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Multicenter Retrospective Analysis of Chemotherapy for Advanced Pancreatic Acinar Cell Carcinoma

Potential Efficacy of Platinum- and Irinotecan-Containing Regimens

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Objectives: The aim of this multicenter retrospective study was to identify the optimal chemotherapeutic regimen for advanced pancreatic acinar cell carcinoma (PACC).

Methods: Fifty-eight patients with histopathologically confirmed advanced PACC who had received chemotherapy between 1996 and 2013 were enrolled. The clinical characteristics of the patients and the treatment efficacy data were collected from the medical records at 16 Japanese institutions, using standardized data collection instrument.

Results: The most commonly selected treatment regimens were gemcitabine-, fluoropyrimidine-, platinum-, and irinotecan-containing regimens. The overall response rate in the patients who received first-line chemotherapy were 7% and 38%, respectively, and the median overall survival was 13.2 months. When the data for all the treatment lines were aggregated, the response rates to gemcitabine-, fluoropyrimidine-, platinum-, and irinotecan-containing regimens were 7%, 18%, 40%, and 29%, respectively. The overall survival tended to be better in patients who had received a platinum-containing regimen (hazard ratio, 0.50; 95% confidence interval, 0.23–1.11; $P = 0.08$) or irinotecan-containing regimen (hazard ratio, 0.42; 95% confidence interval, 0.15–1.19; $P = 0.09$) at least once in the treatment course as compared with those who had not.

Conclusions: Our findings suggested that platinum- and irinotecan-containing regimens exhibited some potential efficacy in patients with advanced PACC.

Key Words: pancreatic neoplasms, acinar cell carcinoma, chemotherapy, 5-fluorouracil, platinum, irinotecan

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Pancreatic acinar cell carcinoma (PACC) is a rare pancreatic exocrine tumor, accounting for 0.2% to 2% of all pancreatic carcinomas.[1–3] More than 50% of patients with PACC have metastatic disease at diagnosis.[2–5] Although the reported prognosis of PACC is better than that of pancreatic ductal adenocarcinoma in both patients treated and not treated by resection,[2–5] the prognosis remains dismal. The reported median overall survival (OS) in metastatic PACC patients treated by chemotherapy is in the range of 12 to 19.6 months.[2,6,7]

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The clinicopathological features and molecular abnormalities of PACC are different from those of pancreatic ductal adenocarcinoma.[8–10] A targeted broad-spectrum sequencing study revealed common mutations, such as *KRAS*, *TP53*, *SMAD4*, and *CDKN2A* mutations, in pancreatic ductal adenocarcinoma; on the other hand, although these mutations were not frequently found,[8] tumor suppressor genes, including ID3, ARID1A, APC, and CDKN2A, are recurrently affected in PACC.[9–11] Although these differences in molecular profiles could explain the difference in the sensitivity to chemotherapy, as well as prognosis between patients with PACC and pancreatic ductal adenocarcinoma, similar chemotherapeutic regimens to those for pancreatic ductal adenocarcinoma have often been used for patients with PACC, because no standard chemotherapeutic regimen(s) has yet been established for PACC. Possible active chemotherapeutic regimens for PACC have been reported from retrospective analyses of several case reports and a few case series; however, these reports are based on the data of only a small number of patients, approximately 20 patients. No prospective trials or multicenter studies focusing on the most suitable chemotherapeutic regimens for PACC have been reported yet.[6,7,12–14] Therefore, we conducted this multicenter retrospective study to clarify which of the available chemotherapeutic agents/regimens might be the most effective for unresectable and recurrent PACC.

MATERIALS AND METHODS

Patients

We conducted this retrospective collective study based on the data obtained from the medical records of patients with PACC at 16 institutions participating in Japan Observational Study Committee of Hepatobiliary and Pancreatic Oncology. We enrolled patients with histopathologically confirmed PACC and selected who received chemotherapy for unresectable or recurrent disease between June 1996 and December 2013. Patients with mixed-type PACC were excluded, as mixed-type PACCs also show some features of adenocarcinoma or neuroendocrine tumor, which would have interfered with the efficacy evaluation of chemotherapy for pure PACC.

Methods

Data on the following background characteristics of the patients were collected using the standardized data collection instrument: age, sex, Eastern Cooperative Oncology Group performance status, clinical symptoms, serum tumor markers, including lipase, α-fetoprotein (AFP), carcinoembryonic antigen (CEA), and carbohydrate antigen 19–9 (CA 19–9), tumor stage (locally advanced or metastatic), sites of distant metastases, pathological diagnosis including immunohistochemistry, and the Ki-67 index. As markers of the efficacy, we collected data on the overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and OS by the chemotherapeutic regimen used.

Statistical Considerations

Tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumors, version 1.1, and classified as complete response, partial response, stable disease, progressive disease, and not evaluable. The ORR was defined as the proportion of all the enrolled patients showing complete response or partial response, and the DCR was defined as the proportion of all enrolled patients showing complete response, partial response or stable disease. Progression-free survival was defined as the period from the initiation of chemotherapy to the confirmation of disease

TABLE 1. Characteristics of All Enrolled Patients

Characteristics	No. Patients (%)
No. enrolled patients, n	58
Age, median (range), y	60.5 (8–81)
Sex	
Male	40 (69)
Female	18 (31)
Eastern Cooperative Oncology Group Performance status	
0	31 (53)
1	23 (40)
2	4 (7)
Clinical symptom(s) at diagnosis	
Abdominal pain	14 (24)
Back pain	12 (21)
Jaundice	5 (9)
Gastrointestinal bleeding	2 (3)
Nausea	2 (3)
Body weight loss	2 (3)
Others	7 (12)
None	14 (24)
Smoking habit, present	24 (44)
Drinking habit, present	19 (36)
Diabetes mellitus, present	10 (18)
Surgical resection, present	17 (29)
Serum marker	
Lipase, UI/l, elevated	11 (55)
Median (range)	79 (8–46,080)
AFP, ng/ml, elevated	16 (47)
Median (range)	6.5 (1–29,390)
CA 19–9, U/l, elevated	18 (33)
Median (range)	14 (0.1–3290)
CEA, ng/ml, elevated	12 (24)
Median (range)	3.5 (1–71)
Disease status	
Metastatic	36 (62)
Locally advanced	5 (9)
Recurrent	17 (29)
Sites of distant metastases	
Liver	40 (68)
Peritoneum	11 (19)
Distant lymph nodes	8 (14)
Lung	5 (9)
Other	3 (5)
Immunohistochemistry-positive	
Trypsin	35 (92)
Chymotrypsin	5 (53)
Lipase	10 (48)
Amylase	3 (60)
Synaptophysin	3 (25)
Chromogranin	9 (50)
Ki-67	
<50%	8 (14)
≥50%	12 (21)
Not assessed	38 (65)

progression or death due to any cause. Overall survival was defined as the period from the initiation of chemotherapy to death from any cause. Surviving patients were censored on their last visit date. The ORR, DCR, and PFS and OS in response to each chemotherapeutic regimen were also compared by the treatment lines in which they were used. Because of the variety of chemotherapeutic regimens used and the limited number of patients showing favorable tumor responses, the ORR and DCR were analyzed as the sum for all treatment lines. The OS was determined in patients who had received the relevant chemotherapeutic regimen at least once during the treatment course. The PFS and OS were estimated, along with the 95% confidence interval (CI), using the Kaplan-Meier method and compared by the log-rank test and by multivariate regression analysis using the Cox proportional hazards model. Statistical analysis was performed using PASW statistics, version 18.0 (SPSS Inc., Chicago, Ill). This study was conducted with the approval of the institutional review board of each of the participating institutions, and in accordance with epidemiological research guidelines.

RESULTS

Characteristics of Patients With Unresectable or Recurrent PACC

At first, a total of 64 patients with histopathologically confirmed unresectable or recurrent PACC between June 1996 and December 2013 seen at any of the 16 participating institutions in Japan were enrolled in this study. However, 6 of these patients had to be excluded from this analysis because they had a mixed neoplasm of the pancreas with an acinar cell carcinoma component. Table 1 shows the characteristics of the enrolled patients. Of the 58 patients with unresectable or recurrent PACC finally enrolled in the study, 75% had at least 1 clinical symptom at diagnosis. Abdominal pain was the most common presenting symptom (24%), followed in frequency by back pain (21%) and jaundice (9%). Two patients (3%) had concomitant gastrointestinal bleeding, but none of the patients had any characteristic skin rash or panniculitis related to the lipase hypersecretion syndrome. Serum levels of lipase, AFP, CA 19–9, and CEA were elevated in 48%, 47%, 33%, and 24% of the patients, respectively. Forty-eight (62%) patients had distant metastasis. The most common metastatic site was the liver (68%), followed by the peritoneum (19%) and distant lymph nodes (14%) (Table 1).

Chemotherapy for Unresectable or Recurrent PACC

Table 2 shows the ORR and DCR in response to the treatment regimens in each treatment line and including all treatment lines. Among the 58 patients who received first-line chemotherapy, the most commonly selected regimens were gemcitabine (GEM) monotherapy (n = 30, 52%), tegafur/gimeracil/oteracil (S-1) monotherapy (n = 11, 19%), and combined GEM plus S-1 therapy (n = 6, 10%). Of the 58, 41 also received second-line chemotherapy,

TABLE 2. ORRs and DCRs in Each and All Treatment Lines

Regimen	First-Line, n (%)	Second-Line, n (%)	Third- or Later-Line, n (%)	All Line, n (%)*
ORRs				
All	4/58 (7)	10/41 (24)	3/20 (15)	17/119 (14)
GEM monotherapy	0/30 (0)	1/6 (17)	0/1 (0)	1/37 (3)
S-1 monotherapy	1/11 (9)	5/23 (22)	0/1 (0)	6/35 (17)†
GEM plus S-1	1/6 (17)	1/3 (33)	0/4 (0)	2/13 (15)
Others‡	2/11 (18)	3/9 (33)	3/14 (21)	8/34 (23)
GEM-based regimen	2/38 (5)	2/10 (20)	0/7 (0)	4/55 (7)
5-FU–based regimen	3/23 (13)	7/29 (24)	2/13 (15)	12/65 (18)
Platinum-based regimen	1/5 (20)	2/5 (40)	3/5 (60)	6/15 (40)§
Irinotecan-based regimen	0/1 (0)	0/0 (ND)	2/6 (33)	2/7 (29)
DCRs				
All	22/58 (38)	23/41 (56)	9/20 (45)	54/119 (45)
GEM monotherapy	10/30 (33)	3/6 (50)	0/1 (0)	13/37 (35)
S-1 monotherapy	4/11 (9)	13/23 (57)	0/1 (0)	17/35 (49)
GEM plus S-1	2/6 (33)	2/3 (67)	1/4 (25)	5/13 (38)
Others†	6/11 (55)	5/9 (56)	7/14 (50)	18/34 (53)
GEM-based regimen	13/38 (34)	6/10 (60)	3/7 (43)	22/55 (40)
FU-based regimen	10/23 (43)	16/29 (55)	5/13 (38)	31/65 (48)
Platinum-based regimen	4/5 (80)	3/5 (60)	4/5 (80)	11/15 (73)‖
Irinotecan-based regimen	1/1 (100)	0/0 (ND)	6/6 (100)	7/7 (100)¶

*All-line: including all treatment lines.

†GEM vs S-1, $P < 0.05$.

‡Ifosphamide plus carboplatin plus etoposide, doxorubicin plus mitomycin C plus 5-FU, followed by GEM, FOLFIRINOX, mitomycin C plus epirubicin plus 5-FU plus cisplatin, FOLFOX, nogitecan plus cyclophosphamide, cisplatin plus pirarubicin plus cyclophosphamide plus vincristine, and cisplatin plus irinotecan.

§GEM vs platinum, $P < 0.01$.

‖GEM vs platinum, $P < 0.01$.

¶GEM vs irinotecan, $P < 0.01$.

ND, not detected.

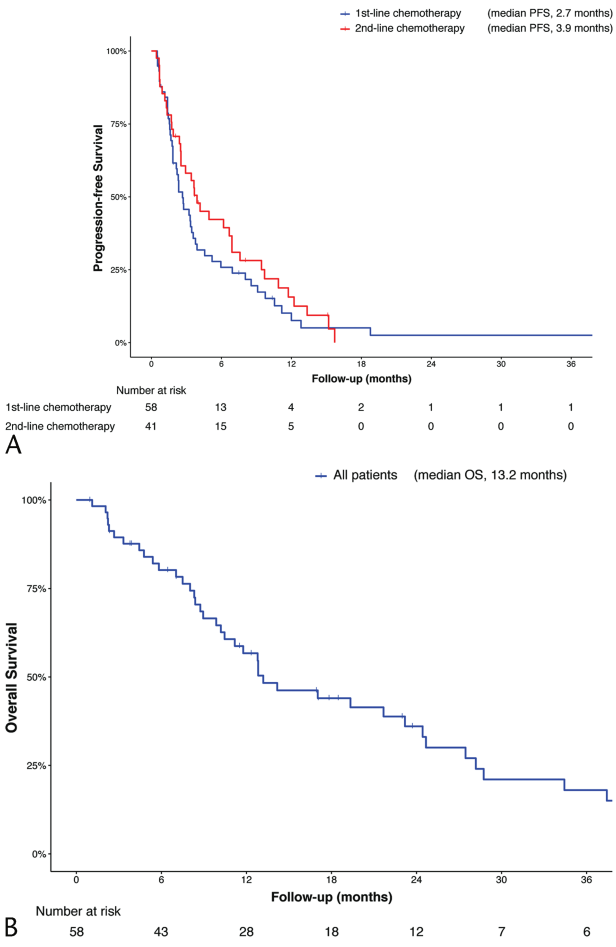

FIGURE 1. Kaplan-Meier curve for PFS in first-line chemotherapy (blue line) and second-line chemotherapy (red line) (A) and OS in all patients (B) with unresectable or recurrent PACC.

for which the most commonly selected regimens were S-1 monotherapy (n = 23, 56%), GEM monotherapy (n = 6, 15%), and GEM plus S-1 therapy (n = 3, 7%). Twenty patients received third- or later-line chemotherapy, and the regimens of other than GEM, S-1 and GEM plus S-1, including a combination of 5-fluorouracil (5-FU), leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX), a combination of 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX), cisplatin plus irinotecan, and so on, were selected in 14 patients.

ORR and DCR

The ORRs in response to first-, second-, and third- or later-line chemotherapies were 7% (4/58), 24% (10/41), and 15% (3/20), respectively. There were no cases of complete response in this population, and partial response was achieved in 17 patients. The chemotherapeutic regimens that elicited partial response included GEM monotherapy (1 patient), S-1 monotherapy (6 patients) GEM plus S-1 (2 patients), FOLFOX (1 patient), FOLFIRINOX (1 patient), cisplatin plus irinotecan (1 patient), cisplatin plus pirarubicin plus cyclophosphamide plus vincristine (1 patient), carboplatin plus ifosphamide plus etoposide (1 patient), doxorubicin plus mitomycin plus 5-fluorouracil (1 patient), mitomycin plus epirubicin plus 5-fluorouracil plus cisplatin (1 patient), and nogitecan plus cyclophosphamide (1 patient). When the ORRs for all treatment lines were aggregated, the ORRs to GEM monotherapy, S-1 monotherapy, and GEM plus S-1 therapy were 3% (1/37), 17% (6/35), and 15% (2/13), respectively. When the regimens were classified as GEM-based, 5-FU-based, platinum-based, and irinotecan-based regimens and the ORRs for all treatment lines were aggregated, the ORRs were 7% (4/55), 18% (12/65), 40% (6/15), and 29% (2/7), respectively.

The DCRs in response to first-, second-, and third- or later-line chemotherapies were 38% (22/58), 56% (23/41), and 45% (9/20), respectively. When the DCRs were aggregated for all treatment lines, the DCRs in response to GEM monotherapy, S-1 monotherapy, and GEM plus S-1 therapy were 35% (13/37), 49% (17/35), and 38% (5/13), respectively. When the regimens were classified as GEM-based, 5-FU-based, platinum-based, and irinotecan-based regimens and the DCRs for all treatment lines were aggregated, the DCRs were 40% (22/35), 48% (31/63), 73% (11/15), and 100% (7/7), respectively.

PFS and OS

The median PFS in response to first-, and second-line chemotherapies were 2.7 months (95% CI, 1.6–3.7) (Fig. 1A), and 3.9 months (95% CI, 2.2–5.7), respectively. The median OS after the initiation of first-line chemotherapy was 13.2 months (95% CI, 7.5–18.9) (Fig. 1B). No significant differences in the OS were observed between patients administered a GEM-based regimen (hazard ratio [HR], 0.90; 95% CI, 0.43–1.91; $P = 0.79$) or 5-FU-based regimen (HR, 2.4; 95% CI, 0.74–8.05; $P = 0.13$) in any treatment line and those who did not receive a GEM-based

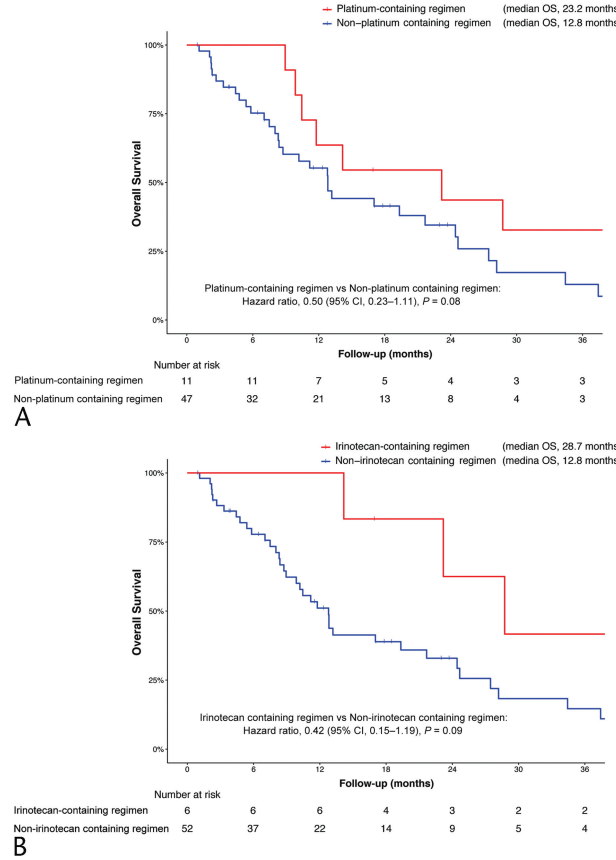

FIGURE 2. Kaplan-Meier curve for OS according to the chemotherapeutic agent used; (A) platinum-containing regimen (red line) vs non-platinum containing regimen (blue line), (B) irinotecan-containing regimen (red line) vs non-platinum containing regimen (blue line).

regimen or 5-FU–based regimen, respectively. On the other hand, a marginally better OS was observed in the patients who received a platinum-based regimen (HR, 0.50; 95% CI, 0.23–1.11; $P = 0.08$) (Fig. 2A) or irinotecan-based regimen (HR, 0.42; 95% CI, 0.15–1.19; $P = 0.09$) (Fig. 2B) in any treatment line as compared with those who did not receive a platinum-based regimen or irinotecan-based regimen, respectively.

DISCUSSION

No standard chemotherapeutic regimen has been established for patients with unresectable or recurrent PACC, because PACC is a rare cancer of the pancreas and no large-scale randomized-controlled trials have been conducted yet for this disease. Only a few retrospective case series with a small number of enrolled patients have been reported so far (Table 3),[6,7,11–28] with even fewer reports of studies in which the efficacies of treatments were analyzed. Furthermore, there are no reliable reports of comparison of the efficacies of various chemotherapeutic agents or regimens. Therefore, we conducted this multicenter retrospective study to evaluate the efficacy of chemotherapy and identify potentially effective agents/regimens for this disease.

In patients with unresectable pancreatic ductal adenocarcinoma, GEM is one of the key agents used, eliciting a tumor response of 5% to 10%.[29] However, the efficacy of GEM seems to differ in patients with unresectable PACC. In the present study, GEM monotherapy was the most frequently selected regimen for first-line therapy (52%), and the majority of the enrolled patients had received GEM monotherapy at least once during the course of their treatment. However, there were no responders to GEM monotherapy in the first-line setting, with only one patient (3%) showing response to GEM monotherapy among the 37 patients treated with the drug in any treatment line. On the other hand, S-1 monotherapy was the most frequently selected second-line treatment regimen (56%), and the ORR in the second-line setting was 22%. The ORR to S-1 monotherapy, including all treatment lines, was 17% (6/35), being significantly better than that to GEM monotherapy. In some previous studies, S-1 as well as capecitabine and 5-FU alone elicited favorable responses. Therefore, 5-FU–containing regimen may be preferable to GEM-containing regimens for patients with unresectable PACC.

A few studies have reported the promising efficacy of platinum-containing regimens.[6,7] Yoo et al[7] reported tumor response to FOLFOX in three of eight patients (ORR, 38%) treated with this regimen in the second- or third-line setting, with a longer PFS than that in patients treated with GEM. Analysis of data collated from previous reports reveals that nearly 50% of patients who showed treatment response had received platinum-containing regimens (Table 3). In the present study, the response rate to platinum (cisplatin, carboplatin, or oxaliplatin)-containing regimens was 40%, which was consistent with the aforementioned reports. Furthermore, the OS tended to be longer in patients who had received platinum-containing regimens as compared with those who had never received any platinum-containing regimen during the course of treatment (Fig. 2A). Also, Lowery et al[6] reported that the response rate to chemotherapy in patients with metastatic PACC was 30% (6/20), and suggested the clinical benefits of combination regimens, including irinotecan. In the present study, the ORR and DCR in response to irinotecan-containing regimens including all treatment lines were 29% and 100%, respectively, although the number of patients was only 7. Furthermore, patients who received irinotecan-containing regimens tended to show a longer OS as compared with those who received irinotecan-containing regimens through their entire treatment course (Fig. 2B). Thus, platinum and irinotecan might be among the key treatment agents for patients with unresectable PACC, and combination regimens, such as FOLFIRINOX,[29] might be promising regimens for unresectable or recurrent PACC, because FOLFIRINOX elicited favorable responses in some case reports.[13,14,16,19]

Our study had some limitations. First, it was a retrospective study, although the number of patients enrolled was larger than in previously reported studies. Second, the PACC patients enrolled received a variety of treatment regimens, and we could not analyze the efficacy of any single regimen excluding GEM or S-1. Third, analysis of the ORR included the sum of all the treatment lines, because the number of patients treated with platinum- or irinotecan-containing regimens was very limited. Generally, the ORR tends to be worse after later lines of therapy than after earlier lines of therapy. Despite platinum- and irinotecan-containing regimens having been selected for later lines of therapy, the ORRs to these agents were more favorable than the response rate to GEM. Fourth, the comparison of the OS between patients who had

TABLE 3. Summary of the Chemotherapy Regimens That Elicited a Response in Patients With Unresectable PACC

Study, Year	Regimen	Reference
Brunetti et al, 2018	GEM + oxaliplatin	14
	GEM + 5-FU	
	FOLFIRINOX	
Li et al, 2018	Olaparib	15
Yoshihiro et al, 2017	FOLFIRINOX	16
Yoo et al, 2017	5-FU + LV	7
	Capecitabine (n = 2)	
	GEM + capecitabine	
	FOLFOX (n = 4)	
Kruger et al, 2016	FOLFOX (n = 2)	13
	Capecitabine	
	FOLFIRINOX (n = 3)	
	GEM + oxaliplatin	
	GEM + erlotinib	
Béchade et al, 2016	GEM + oxaliplatin	17
Furukawa et al, 2015	S-1 + cisplatin	18
Schempf et al, 2014	FOLFIRINOX	19
Morales et al, 2013	Capecitabine + oxaliplatin	20
Cananzi et al, 2013	Docetaxel + irinotecan + cetuximab	21
Simon et al, 2012	FOLFOX	22
Yamamoto et al, 2012	S-1	23
Armstrong et al, 2011	Liposomal doxorubicin	24
Lowery et al, 2011	GEM + oxaliplatin (n = 2)	6
	GEM + cisplatin	
	GEM + erlotinib	
	GEM + docetaxel + capecitabine	
	Cisplatin + irinotecan	
	FOLFIRI	
	Floxuridine + irinotecan	
Seki et al, 2009	S-1	25
Sorscher, 2009	GEM + 5-FU + LV	26
Distler et al, 2009	5-FU	27
Riechelmann et al, 2003	PTX	28
Holen et al, 2002	5-FU + LV + irinotecan	12
	Cisplatin + cytarabine + caffeine	

FOLFIRI, 5-FU + LV + irinotecan; LV, leucovorin; PTX, paclitaxel.

received platinum- or irinotecan-containing regimens at least once during their treatment course and those who had not was insufficient, because host-related factors, including PS, as well as tumor-related factors, including the tumor burden and tumor aggressiveness, could have influence on the OS. Therefore, our findings need to be validated in other cohorts and in well-designed, prospective clinical trials.

In conclusion, platinum- and irinotecan-containing regimens, such as FOLFIRINOX, are potentially beneficial drugs/regimens for unresectable or recurrent PACC. Some prospective clinical trials are warranted to clarify whether these regimens are consistently effective in patients with unresectable or recurrent PACC.

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