22 (43.1)  | 19 (76.0)            | 0.014‡  |
| Grade 3, 4 (%)       | 0 (0)      | 1 (4.0)              | 0.329†  |
| Nausea               |            |                      |         |
| All grade (%)        | 13 (25.5)  | 13 (52.0)            | 0.042‡  |
| Grade 3, 4 (%)       | 1 (2.0)    | 0 (0)                | 1†      |
| Fatigue              |            |                      |         |
| All grade (%)        | 16 (31.4)  | 17 (68.0)            | 0.005‡  |
| Grade 3, 4 (%)       | 0 (0)      | 0 (0)                | —       |
| PN                   |            |                      |         |
| All grade (%)        | 27 (52.9)  | 23 (92.0)            | <0.001† |
| Grade 3, 4 (%)       | 1 (2.0)    | 4 (16.0)             | 0.038†  |

†Fisher’s exact test.
‡Chi-square test. Bold values indicate P < 0.05.
FN, febrile neutropenia; mFOLFIRINOX, modified fluorouracil/leucovorin plus irinotecan and oxaliplatin; PN, peripheral sensory neuropathy.
Appropriate use of G-CSF could contribute to safe continuation of mFOLFIRINOX without severe infectious diseases. Among the nonhematological toxicities, the rate of grade 3–4 PN was significantly higher in the mFOLFIRINOX group (16.0%). In a single-arm retrospective study of mFOLFIRINOX as a second-line chemotherapy after GnP failure, the frequency of grade 3–4 PN was reported to be 10.6%.\textsuperscript{17} Because GnP frequently causes PN,\textsuperscript{6} the risk of severe PN may increase during mFOLFIRINOX treatment after GnP treatment. Clinicians should be attentive of patients who experience PN during GnP treatment.

The current study had limitations. First, this study was a retrospective study performed at a single referral center. Although the baseline characteristics of the patients were different, mFOLFIRINOX was identified as an independent factor associated with favorable PFS. Another limitation was that the sample size of the study was small. Thus, to clarify the survival

### Table 4

| Factor                        | Univariate HR (95% CI) | Univariate P value | Multivariate HR (95% CI) | Multivariate P value |
|-------------------------------|------------------------|---------------------|--------------------------|----------------------|
| Age                           |                        |                     |                          |                      |
| <65 years                     | 1                      |                     |                          |                      |
| ≥65 years                     | 1.330 (0.829–2.133)    | 0.237               |                          |                      |
| Sex                           |                        |                     |                          |                      |
| Female                        | 1                      |                     |                          |                      |
| Male                          | 1.045 (0.663–1.647)    | 0.851               |                          |                      |
| ECOG PS                       |                        |                     |                          |                      |
| 0                             | 1                      |                     |                          |                      |
| 1 or 2                        | 1.029 (0.645–1.641)    | 0.904               |                          |                      |
| Body mass index               |                        |                     |                          |                      |
| <20 kg/m\(^{2}\)              | 1                      |                     |                          |                      |
| ≥20 kg/m\(^{2}\)              | 0.843 (0.516–1.375)    | 0.493               |                          |                      |
| Tumor location                |                        |                     |                          |                      |
| Body/tail                     | 1                      |                     |                          |                      |
| Head                          | 1.432 (0.897–2.287)    | 0.133               | 1.357 (0.846–2.176)      | 0.205                |
| Number of metastatic sites    |                        |                     |                          |                      |
| 1–3                           | 1                      |                     |                          |                      |
| ≥4                            | 1.157 (0.612–1.938)    | 0.578               |                          |                      |
| Lymph node involvement        |                        |                     |                          |                      |
| No                            | 1                      |                     |                          |                      |
| Yes                           | 1.079 (0.654–1.781)    | 0.765               |                          |                      |
| Biliary drainage              |                        |                     |                          |                      |
| No                            | 1                      |                     |                          |                      |
| Yes                           | 1.152 (0.720–1.843)    | 0.556               |                          |                      |
| NLR                           |                        |                     |                          |                      |
| <3                            | 1                      |                     |                          |                      |
| ≥3                            | 1.118 (0.694–1.801)    | 0.647               |                          |                      |
| CA19-9                        |                        |                     |                          |                      |
| <1000 IU/mL                   | 1                      |                     |                          |                      |
| ≥1000 IU/mL                   | 1.225 (0.778–1.929)    | 0.380               |                          |                      |
| CEA                           |                        |                     |                          |                      |
| <10 ng/mL                     | 1                      |                     |                          |                      |
| ≥10 ng/mL                     | 1.329 (0.816–2.165)    | 0.253               |                          |                      |
| Albumin                       |                        |                     |                          |                      |
| <3.5 mg/mL                    | 1                      |                     |                          |                      |
| ≥3.5 mg/mL                    | 0.550 (0.343–0.882)    | 0.013               | 0.631 (0.389–1.023)      | 0.062                |
| Creatinine                    |                        |                     |                          |                      |
| <0.7 mg/dL                    | 1                      |                     |                          |                      |
| ≥0.7 mg/dL                    | 0.915 (0.581–1.440)    | 0.700               |                          |                      |
| Second-line chemotherapy      |                        |                     |                          |                      |
| S1                            | 1                      |                     |                          |                      |
| mFOLFIRINOX                   | 0.526 (0.320–0.866)    | 0.012               | 0.557 (0.336–0.925)      | 0.024                |

Bold values indicate \( P < 0.05 \).

ALP, alkaline phosphatase; CEA, carcinoembryonic antigen; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FBS, fasting blood sugar; HR, hazard ratio; MPD, main pancreatic duct; NLR, neutrophil-to-lymphocyte ratio; P-amylase, pancreatic amylase; PS, performance status.
benefit of mFOLFIRINOX, further multicenter, large-scale studies are required.

In conclusion, mFOLFIRINOX as a second-line regimen contributed to favorable treatment outcomes. Patients treated with mFOLFIRINOX experienced more frequent adverse events than patients treated with S-1. Additionally, mFOLFIRINOX was identified as an independent factor associated with favorable PFS, suggesting that mFOLFIRINOX could be a promising treatment option for patients with GnP failure.

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