

Irinotecan combined with oxaliplatin and S-1 in patients with metastatic pancreatic adenocarcinoma: a single-arm, three-centre, prospective study

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Abstract

Objective: To study the efficacy and toxicity of irinotecan combined with oxaliplatin and S-1 in patients with metastatic pancreatic adenocarcinoma.

Patients and methods: Previously untreated patients with cytologically or histologically confirmed metastatic pancreatic adenocarcinoma underwent a treatment regimen consisting of an intravenous infusion of irinotecan 165 mg/m² and oxaliplatin 85 mg/m² on day 1, and oral S-1 40 mg/m² twice daily on days 1–14, repeating the regimen every 21 days until one of the following occurred: disease progression, intolerable toxicity, or patient death. The primary endpoint was overall survival (OS), and the secondary endpoints were progression-free survival (PFS), response rate, toxicity, and quality of life. This ongoing study had been registered on ClinicalTrials.gov, NCT03726021.

Results: A total of 41 patients were enrolled in this study, 18 men and 23 women. The median PFS was 4.33 months [95% confidence interval (CI): 2.83–5.88] and the median OS was 11.00 months (95% CI: 9.16–12.84). There were no instances of a complete response; the partial response, stable disease, and disease progression rates were 39.02% (16/41), 29.27% (12/41), and 31.71% (13/41), respectively.

The most common adverse side effects were mild to moderate nausea, vomiting, neutropenia, and thrombocytopenia. Grade 3 or 4 neutropenia and thrombocytopenia were observed in 29.27% (12/41) and 12.20% (5/41) of the patients, respectively. No treatment-related death was observed.

Conclusion: Irinotecan combined with oxaliplatin and S-1 is a safe and effective treatment for metastatic pancreatic adenocarcinoma, and any toxicities are mild to moderate and tolerable. A larger study population is needed for further evaluation.

Keywords: chemotherapy, FOLFIRINOX, overall survival, pancreatic adenocarcinoma, prospective

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Introduction

In recent years, there has been an increase in the global death rates associated with pancreatic adenocarcinoma, with a 5-year overall survival (OS) rate of only 3%.^{1,2} Despite intensive research in this field, none of the novel antineoplastic agents, such as checkpoint inhibitors or targeted agents, have shown promising results.^{3,4}

Surgical resection is an option for only 20% of patients at the time of diagnosis, with the 5-year survival below 30% for a combined treatment of resection with fluorouracil or gemcitabine adjuvant therapy, for patients diagnosed in the early stages of the disease.⁵ Most patients diagnosed later, with unresectable, locally advanced masses or metastatic disease at the time of diagnosis,

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making palliative chemotherapy a mainstay treatment, albeit with poor outcomes.⁶

Single-agent chemotherapy with gemcitabine has been the standard of care in first-line treatment of metastatic pancreatic adenocarcinoma since the 1990s, which increased the median OS to 5.65 months from the previous median OS of 4.41 months in patients treated with 5-fluorouracil (5-FU).⁷ FOLFIRINOX (FOLinic acid, Fluorouracil, IRINotecan, OXaliplatin) and albumin-bound paclitaxel (nab-paclitaxel), introduced in 2011 and 2014, respectively, in addition to gemcitabine, increased the median OS to 8.5–12.7 months.^{8–10} No other agents were reported to have improved survival rates in the preceding 5 years. Using the Korean Pancreatic Cancer Registry, a comparison of FOLFIRINOX and nabPGem showed no significant difference in overall survival between the two chemotherapy regimens (11.5 *versus* 12.7 months, $p=0.286$).¹⁰ Furthermore, in 2019, Vogl *et al.*¹¹ reported a retrospective study involving 83 patients with locally advanced or metastatic pancreatic cancer, who were treated with FOLFIRINOX or nabPGem as the first-line treatment, and reported an OS of 12.6 months. In their study, 48/83 patients received FOLFIRINOX followed by nabPGem (nab-Paclitaxel Gemcitabine), or nabPGem followed by FOLFIRINOX, with median OS 13.7 and 13.8 months, respectively.

S-1, a novel oral dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine, based on the biochemical modulation of 5-FU, was developed in the 1990s for the treatment of gastric cancer. It contains tegafur and two types of enzyme inhibitors, 5-chloro-2,4-dihydroxypyridine and potassium oxonate, in a molar ratio of 1:0.4:1. In pharmacokinetic studies, S-1 shows a high 5-FU concentration in blood for long periods.¹² When used as adjuvant therapy for resected pancreatic cancer, it resulted in a significantly longer overall and relapse-free survival when compared with gemcitabine.¹³ S-1 is widely used in Asian countries to treat patients with gastric cancer, colorectal cancer, and pancreatic cancer because of its decreased side effects when compared with gemcitabine.^{13–16}

FOLFIRINOX, more effective than other experimental treatments, is associated with an increased frequency and severity of adverse events, which limits its use to patients with a higher performance status.¹⁷ Therefore, the development of a

chemotherapy regimen with higher efficacy and lower toxicity is critically important.

Methods

Study design and patient selection

This is an ongoing prospective, single-arm, three-centre study. Enrolled patients were either cytologically or histologically confirmed to have metastatic pancreatic adenocarcinoma and had not started treatment. Other histologies, such as neuroendocrine or acinar cell carcinoma, were not included. Previous adjuvant therapy after surgical resection was not an exclusion criterion. Participants were required to have measurable disease based on Response Evaluation Criteria in Solid Tumour version 1.1 (RECIST v.1.1),¹⁸ defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter should be recorded) as ≥ 10 mm, using spiral computed tomography (CT) or magnetic resonance imaging (MRI). Furthermore, participants were all 18 years or older, with adequate organ and marrow function, and Eastern Cooperative Oncology Group (ECOG) performance status scores ≤ 2 .

Irinotecan 165 mg/m² and oxaliplatin 85 mg/m² were administered *via* intravenous infusion on day 1, and S-1 40 mg/m² was administered orally on days 1–14. This cycle was repeated every 21 days until one of the following occurred: disease progression, intolerable toxicity, or patient death. One dose reduction of 20% of the initial dosage was permitted.

The protocol and all modifications were approved by the Ethics Committee of the Affiliated Qingdao Central Hospital of Qingdao University (Approval number: QDCH2018-10-28) and were performed in compliance with the provisions of the Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws. Informed consent was obtained from all patients prior to enrolment.

Outcomes and assessment

The primary endpoint of the study was OS, which was measured from enrolment date to death. The secondary endpoints were progression-free survival (PFS), response rate, toxicity, and quality of life (QOL). Tumour responses, which were assessed using RECIST v.1.1,¹⁸ were observed during the trial period and classified as the following: complete response (disappearance of tumour lesions), partial

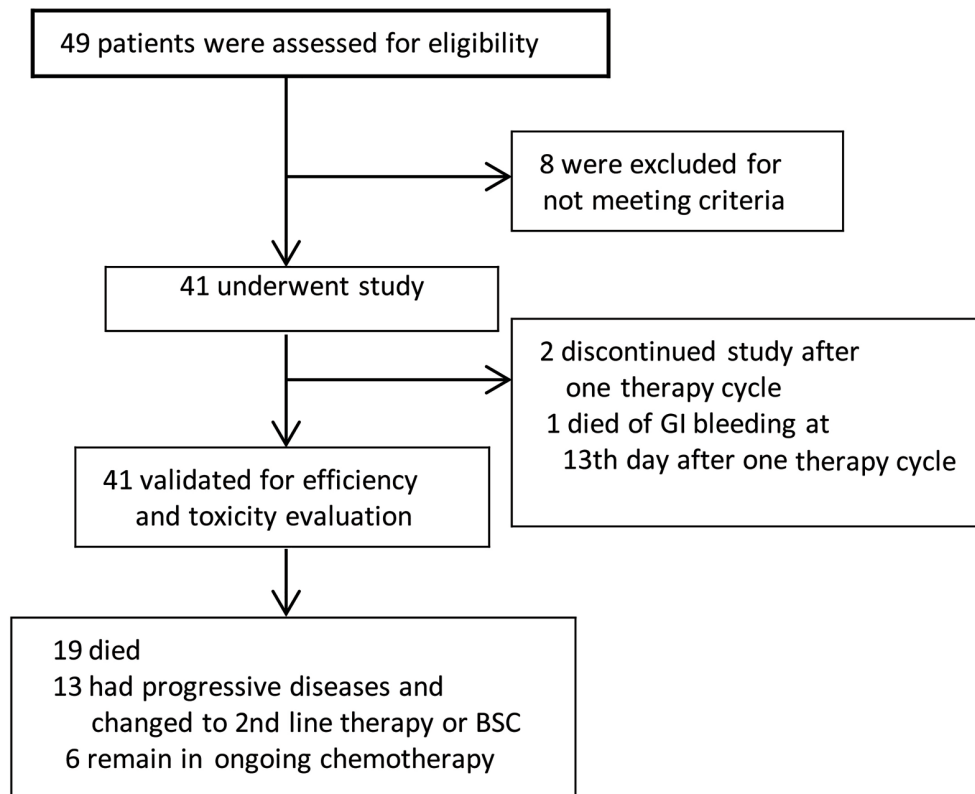


Figure 1. Screening, group assignment, and outcomes. The cut-off date was 30 April 2019, and the last follow-up date was 28 October 2019. BSC, best supportive care; GI, gastrointestinal.

response (a decrease of at least 30% in the sum of tumour lesion sizes), stable disease (steady state of disease), or progressive disease (an increase $\geq 20\%$ in the sum of tumour lesion sizes). All adverse events were recorded and classified by grade, according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.¹⁹ The QOL of patients was accessed at baseline and at each follow-up, using the Karnofsky Performance Status (KPS) scale, and was recorded as: apparently improved (increase in KPS ≥ 20), improved (increase in KPS ≥ 10), stable (no apparent change in KPS score), and reduced (KPS decline of ≥ 10).

Tumour measurements with abdominal CT or MRI were performed at screening, and every 6–8 weeks thereafter. Patients' compliance, treatment safety, and side effects were assessed every 3 weeks, at each check-up.

Statistical analysis

Based on the Cox proportional hazards model, and taking into account the influence of gender (male or

female), ECOG performance status score, hazard ratio (HR), and 95% confidence interval (CI) were calculated in the full analysis population. PFS and OS curves were analysed by using Sigmaplot 14.0 (Systat Software Inc., San Jose, CA, USA), performing a Kaplan–Meier log-rank test in the intention-to-treat (ITT) population. Efficacy data was analysed on an ITT basis, which included all enrolled patients, regardless of whether they received treatment or not. All enrolled patients who received at least one dose of the study treatment were included in safety analyses. Periodic safety monitoring and interim efficacy assessments were done by an independent data monitoring committee. This ongoing trial has been registered with ClinicalTrials.gov, NCT03726021.

Results

From January 2018 to April 2019, 49 patients were screened, 41 of which were enrolled in the present study. The remaining eight patients were excluded from the study during screening, as they did not meet the inclusion standards (Figure 1).

Table 1. Patients' baseline characteristics.

Variable	N=41
Age, years	57 (43–80)
Sex, n (%)	
Male	18 (43.9)
Female	23 (56.1)
Histology, n (%)	
Ductal adenocarcinoma	40 (97.6)
Adenocarcinoma undifferentiated	1 (2.4)
Chemotherapy, n (%)	
1–6 cycles	11 (26.8)
>7 cycles	30 (73.2)
ECOG performance status, n (%)	
0	2 (4.9)
1	19 (46.3)
2	20 (48.8)
No. of metastatic sites involved	
Median	2
Range	1–3
Metastatic tumour sites, n (%)	
Liver	31 (75.61)
Lung	2 (4.88)
Lymph nodes	21 (51.22)
Peritoneum	7 (17.07)
Others	6 (14.63)
ECOG, Eastern Cooperative Oncology Group.	

All of the patients recruited for this study were Chinese. Age, gender, performance status, and histology are listed in Table 1. All patients were classified as stage IV, based on the American Joint Committee on Cancer 2007 staging system, and had at least one measurable lesion. Of the 41 patients, 23 (56.1%) were women, and (97.6%) had ductal adenocarcinoma based on histology. Patients with an ECOG performance status score of 0–2 were qualified for the study. The median age was 57 (43–80) years old. All patients received at

least one cycle of chemotherapy, with a median of nine cycles (range: 1–14 cycles). The last follow-up date was 28 October 2019. The median follow-up time was 13 months (Table 1). Of the 41 patients, eight (19.51%) patients had a dose reduction, six of which resulted from haematologic toxicities and two from grade 3–4 diarrhoea.

The median PFS was 4.33 months, 95% CI: 2.83–5.88 [Figure 2(A)] and the median OS was 11.00 months, 95% CI: 9.16–12.84 [Figure 2(B)]. All 41 patients completed at least one cycle of chemotherapy and were evaluated for efficacy and toxicity. There were no patients with a complete response. The partial response, stable disease, and disease progression rates were 39.02% (16/41), 29.27% (12/41), and 31.71% (13/41), respectively (Table 2). QOL was assessed at the baseline screening and at each follow-up. The apparently improved, improved, stable, and reduced rates were 7.32% (3/41), 24.39% (10/41), 31.71% (13/41), and 36.59% (15/41), respectively (Table 2).

The most common side effects were mild to moderate hand–foot syndrome, sensory neuropathy, nausea, anorexia, diarrhoea, constipation, and adverse haematologic events. Grade 3 or 4 neutropenia and thrombocytopenia occurred in 29.27% (12/41) and 12.20% (5/41) of the patients, respectively. No treatment-related deaths were observed (Table 3).

Discussion

Pancreatic cancer has the lowest 5-year survival rate of all commonly diagnosed malignancies.^{1–3} Even with the most effective poly-chemotherapy protocols, which can only be administered to select patients with good performance status, the median OS of stage IV patients does not exceed 1 year.⁵ Efforts to optimize symptom control in patients with advanced diseases, in particular biliary drainage, pain control, and nutrition, may facilitate the benefits of palliative chemotherapy.

Gemcitabine became the standard regimen for the treatment of advanced pancreatic adenocarcinoma after a randomized trial which showed significant improvement in the median OS, from 4.4 months to 5.6 months, when compared with 5-FU.⁷ The median OS was not significantly improved until 2011; one study found the median OS for FOLFIRINOX to be 11.1 months, compared with 6.8 months for gemcitabine.⁹ The same study

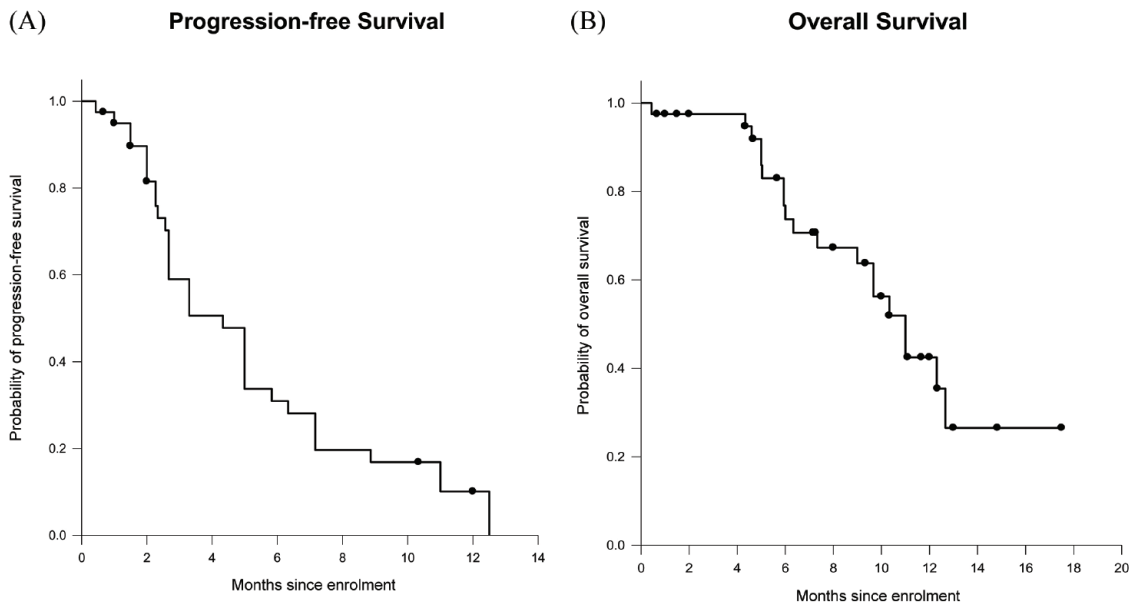


Figure 2. Kaplan–Meier analysis of progression-free survival (PFS) and overall survival (OS). Of the enrolled 41 patients, the median PFS (A) was 4.33 months [95% confidence interval (CI): 2.83–5.88] and median OS (B) was 11.00 months (95% CI: 9.16–12.84).

Table 2. Summary of efficiency measures.

Variable	N = 41
mPFS, ITT, months	4.33 (95% CI: 2.83–5.88)
mOS, ITT, months	11.00 (95% CI: 9.16–12.84)
Type of response, <i>n</i> (%)	
CR	0
PR	16 (39.02)
SD	12 (29.27)
PD	13 (31.71)
ORR, CR+PR	16 (39.02)
DCR, ORR+SD	28 (68.29)
Quality of life, <i>n</i> (%)	
Apparently improved	3 (7.32)
Improved	10 (24.39)
Stable	13 (31.71)
Reduced	15 (36.59)

CR, complete response; DCR, disease control rate; ITT, intention-to-treat; mOS, median overall survival; mPFS, median progression-free survival; ORR, overall response rate; PD, progression disease; PR, partial response; SD, stable disease.

Table 3. Summary of adverse events.

Adverse events, cases (%)	N=41		
	All grades	Grade 3–4	Grade 5
Hand–foot syndrome	19 (46.34)	2 (4.88)	0 (0)
Sensory neuropathy	15 (36.59)	0 (0)	0 (0)
Anorexia	16 (39.02)	1 (2.44)	0 (0)
Nausea	8 (19.51)	2 (4.88)	0 (0)
Vomiting	4 (9.76)	1 (2.44)	0 (0)
Diarrhoea	7 (17.07)	1 (2.44)	0 (0)
Constipation	9 (21.95)	0 (0)	0 (0)
Alopecia	3 (7.32)	0 (0)	0 (0)
Neutropenia	27 (65.85)	12 (29.27)	0 (0)
Anaemia	7 (17.07)	0 (0)	0 (0)
Thrombocytopenia	13 (31.71)	5 (12.20)	0 (0)
Gastrointestinal bleeding	3 (7.32)	0 (0)	1 (2.44)

further showed that the objective response rate for FOLFIRINOX increased to 31.6% from 9.4%, and the PFS increased to 6.4 months from 3.3 months, compared with gemcitabine.

A phase I/II trial to test the maximum dose of nab-paclitaxel with gemcitabine was carried out; the regimen included three doses of nab-paclitaxel (100, 125, or 150 mg/m²), followed by gemcitabine 1000 mg/m² on days 1, 8, and 15, every 28 days.²⁰ The maximum tolerated dose (MTD) was 1000 mg/m² of gemcitabine plus 125 mg/m² of nab-paclitaxel, once a week for 3 weeks, every 28 days. Patients had a median PFS of 7.9 months, median OS of 12.2 months, and a 1-year survival rate of 48% at the MTD; however, there were several grade 3–4 haematologic and non-haematologic events. Recently, nab-paclitaxel and nanoliposomal irinotecan in combination with gemcitabine or with 5-FU/LV has been licensed for the treatment of metastatic pancreatic adenocarcinoma.^{6–8} The survival difference between genders was also studied, and in the FOLFIRINOX group, the median OS was found to be longer for females than males (13.1 *versus* 10.3 months, respectively; HR=0.73). Similarly, median PFS was superior (7.2 *versus* 5.9 months; HR=0.79) in female patients. However, in both cases, the differences between median OS and median PFS were not statistically significant ($p=0.10$ and $p=0.169$,

respectively).²¹ Tumour size was also a factor associated with patients' survival, which influenced PFS (HR=1.348; $p=0.008$) and OS (HR=1.35; $p=0.006$) respectively.²²

In our study, the median PFS was 4.33 months and the median OS was 11.00 months. The partial response, stable disease, and disease progression rates were 39.02%, 29.27%, and 24.39%, respectively. This was very close to those for FOLFIRINOX and modified FOLFIRINOX chemotherapy treatments.^{9,23} Grade 3 or 4 neutropenia had a rate of 29.27% in our study, which was lower than in the other triple drug studies, but higher than for modified FOLFIRINOX. In previous studies using irinotecan, oxaliplatin, and/or S-1 chemotherapy for pancreatic or gastrointestinal cancer,^{9,15,16,20,23,24} the dosage administered was relatively high compared with in our study. Furthermore, grade 3 or 4 neutropenia or thrombocytopenia occurred more frequently than in this study. This implies that a higher dosage is likely the main cause of high grade homological toxicities. The occurrence of grade 1–2 hand–foot syndrome and diarrhoea was higher in our study, which was likely due to the administration of S-1. Overall, the toxicities seen were mild to moderate, and were tolerable. The median treatment was 9 (1–14) cycles, which may have contributed to a longer OS in this study.

In this study, 20/41 (48.8%) patients had an ECOG performance status of 2, which is higher than other published studies. We postulate that this is due to the relatively small number of patients enrolled and the short study period.

The present study, however, does have some limitations. This is a single-arm study with relatively small sample size, which can potentially cause selection bias. The relatively short follow-up period compared with other studies can affect the statistical power. The predictive value of the balanced variables in this study should be further explored in randomized settings.

Conclusion

A combination irinotecan, oxaliplatin, and S-1 regimen is safe and effective for the treatment of metastatic pancreatic adenocarcinoma in patients with a poor performance status. Overall the toxicity of the dosages described was mild to moderate and tolerable. Additional studies with a larger sample sizes and treatment arms are required to confirm the results of this study.

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Author contributions

KN, CZ, and YJ designed the study. LZ, YY, HL, and XG enrolled and followed up patients. ZZ prepared figures. YJ did the statistical analysis. KN helped to write the manuscript. All authors read and approved the final manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.


Ethics approval and consent to participate

The protocol and all modifications were approved by the Ethics Committee of the Affiliated Qingdao Central Hospital of Qingdao University (Approval number: QDCH2018-10-28) and were performed in compliance with the provisions of the Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws. Informed consent was obtained from all patients prior to enrolment. Data, materials, and consent for publication are all available.

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