Multicenter Retrospective Analysis of Chemotherapy for Advanced Pancreatic Acinar Cell Carcinoma

Potential Efficacy of Platinum- and Irinotecan-Containing Regimens

Hideaki Takahashi, MD, PhD,* Masafumi Ikeda, MD, PhD,* Satoshi Shibata, MD, PhD,† Hiroshi Imaoka, MD, PhD,‡ Akiko Todaka, MD, PhD,§ Kazuhiro Shiotani, MD,#! Kei Yane, MD,¶ Yasushi Kojima, MD, PhD,# Akinori Asagiri, MD, PhD,## Masato Ozaka, MD,### Ryoji Takada, MD,## Yoshikuni Nagashio, MD, PhD,#### Shigeru Horiguchi, MD, PhD,##### Akiyoshi Kasuga, MD,### Eiichiro Suzuki, MD, PhD,#### Takeshi Terashima, MD, PhD,##### Makoto Ueno, MD,** Chigusa Morizane, MD,†† and Junji Furuse, MD, PhD###

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 instruments.

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 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

(Pancreas 2021:50: 77–82)

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,2,6 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.6,7
The clinicopathological features and molecular abnormalities of PACC are different from those of pancreatic ductal adenocarcinoma. 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, tumor suppressor genes, including ID3, ARID1A, APC, and CDKN2A, are recurrently affected in PACC. 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. 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 progression.

| 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, U/l, elevated Median (range) 79 (8–46,080) |
| | AFP ng/ml, elevated Median (range) 16 (47) |
| | CA 19–9, U/l, elevated Median (range) 18 (33) |
| | CEA, ng/ml, elevated Median (range) 14 (0.1–3290) |
| 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, nitoguanine plus cyclophosphamide, cisplatin plus pirarubicin plus cyclophosphamide plus vineristine, and cisplatin plus irinotecan.
§GEM vs platinum, P < 0.01.
¶GEM vs irinotecan, P < 0.01.
ND, not detected.
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. 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.

**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 regimen.
CI, 0.15; 95% CI, 0.23–1.11; \( P = 0.08 \) (Fig. 2A) or irinotecan-based regimen (HR, 0.42; 95% CI, 0.23–1.11; \( P = 0.09 \) (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 Even with 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.5,7 Yoo et al2 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 collected 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 al2 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 + 5-FU | 14 |
| Li et al, 2018 | Olaparib | 15 |
| Yoshihiro et al, 2017 | FOLFIRINOX | 16 |
| Yoo et al, 2017 | 5-FU + LV | 17 |
| Kruger et al, 2016 | Capectabine (n = 2) | 18 |
| Béchade et al, 2016 | GEM + oxaliplatin | 19 |
| Furukawa et al, 2015 | S-1 + cisplatin | 20 |
| Schempf et al, 2014 | FOLFIRINOX | 21 |
| Morales et al, 2013 | Capecitabine + oxaliplatin | 22 |
| Cananzi et al, 2013 | Docetaxel + irinotecan + cetuximab | 23 |
| Simon et al, 2012 | FOLFOX | 24 |
| Yamamoto et al, 2012 | S-1 | 25 |
| Armstrong et al, 2011 | Liposomal doxorubicin | 26 |
| Lowery et al, 2011 | GEM + oxaliplatin (n = 2) | 27 |
| Seki et al, 2009 | S-1 | 28 |
| Sorsch, 2009 | GEM + 5-FU + LV | 29 |
| Distler et al, 2009 | FOLFOX | 30 |
| Riechelmann et al, 2003 | PTX | 31 |
| Holen et al, 2002 | 5-FU + LV + irinotecan | 32 |

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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.

ACKNOWLEDGMENTS

This work was conducted at the Japan Observational Study Committee of Hepatobiliary and pancreatic Oncology (JOS-HPB).

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