Systemic Chemotherapy for Advanced Rare Pancreatic Histotype Tumors

A Retrospective Multicenter Analysis

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Objectives: Two issues were put forth by clinicians in the management of the advanced stages of rare variants of pancreatic ductal adenocarcinoma and other exocrine histotypes with peculiar clinical and pathological features: Do chemotherapy regimens recommended in pancreatic ductal adenocarcinoma patients have a clinical activity in rare pancreatic tumors? Or should other chemotherapy combinations be considered in this subset of patients?

Methods: We conducted a multicenter retrospective study that collected data from 2005 to 2016 at 14 Italian cancer centers with the aim to evaluate tumor response and time to progression for first- and second-line and overall survival.

Results: Of approximately 4300 exocrine pancreatic cancer patients, 79 advanced cases affected by rare histological types were identified, with pancreatic acinar cell cancer (n = 23), pancreatic adenosquamous cancer (n = 16), and mucinous cystic neoplasm with an associated invasive mucinous cystadenocarcinoma (n = 15) most represented. Survival analyses for each subgroup in relation with the different chemotherapy regimens showed the lack of statistical significance correlations.

Conclusions: Because of the lack of clinical trials in patients affected by these rare pancreatic histotypes, only their molecular classification would help clinicians in future therapeutic choice.

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Pancreatic ductal adenocarcinoma (PDAC) represents approximately 85% of all pancreatic malignancies.[1] According to the World Health Organization classification, the remaining rare pancreatic histotypes are represented by variants of PDAC, very rare carcinomas of probable ductal differentiation, and other exocrine variants.[2] Among these rare malignancies, those with a higher incidence are pancreatic adenosquamous carcinoma (PASC) (1%–4%),[3] pancreatic acinar cell carcinoma (PACC) (<2%),[4] cystic tumors (approximately 10%, with very low incidence of malignant cases),[5] and pancreatic undifferentiated and osteoclast-like carcinoma (<1%).[6] Pancreatic carcinosarcoma is considered as a separate entity because of its exceedingly rare occurrence and its characterized dual epithelial and mesenchymal histological feature.[7]

More than half of these patients show advanced disease at the onset, whereas most of them (57%–100%) relapse after curative surgery.[8] Because of the low incidence of these malignancies, their main clinical features are reported only in case series or in retrospective observational analyses. Furthermore, patients affected by these rare pancreatic tumors are excluded from clinical trials that evaluate systemic treatments. The following 2 issues were put forth by clinicians in the management of the advanced stages of these patients: Do chemotherapy regimens recommended in PDAC patients have a clinical activity in rare pancreatic tumors? Or should other chemotherapy combinations be considered in this subset of patients? These questions prompted this multicentric retrospective study that evaluated the activity and the efficacy of different chemotherapy regimens used over time in patients with advanced pancreatic tumors. We also reviewed the current literature on these histological variants, focusing our attention on systemic treatments.

MATERIALS AND METHODS

This retrospective, noninterventional study collected data from 2005 to 2016 of all patients observed at 14 Italian cancer centers who were affected by one the following rare histological types of advanced pancreatic cancer, diagnosed according to World Health Organization criteria: PASC, pancreatic squamous cell carcinoma (PSCC), signet ring cell carcinoma of the pancreas (SRCCP), undifferentiated (anaplastic) carcinoma, osteoclast-like

TABLE 1. Demographics of Patients With Rare Exocrine Histotypes (n = 79)

Patients Characteristics	Frequency (%) or Median (IQR)
Age, y	65.2 (57.9–70.6)
Histotype	
PACC	23 (29.1)
PASC	16 (20.2)
Carcinosarcoma	5 (6.3)
Medullary carcinoma	1 (1.3)
Osteoclast-like carcinoma	2 (2.5)
Pancreatoblastoma	1 (1.3)
PSPPC	4 (5.1)
Undifferentiated carcinoma	3 (3.8)
Clear cell carcinoma	2 (2.5)
PSCC	3 (3.8)
SRCCP	4 (5.1)
MPCAC	15 (18.9)
T	
1	1 (1.3)
2	16 (20.2)
3	44 (55.7)
4	13 (16.5)
Unavailable	5 (6.3)
Primary tumor location	
Head	61 (77.2)
Body	8 (10.1)
Tail	10 (12.7)
N	
0	21 (26.6)
1	40 (50.6)
Unavailable	18 (22.8)
M	
0	40 (50.6)
1	39 (49.4)
Stage at diagnosis	
I/II	25 (31.6)
III	13 (16.5)
IV	41 (51.9)
First line	
Yes	79 (100)
Second line	
Yes	41 (51.9)

PSPPC indicates pancreatic solid paseudopapillary carcinoma.

giant cell carcinoma, mucinous cystic neoplasm with an associated invasive mucinous cystadenocarcinoma of the pancreas (MPCAC), PACC, pancreatoblastoma, pancreatic solid pseudopapillary carcinoma, and carcinosarcoma. Moreover, clear cell carcinoma and medullary carcinoma of the pancreas represent very rare variants of PDAC.

Information regarding patients was reviewed for basic clinical features, chemotherapeutic regimens, and outcomes. Data were collected by clinical and electronic records of participating centers and analyzed by the coordinating center (National Cancer Institute "Giovanni Paolo II," Bari, Italy).

The baseline characteristics of the patients were described and reported as frequencies (%) for categorical variables or median with interquartile range (IQR) for continuous variables. Tumor responses were evaluated according to the Response Evaluation Criteria in Solid Tumor version 1.1.[9] Time to tumor progression (TTP [TTP-1 and TTP-2]) were calculated as the time between the start of first- and second-line chemotherapy and the documented tumor progression, respectively. Overall survival (OS) was calculated from the date of first chemotherapy cycle to the date of death due to any cause. Survival statistics (TTP-1, TTP-2, and OS) were estimated using the Kaplan-Meier method and compared among groups of interest (PASC, PACC, and MPCAC) using the log-rank test. If patients were alive, they were censored at the time of last follow-up. Survival analyses for each subgroup in relation with the different chemotherapy regimens were also performed. Results were expressed as median with corresponding 95% confidence intervals (95% CIs) and graphically reported as curves or histograms. The statistical significance was achieved at $P < 0.05$. All the analyses were performed with the Statistical Analysis System (version 9.4; SAS Institute, Cary, NC).

This study was approved by the Ethical Committee of the National Cancer Institute "Giovanni Paolo II," Bari, Italy, and performed according to the Helsinki Declaration.

RESULTS

After reviewing the records of approximately 4300 exocrine pancreatic cancer patients, 79 advanced cases affected by the above rare, histological types were identified. Baseline features

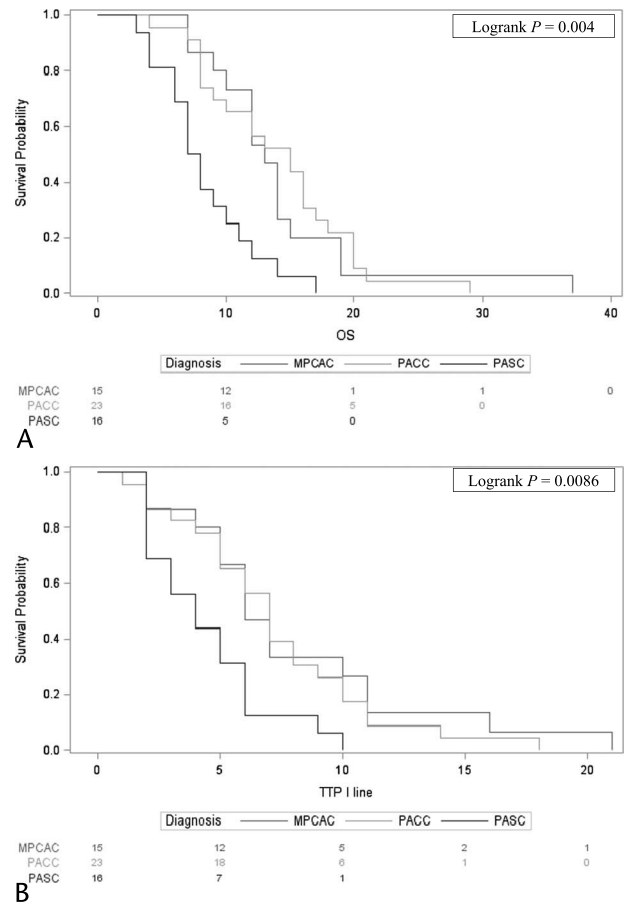

FIGURE 1. Kaplan-Meier curves of OS and TTP-1 according to 3 principal groups of diagnosis. Survival analysis reveals that patients with a diagnosis of PASC have a significantly worse OS (A) and TTP-1 (B) compared with patients with other diagnosis (log-rank $P < 0.05$). **Editor's note:** A color image accompanies the online version of this article.

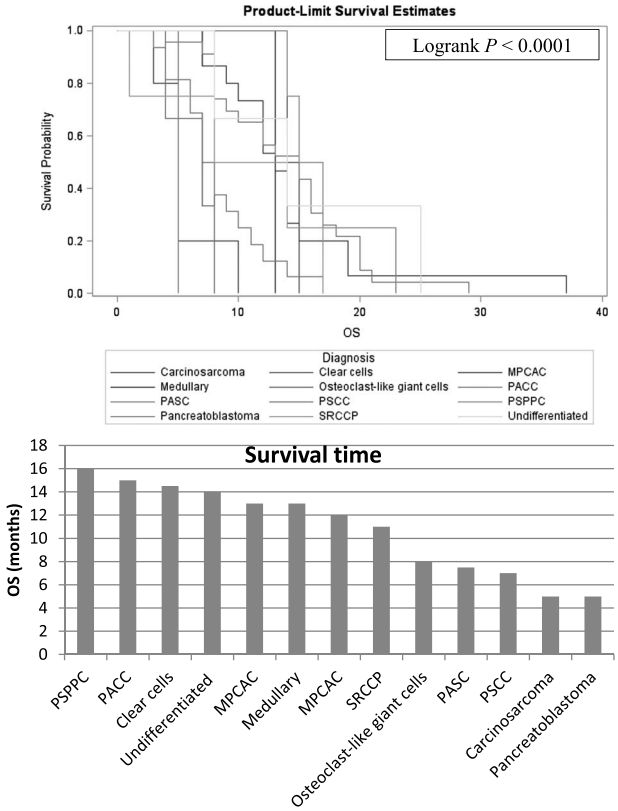

FIGURE 2. Kaplan-Meier curves of OS according to all groups of diagnosis. Survival analysis reveals that patients with a significantly worse OS are those with the following diagnosis: PSCC, carcinosarcoma, and pancreatoblastoma (log-rank $P < 0.0001$). **Editor's note:** A color image accompanies the online version of this article.

are reported in Table 1. Median age was 65 years (IQR, 58–70 years). The most frequent histotypes were PACC (n = 23 [29.1%]), PASC (n = 16 [20.2%]), and MPCAC (n = 15 [18.9%]). Fifty-four patients (68.3%) presented an advanced stage at diagnosis, with most of the tumors localized at the head of the pancreas. The remaining patients developed metastases after surgery, which were followed, in some cases, by adjuvant treatments. Thirteen different chemotherapy schedules, mostly gemcitabine based, and 16, mostly fluoropyrimidine (FP) based, have been administrated in the first- and second-line settings, respectively.

Among the groups of interest, median OSs (mOSs) were 15 months (95% CI, 10–16 months), 13 months (95% CI, 12–14 months), and 7.5 months (95% CI, 6–10 months) for PACC, MPCAC, and PASC, respectively (log-rank $P = 0.0007$) (Fig. 1A); PACC, MPCAC, and PASC showed TTP-1 of 7 months (95% CI, 5–8 months), 6 months (95% CI, 5–10 months), and 4 months (95% CI, 2–6 months), respectively (log-rank $P = 0.0227$) (Fig. 1B). No statistically significant difference was found among the groups of interest for TTP-2.

In Figure 2, a comparison among the mOSs of all histological subgroups has been reported both as curves and as histograms. Pancreatic solid pseudopapillary carcinoma has a better survival with an mOS of 16 months (95% CI, 14–23 months) than the others. A worse prognosis has been observed among the following subgroups: PSCC (mOS of 7 months), carcinosarcoma (mOS of 5 months), and pancreatoblastoma (mOS of 5 months).

Survival analyses for each subgroup in relation with the different chemotherapy regimens showed lack of statistical significance correlations (data not shown). Nevertheless, we noticed an intriguing trend in mOS of PACC patients (Fig. 3). In fact, patients treated with FP plus oxaliplatin seem to have a better survival respect to patients who did not receive it (Fig. 3A). Moreover, patients treated with gemcitabine alone had a worse survival than the others (Fig. 3B).

Clinical data of each patient according to different histotypes are summarized in Table 2 and analyzed below.

Pancreatic Adenosquamous Carcinoma

The following first-line chemotherapy regimens were used in the 16 evaluated patients who were evaluated: gemcitabine plus nab-paclitaxel (3 patients), gemcitabine plus oxaliplatin (GEMOX) (3 patients), gemcitabine plus 5-fluorouracil (5-FU) (4 patients), gemcitabine alone (3 patients), 5-FU plus oxaliplatin and irinotecan (FOLFIRINOX) (1 patient), 5-FU plus leucovorin plus oxaliplatin (FOLFOX) (1 patient), and 5-FU plus cisplatin (1 patient). Six patients received one of the following second-line treatments: 5-FU plus leucovorin plus irinotecan (FOLFIRI) (3 patients), capecitabine (1 patient), and FOLFOX (2 patients).

In the first-line setting, only 1 patient (in 3) treated with gemcitabine achieved a partial response (PR), whereas 9 patients and 6 patients achieved a stable disease (SD) and a progression of disease (PD), respectively. Two patients showed a prolonged

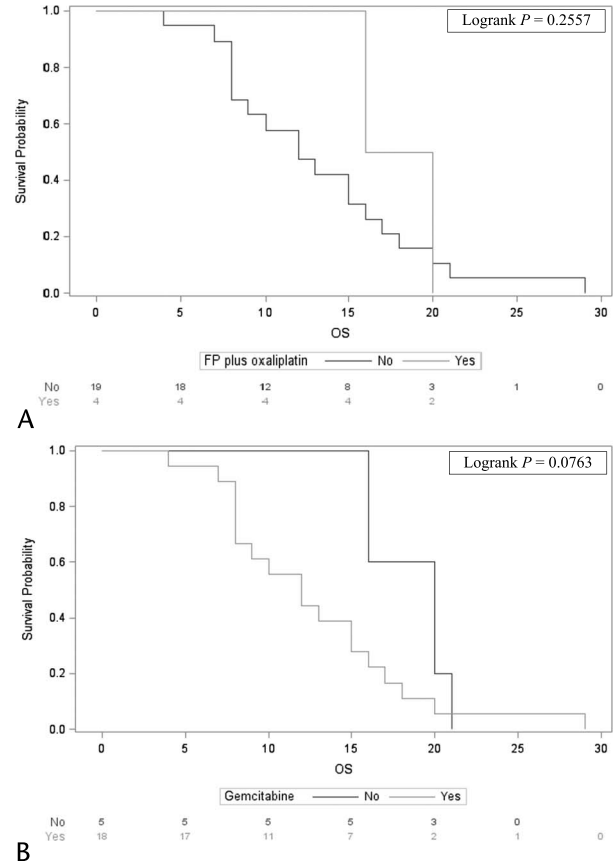

FIGURE 3. Kaplan-Meier curves of OS in patients with PACC diagnosis according to FP plus oxaliplatin (A) gemcitabine (B) treatments. Survival analysis reveals an intriguing trend in OS despite the lack of statistical significance: patients treated with FP plus oxaliplatin seem to have a better survival than the others (A). On the contrary, patients treated with gemcitabine alone have a worse survival than the others (B). **Editor's note:** A color image accompanies the online version of this article.

TABLE 2. Treatment, Response, and TTP for First- and Second-Line Treatment With OS for Each Patient of Our Collection

N. pts	First Line	Response	TTP-1, mo	Second Line	Response 2	TTP-2, mo	OS, mo
Acinar cell carcinoma							
1	Gemcitabine + nab-paclitaxel	SD	8	Gemcitabine + capecitabine	SD	6	20
2	Gemcitabine + nab-paclitaxel	PD	3				8
3	Gemcitabine + nab-paclitaxel	PD	1				4
4	Gemcitabine + oxaliplatin	PR	11	Capecitabine	SD	11	29
5	Gemciatbine + oxaliplatin	SD	6	De Gramont	SD	5	12
6	Gemciatbine + oxaliplatin	PD	2	Nab-paclitaxel	PD	2	9
7	Gemciatbine + 5-FU	PR	7	Taxol	PD	1	13
8	Gemciatbine + 5-FU	SD	14				17
9	PEXG	SD	10				12
10	PEXG	SD	7	Gemcitabine + oxaliplatin	SD	4	15
11	PEXG	SD	6				8
12	PEXG	SD	5				8
13	PEXG	SD	5				7
14	Gemcitabine	SD	11				18
15	Gemcitabine	SD	9	De Gramont	PD	1	15
16	Gemcitabine	SD	8				10
17	Gemcitabine	SD	4	Capecitabine	PD	2	8
18	Gemcitabine	PD	2	FOLFIRINOX	PR	8	16
19	5-FU + cisplatin	SD	10				16
20	5-FU + cisplatin	SD	5	FP-oxaliplatin	SD	12	20
21	FP-oxaliplatin	SD	7	Epirubicin + cisplatin	SD	6	16
22	FP-oxaliplatin	SD	7	Gemcitabine	SD	6	20
23	Epirubicin + cisplatin	SD	18				21
Adenosquamous carcinoma							
1	Gemcitabine + nab-paclitaxel	SD	6				7
2	Gemcitabine + nab-paclitaxel	SD	3				6
3	Gemcitabine + nab-paclitaxel	PD	3				4
4	Gemciatbine + oxaliplatin	SD	6	FOLFIRI	PR	6	17
5	Gemciatbine + oxaliplatin	SD	5	FOLFIRI	PD	1	8
6	Gemciatbine + oxaliplatin	PD	2				6
7	Gemcitabine + 5-FU	SD	4	Capecitabine	PD	2	8
8	Gemciatbine + 5-FU	SD	4				7
9	Gemciatbine + 5-FU	PD	2	FOLFOX	SD	3	7
10	Gemciatbine + 5-FU	PD	2				4
11	Gemcitabine	PR	5	FOLFOX	SD	7	14
12	Gemcitabine	SD	10				11
13	Gemcitabine	PD	2	FOLFIRI	SD	6	9
14	FOLFIRINOX	SD	9				12
15	FP-oxaliplatin	SD	6				10
16	5-FU + cisplatin	PD	2				3
Carcinoma with medullary histology							
1	GEMOX	8	8	De Gramont	PD	2	13
Carcinosarcoma							
1	Adriamycin-ifosfamide	SD	8				10
2	Gemcitabine + nab-paclitaxel	PD	3	Epirubicin	PD	1	5
3	Gemcitabine + 5-FU	PD	2	Capecitabine	PD	2	5
4	Gemcitabine + 5-FU	PD	2				3
5	Gemciatbine + nab-paclitaxel	PD	1				5
Clear cell carcinoma							
1	Gemcitabine + nab-paclitaxel	PR	11	Capecitabine + oxaliplatin	PD	3	15
2	Gemcitabine + oxaliplatin	PR	6	Capecitabine	SD	4	14

(Continued on next page)

TABLE 2. *(Continued)*

N. pts	First Line	Response	TTP-1, mo	Second Line	Response 2	TTP-2, mo	OS, mo
Mucinous cystoadenocarcinoma							
1	Gemcitaibine + nab-paclitaxel	PD	2	FOLFOX	PR	9	13
2	Gemcitaibine + cisplatin	SD	10	FOLFIRI	SD	6	19
3	Gemcitaibe + cisplatin	SD	7	FOLFIRI	SD	5	15
4	Gemcitaibine + cisplatin	PR	21	Nab-paclitaxel	SD	8	37
5	Gemciatbibne + oxaliplatin	SD	6	FOLFIRI	PD	2	10
6	Gemcitaibine + erlotinib	PR	11	Capecitabine	PD	2	14
7	Gemcitabine + erlotinib	PD	4	Capecitabine + oxaliplatin	PD	2	12
8	PEXG	SD	5				7
9	Gemcitabine	SD	16				19
10	Gemcitabine	SD	6	Gemcitabine + cisplatin	PD	3	12
11	Gemcitabibine + 5-FU	PD	2	Capecitabine	PD	2	7
12	Gemcitabine + 5-FU	SD	11				14
13	FOLFIRINOX	SD	5	Gemcitabine + nab-paclitaxel	SD	3	9
14	FOLFIRINOX	SD	7	Gemcitabine	PD	3	12
15	FOLFIRINOX	SD	6	Gemcitabine + nab-paclitaxel	PD	3	14
Osteoclast-like carcinoma							
1	Trabectedin	PD	2	PEXG	SD	5	8
2	Gemcitabine	SD	6				8
Pancreatoblastoma							
1	PEXG	PD	4				5
Signet ring cell carcinoma							
1	Gemcitabine + 5-FU	SD	5				8
2	Gemcitabine	SD	12	Capecitabine	PD	1	17
3	Gemcitabine	SD	13				14
4	FOLFIRINOX	PD	1				1
Solid pseudopapillary carcinoma							
1	Gemcitabine + oxaliplatin	SD	5	Gemcitabine + 5-FU	SD	9	17
2	Gemcitabine + oxaliplatin	PD	2	Gemcitabine + 5-FU	SD	8	14
3	Gemcitabine + 5-FU	SD	5	Capecitabine	SD	6	15
4	Gemcitabine	SD	22				23
Squamous cell carcinoma							
1	Gemcitabine + cisplatin	SD	5	Gemcitabine	PD	1	7
2	Gemcitabine	PD	3				4
3	Gemcitabine	SD	7				8
Undifferentiated (anaplastic) carcinoma							
1	Gemcitabine + nab-paclitaxel	SD	6				8
2	Gemcitaibine + nab-paclitaxel	PR	7				14
3	Gemcitabine + 5-FU	PD	1	FOLFIRI	PR	24	25

GEMCAP indicates gemcitabine plus capecitabine.

SD with TTP-1 of 10 and 9 months for gemcitabine and FOLFIRINOX, respectively. Within the group of patients who underwent a second-line chemotherapy, we observed 1 patient with PR with an OS of 17 months, 3 with SD, and 2 with PD. In this setting, FOLFIRI was associated with 1 PR (TTP-2 of 6 months) and 1 SD (TTP-2 of 7 months). Five patients showed an OS of 10 months or longer. Four of them received an oxaliplatin-based regimen.

Other Exocrine Ductal Pancreatic Adenocarcinoma Variants

Two of the 4 patients affected by SRCCPs received gemcitabine alone as first-line therapy. Both of them showed an SD with 12 and 13 months of TTP-1 and 17 and 14 months of OS, respectively. We observed the lack of activity of FOLFIRINOX in the only patient who received this chemotherapy regimen. Capecitabine as second-line therapy resulted ineffective in 1 patient.

Of 3 patients with PSCC, 2 received gemcitabine with 1 SD (7 and 8 months of TTP-1 and OS, respectively) and 1 PD (3 and 4 months of TTP-1 and OS, respectively). The third patient treated with gemcitabine plus cisplatin achieved an SD (5 and 7 months of TTP-1 and OS, respectively). No second-line therapies were performed in these patients.

The combination of gemcitabine plus nab-paclitaxel was administered in 2 patients affected by undifferentiated (anaplastic) carcinoma, with 1 PR (7 and 14 months of TTP-1 and OS, respectively) and 1 SD (6 and 8 months of TTP-1 and OS, respectively). The combination of gemcitabine plus 5-FU was ineffective in the third patient who showed a PR to FOLFIRI as second-line chemotherapy with a PR and a TTP-2 of 24 months. This last patient achieved an OS of 25 months.

Two patients suffering from osteoclast giant-like cell carcinoma received trabectedin and gemcitabine as first-line chemotherapy with a PD (TTP-1 of 2 months) and an SD (TTP-1 of 6 months), respectively. The former was treated with combination of cisplatin, epirubicin, capecitabine, and gemcitabine (PEXG) as second-line treatment with an SD and 5 months of TTP-2. Both of them achieved an OS of 8 months.

Very Rare Ductal Pancreatic Adenocarcinoma Variants

Among patients with very rare variants of the PDAC, 2 of them were affected by clear cell carcinoma. Both achieved a PR after gemcitabine plus nab-paclitaxel and GEMOX, respectively. Time from first-line chemotherapy to tumor progression were 11 and 6 months, respectively. They received capecitabine plus oxaliplatin (XELOX) and capecitabine as second-line chemotherapy, with 1 PD and 1 SD, respectively. Overall survivals were 15 and 14 months, respectively.

The only patient with pancreatic carcinoma with medullary histology was treated with GEMOX and de Gramont as first- and second-line treatment with an SD (TTP-1 of 8 months) and PD (TTP-2 of 2 months), respectively. Overall survival was 13 months.

Mucinous Cystadenocarcinoma of the Pancreas

We assessed 15 patients affected by MPCAC. They received the following first-line regimens: gemcitabine plus nab-paclitaxel (1 patient), gemcitabine plus cisplatin (3 patients), GEMOX (1 patient), gemcitabine plus erlotinib (2 patients), cisplatin plus epirubicin plus capecitabine plus gemcitabine (PEXG) (1 patient), gemcitabine (2 patients), gemcitabine plus 5-FU (2 patients), and FOLFIRINOX (3 patients). Ten patients achieved an SD, and 3 patients achieved a PD. Only 2 patients achieved a PR with gemcitabine plus erlotinib (TTP-1 of 11 months) and with gemcitabine plus cisplatin (TTP-1 of 21 months), respectively. This latter received a second-line therapy with nab-paclitaxel with an SD and TTP-2 and OS of 8 and 37 months, respectively. Four patients achieved an OS equal to or greater than 15 months. Three of them received gemcitabine plus cisplatin as first-line therapy.

Twelve patients received one of the following second-line treatments: FOLFOX (1 patient), FOLFIRI (3 patients), nab-paclitaxel (1 patient), capecitabine (2 patients), XELOX (1 patient), gemcitabine plus cisplatin (1 patient), gemcitabine plus nab-paclitaxel (2 patients), and gemcitabine (1 patient). One patient treated with FOLFOX achieved a PR with 9 months of TTP-2. Four patients achieved an SD (1 of them treated with nab-paclitaxel reaching 8 months of TTP-2), and 7 achieved a PD.

Pancreatic Acinar Cell Carcinoma

The following first-line chemotherapy regimens were used in the 23 evaluable patients: gemcitabine plus nab-paclitaxel (3 patients), GEMOX (3 patients), gemcitabine plus 5-FU (2 patients), PEXG (5 patients), gemcitabine (5 patients), 5-FU plus cisplatin (2 patients), FP plus oxaliplatin (2 patients), and epirubicin plus cisplatin (1 patient). Two cases of PR were obtained with GEMOX and gemcitabine plus 5-FU (TTP-1: 11 and 7 months), respectively. We observed 17 SD and 4 PD cases. A patient treated with the combination of epirubicin plus cisplatin reached a prolonged SD with 18 months of TTP-1.

Twelve patients received one of the following second-line treatments: gemcitabine plus capecitabine (1 patient), capecitabine (2 patients), de Gramont (2 patients), nab-paclitaxel (1 patient), paclitaxel (1 patient), GEMOX (1 patient), FOLFIRINOX (1 patient), FOLFOX (1 patient), epirubicin plus cisplatin (1 patient), and gemcitabine (1 patient). Only 1 patient treated with FOLFIRINOX achieved a PR. Two patients underwent a long SD with a TTP-2 of 11 and 12, after capecitabine and FOLFOX, respectively. Overall survival was equal to or greater than 20 months in 5 patients.

Solid Pseudopapillary Neoplasms With High-Grade Malignant Transformation

Two patients were treated with GEMOX, achieving 1 SD and 1 PD with TTP-1 of 5 and 2 months, respectively. Both of them received gemcitabine plus 5-FU as second line, achieving an SD with TTP-1 of 9 and 8 months, respectively. One patient received a first-line treatment with gemcitabine plus 5-FU followed by capecitabine after progression, with an SD for both treatments and an OS of 15 months. It was interesting to observe that a patient treated with gemcitabine alone achieved a long-duration SD with TTP-1 and OS of 22 and 23 months, respectively.

Pancreatoblastoma

The only patient with pancreatoblastoma reported in this study received PEXG as first-line therapy, achieving an SD, with 4 and 5 months of TTP-1 and OS, respectively.

Pancreatic Carcinosarcoma

Five patients were treated with gemcitabine plus nab-paclitaxel (2 patients), gemcitabine plus 5-FU (2 patients), and adriamycin plus ifosfamide (1 patient), with only 1 SD obtained with the latter chemotherapy regimen. Only 2 patients received a second-line treatment with epirubicin and capecitabine, respectively. Both of them showed a PD.

DISCUSSION

Systemic chemotherapeutic regimens for advanced rare histological types of pancreatic cancer are not established. So far, in most of the cases, clinicians have chosen antineoplastic drugs according to result of clinical trials considering PDAC patients. In the past, gemcitabine alone[10] or in combination with a platinum salt[11,12] or an FP[13,14] represented the most used regimens. In the last few years, FOLFIRINOX,[15] PEXG,[16] and nab-paclitaxel plus gemcitabine[17] became the criterion standard in the first-line setting of fit PDAC patients.To the best of our knowledge, this is the first multicentric retrospective analysis of systemic treatments performed in patients with advanced pancreatic exocrine phenotypes different from PDAC.

Pancreatic Adenosquamous Carcinoma

Pancreatic adenosquamous carcinoma represents 1% to 4% of all exocrine pancreatic cancers. It is characterized by a bad prognosis,[18–20] with an OS of 4 months reported in a Surveillance, Epidemiology, and End Results database.[21] Despite several data regarding clinical and pathological features,[22,23] very little information is available regarding systemic therapeutic options. In particular, the role of cisplatin or oxaliplatin in addition to gemcitabine has been supported by a study performed in an adjuvant setting, which reported a significantly longer median survival associated with this combination compared with gemcitabine or 5-FU alone.[24] In the metastatic setting, a retrospective analysis by Imaoka et al[25] considered 22 patients with advanced PASC who received gemcitabine alone (16 patients), gemcitabine plus S1 (1 patient), 5-FU plus concurrent radiotherapy (1 patient), or best supportive care (3 patients), with no information regarding efficacy and activity of these treatments. De Souza and Saif[26] reported the result obtained in 2 patients with advanced disease treated with gemcitabine in combination with cisplatin and oxaliplatin. The first patient achieved an SD with a TTP-1 of 8 months; the second achieved a PR with a TTP-1 of 6 months. Capecitabine

represented the second-line treatment for both of them with TTP-2 of 18 and 24 weeks, respectively.[26] In our study, we observed the clinical activity of oxaliplatin-based regimens in 3 untreated patients.

Pancreatic Squamous Cell Carcinoma

Pancreatic squamous cell carcinoma represents approximately 0.2% of all pancreatic exocrine malignancies.[27] Only single case reports are available in literature that consider the treatment of patients with advanced disease. The combination of 5-FU plus cisplatin was associated with on OS from 6 to 15 months.[28–30] De Souza and Saif[31] administered the combination of gemcitabine plus cisplatin with an SD and a progression-free survival (PFS) of 6 months. This patient received 5-FU and leucovorin as second-line therapy with an SD and a PFS of 3 months. In another patient, the combination of gemcitabine plus oxaliplatin was associated with 6 and 9 months of PFS and OS, respectively.[32] Al-Shehri et al[33] evaluated the combination of gemcitabine plus carboplatin who underwent a PD with an OS of 4 months. Our data are consistent with the above literature in terms of OS obtained with gemcitabine alone or in combination with cisplatin.

Signet Ring Cell Carcinoma of the Pancreas

Very few case reports are available in literature with no data regarding the treatment in advantage stages.[34–37] In our series, gemcitabine alone was associated with a good activity and efficacy profile. On the contrary, we observed the lack of activity of FOLFIRINOX in 1 patient with a TTP-1 of only 1 month.

Undifferentiated (Anaplastic) Carcinoma

This histotype has been referred to with several names: pleomorphic carcinoma, pleomorphic giant cell carcinoma, round cell carcinoma, spindle cell carcinoma, and mainly undifferentiated (anaplastic) carcinoma.[38] This tumor represents approximately 2% to 7% of all pancreatic carcinomas.[39,40] The North American National Cancer Data Base reported an mOS of 11.1 months based on the consideration of all stages.[41] Even for this histotype, clinical,[42] pathological, and biomolecular[43] features have been exhaustively studied. Because of its aggressive behavior and rapid recurrence, benefits of systemic therapies have not yet been demonstrated.[44] Wong et al.[45] administered GEMOX in combination with radiofrequency ablation of stable liver metastases and obtained an SD with an OS of 15 months. Interestingly, Wakatsuki et al[46] used a chemosensitivity testing with ATP assay using fresh specimens of pleiomorphic pancreatic cancer from a patient with metastatic disease with the aim to predict the activity of anticancer agents in this tumor. The assay revealed a high chemosensitivity to paclitaxel. The patient was treated with this drug achieving a complete response (CR) after 2 cycles and a disease-free survival of 23 months.[46] Ungaro et al[47] reported the lack of activity of cisplatin plus gemcitabine in a patient who received FOLFIRI in combination with high-intensity focused ultrasound with a PR. Shinagare et al[48] described the history of a patient treated with FOLFIRINOX who showed a PR even if OS was only of 5 months because of the deterioration of the clinical status. Interestingly, even if in only 2 cases, for the first time we reported a favorable activity profile of the combination of gemcitabine plus nab-paclitaxel in this subset of patients.

Osteoclast Giant-like Cell Carcinoma

This rare histotype shows similar histological features to pleomorphic giant cell carcinoma from which it differs because of the presence of cells simulating giant cell tumor of the bone.[49] It accounts for less than 1% of all pancreatic malignancies.[50] The North American National Cancer Data Base reported an mOS of 48 months including all stages,[41] even if mOS for patients with advanced disease was less than 1 year with few exceptions.[51] The combination of gemcitabine plus erlotinib was associated with a rapid PD.[52] Yoshioka et al[53] treated an elderly patient with metastatic disease with gemcitabine alone with a CR after 5 months. Time from first-line chemotherapy to tumor progression and OS were 12 and 19 months, respectively. Similarly, Chiarelli et al[54] described the history of a patient treated with gemcitabine alone with an SD and 6 and 10 months of TTP-1 and OS, respectively. Jones et al[55] obtained a PR after neoadjuvant FOLFIRINOX. We confirmed the clinical activity of gemcitabine in our patient.

Pancreatic Clear Cell Carcinoma

Very few data are available regarding the incidence and survival of these patients.[56–58] Gemcitabine alone and mitomycin plus 5-FU combination had no activity in a patient with metastatic disease.[59,60] For the first time, we reported a promising activity profile of gemcitabine-based chemotherapy regimens in 2 patients who showed OSs of 15 and 14 months, respectively. Furthermore, similar positive results have been obtained with the combination of gemcitabine plus nab-paclitaxel, in a patient for whom TTP-1 and OS were 11 and 15 months, respectively.

Pancreatic Carcinoma With Medullary Histology

Overall 2- and 5-year survival rates of this tumor are approximately 29% and 13%, respectively.[61] No data are available regarding chemotherapy treatment. We reported the unique case of a patient treated with GEMOX as first-line chemotherapy, who achieved an SD with a TTP-1 of 8 months.

Mucinous Cystadenocarcinoma of the Pancreas

The incidence of this malignancy ranges from 2.4% to 14% of all pancreatic malignancies.[62,63] The Surveillance, Epidemiology, and End Results database approximately estimated that the mOS calculated in patients with advanced disease was 4 months.[64]

Few indications are available in advanced setting. Obayashi et al[65] described the history of a patient with liver metastases treated with 16 courses of GEMOX who achieved a CR on hepatic metastases followed by the resection of the primary mass. Similarly, a patient with peritoneal and ovarian metastases was treated with 12 cycles of GEMOX with a PR, which allowed the surgical resection of primary and metastatic lesions.[66] A patient with metastatic disease treated with gemcitabine alone achieved a marked shrinkage of the metastatic lesions.[67] Werner et al[68] treated 5 patients with gemcitabine, achieving PR in 1, SD in 1, and PD in 3 patients, with an mOS of 11 months. On the contrary, gemcitabine-based combinations were associated with a short OS in 2 other patients.[69,70] In our series, we confirmed the activity of the combination of gemcitabine plus cisplatin. Furthermore, 3 patients had FOLFIRINOX achieving an SD. The combination of gemcitabine plus nab-paclitaxel was ineffective in both first- and second-line settings in our 3 patients.

Pancreatic Acinar Cell Carcinoma

Pancreatic acinar cell carcinoma is another rare pancreatic exocrine tumor (1%–2% of all cases)[4] with an mOS of 17 to 19 months in the advanced stages.[71,72] For what concerns systemic treatments, a retrospective study considering 18 patients at Memorial Sloan Kettering Cancer Center reported only 2 patients

TABLE 3. Analysis of Treatment, Response, and TTP for First- and Second-Line Treatment With OS in Literature Reports

Ref.	First Line	Response	TTP-1, mo	Second Line	Response 2	TTP-2, mo	OS, mo
Adenosquamous cell carcinoma							
26	Gemcitabine + cisplatin	SD	8	Capecitabine	SD	4	NR
26	Gemcitabine + oxaliplatin	PR	6	Capecitabine	SD	6	NR
Squamous cell carcinoma							
31	Gemcitabine + cisplatin	SD	6	De Gramont	SD	3	NR
32	Gemcitabine + oxaliplatin	SD	6				9
33	Gemcitabine + carboplatin	PD	NR				4
Undifferentiated (anaplastic) carcinoma							
45	GEMOX + RF (liver metastases)	SD	NR				15
46	Paclitaxel	CR					23
47	Cisplatin + gemcitabine	PD	1	FOLFIRI + high-intensity focused ultrasound	PR	NR	NR
48	FOLFIRINOX	PR	NR				5
Osteoclast giant-like cell carcinoma							
52	Gemcitabine plus erlotinib	SD	8				10
53	Gemcitabine	CR	12				19
54	Gemcitabine	SD	6				10
55	FOLFIRINOX	PR	NR				NR
Mucinous cystoadenocarcinoma							
65	GEMOX	CR					22
66	GEMOX	PR	NR				NR
67	Gemcitabine	PR	NR				NR
68	Gemcitabine-based treatment (5 patients)	1 PR, 1 SD, and 3 PD					11 (Median)
69	Gemcitabine-based CT	SD	NR				6
70	Gemcitabine-based CT	PD	NR				3
Acinar cell carcinoma							
73	FOLFIRI	PR	NR				7 (Not for disease)
73	Cytarabine, cisplatin, and caffeine	PR	6				NR
73	5-FU	SD	NR				NR
72	Gemcitabine + irinotecan	SD	25				30
72	Gemcitabine + irinotecan	SD	8	GEMOX	PR	5	35
72	Gemcitabine	PD	2	Cisplatin + irinotecan	PR	25	34
72	Gemcitabine + capecitabine	SD	9	FOLFIRI	PD	3	21
72	GTX	PR	11	GEMOX	NR	NR	44
72	GTX	SD	7				11
72	Gemcitabine + cisplatin	PR	NR	GEMOX	PD	3	68+
74	Gemcitabine	PD	2	S1	PR	NR	13
74	Gemcitabine	SD	6	S1	SD		10
75	Capecitabine	PR	12	FOLFOX	PR	6	43+
75	FOLFOX	PR/SD	12	FOLFIRI	SD	3	26
75	Gemcitabine + erlotinib	PD	6	FOLFOX	SD	22	68
75	Gemcitabine	SD	7	Pemetrexed	PD	NR	34
75	FOLFIRINOX	SD	5	Gemcitabine + nab-palitaxel	PD	NR	9
75	GEMOX	PD	3	Capecitabine	SD	56	150+
75	Gemcitabine + erlotinib	PD	2	Capecitabine	PD	2	6
75	FOLFIRINOX	PR	8	Gemcitabine + nab-palitaxel	PD	3	19
75	Gemcitabine	PD	1				4
75	Gemcitabine + erlotinib	PD	2	FOLFIRINOX	PR	9	25
75	FOLFIRINOX	PR	14				15+

(Continued on next page)

TABLE 3. *(Continued)*

Ref.	First Line	Response	TTP-1, mo	Second Line	Response 2	TTP-2, mo	OS, mo
75	GEMOX	PR	6	(Shift to) gemcitabine + erlotinib	PR	13	45
76	S1	PR	NR				24
77	S1	SD					73+
78	FOLFIRINOX	SD	9				NR
79	FOLFIRINOX	CR (liver met) SD (primary)	NR				NR
Solid pseudopapillary carcinoma							
89	Tamoxifen	SD	NR				22
90	5-FU + doxorubicin + mitomycin-C	PD	NR				NR
91	Cisplatin + 5-FU	PR	NR				NR
92	Cisplatin + ifosfamide + etoposide + vincristine	PR	NR				NR
93	VP-16, cisplatin, cyclophosphamide, doxorubicin, and vincristine	PR	NR				24
94	5-FU + concomitant RT	PD	NR	Gemcitabine	PR	NR	NR
Pancreatoblastoma							
100	Cisplatin + doxorubicin	Mixed radiographic response	3	Docetaxel + gemcitabine	PD	NR	5
101	Streptozocin, doxorubicin, and gemcitabine + chemoembolization with radiolabeled somatostatin	CR	51				NR
96	Cisplatin + doxorubicin	NR	NR				<10
Pancreatic carcinosarcoma							
106	Gemcitabine	SD/PD	NR				NR

CT indicates chemotherapy; GTX, gemcitabine, capecitabine, and docetaxel; NR, not reported; Ref, reference.

with PR obtained with FOLFIRI and the combination of cytarabine plus cisplatin and caffeine, respectively.[73] Six patients with PR were reported at the same institution in another retrospective study with the following regimens: GEMOX (2 patients), gemcitabine-docetaxel-capecitabine (1 patient), cisplatin plus irinotecan (1 patient), cisplatin plus gemcitabine (1 patient), and gemcitabine plus erlotinib (1 patient). One patient received GEMOX as second-line therapy with a PR and a TTP-2 of 6 months.[72] No data supported the activity of gemcitabine alone as first-line therapy in this subset of patients.[74,75] One patient treated with GEMOX (8 cycles) achieved a PR. Subsequently, the treatment was switched to gemcitabine plus erlotinib with a PR (13 months).[75] Seki et al[74] reported 2 Asian cases of advanced PACC treated with S1 after the failure of first-line treatment with gemcitabine achieving PR in 1 and SD in 1 with 13 and 10 months of OS, respectively. In another patient, S1 alone was associated with a PR and an OS of 24 months.[76] Sumiyoshi et al[77] described a patient with advanced PACC treated with S1 after distal pancreatectomy with evidence of peritoneal involvement who was alive 73 months after the diagnosis. FOLFOX or FOLFIRINOX obtained PR in 4 and prolonged SD in 2. In particular, the use of FOLFIRINOX as first-line therapy led to an SD with 3 months of PFS and 2 with PR with a PFS of 6 and 14 months, respectively. One patient treated with this regimen in second-line therapy achieved a PR with a PFS of 9 months.[75] Similarly, Callata-Carhuapoma et al[78] reported the history of a patient who achieved a prolonged SD (TTP of 9 months) after FOLFIRINOX. Also, a 63-year-old patient treated with the same regimen achieved a CR of hepatic lesions and a PR of pancreatic mass.[79] Pfrommer et al[80] reported the unique case of a young man with an advanced mixed PACC and PDAC who showed an exceptional response to FOLFIRINOX. After a perioperative administration of cisplatin and doxorubicin (PLADO regimen), he underwent a Whipple duodenopancreatectomy with simultaneous wedge resection of liver metastases. At the recurrence, a first-line chemotherapy with 2 cycles of ifosfamide, carboplatin, and etoposide (ICE regimen) was performed with a PR. Soon after, he received 2 liver transplantations (right hemiliver) from both his brother and a cadaveric liver graft after 10 days. Five months later, multiple new lung metastases were detected. So far, he was administered FOLFIRINOX regimen with a complete metabolic response and a partial radiological response of all lung lesions. Because of the excellent response to FOLFIRINOX, the authors decided to consolidate this result with tandem high-dose chemotherapy using carboplatin, etoposide, and paclitaxel as conditioning regimen followed by autologous stem cell transplantation. Six months later, FOLFIRINOX was started again because of a new lung progression with a PR. At the time of publication, approximately 45 months after diagnosis, the patient was still alive. Disappointing results have been obtained with the combination of gemcitabine plus nab-paclitaxel in 2 cases.[76]

Very few data are available in the second-line setting. Yoo et al[81] reported 8 cases who received gemcitabine alone (4 patients) or FOLFOX (4 patients), respectively. No responses were obtained in the first group. Patients treated with FOLFOX presented 3 PR and 1 SD case with a median PFS of 6.5 months.

Lastly, some authors considered the administration of somatostatin analogs in the care and prevention of fat necrosis

nodule, an event that has been reported in these patients with the resolution of fat panniculitis associated with PACC.[82–84]

In our series, we confirmed the activity of FOLFIRINOX that was administered as second-line therapy in 1 patient who showed a PR. A patient treated with the combination of epirubicin plus cisplatin reached a TTP-1 of 18 months. Intriguingly, 5 patients receiving a platinum salt achieved an OS equal to or longer than 20 months. Moreover, 12 patients had an OS equal to or longer than the mOS of our cases (15 months); 10 of them were treated with a platinum compound in the first- or second-line settings, or both. Contrasting data emerged from the use of gemcitabine plus nab-paclitaxel. On one side, 1 of 3 patients treated with this combination reached SD with 8 and 20 months of TTP-1 and OS, respectively. On the contrary, 2 of them experienced a rapid PD with OSs of 8 and 4 months, respectively.

In summary, gemcitabine alone does not have a role in PACC patients, as has been demonstrated in our results (Fig. 3B). According to our findings (Fig. 3A) and literature data, the combination of an FP with a platinum salt is associated with a favorable activity and efficacy profile. As for the newest chemotherapy combination regimen, FOLFIRINOX could represent a valuable therapeutic option.

Solid Pseudopapillary Neoplasms With High-Grade Malignant Transformation

This tumor, which represents 2% to 3% of all pancreatic malignancies,[85] is characterized by a low malignant potential, due to its benign morphology and nonfrequent metastasis.[86,87] As a consequence, it displays a good prognosis, with an mOS of 8 years.[88] So far, malignant transformation in solid pseudopapillary neoplasms is exceedingly rare, although when it occurs neoplasms became highly aggressive.

Intriguingly, Sclafani et al[89] described the history of a patient with metastatic disease with positive estrogen receptors treated with tamoxifen with an OS of 22 months. A combination of 5-FU, doxorubicin, and mitomycin-C was not effective in a case report.[90] On the contrary, the combination of cisplatin plus 5-FU in a locally advanced tumor was associated with a PR, allowing the surgical resection of the tumor.[91] A combination of cisplatin, ifosfamide, etoposide, and vincristine was associated with a PR of liver metastases, which allowed a radiofrequency-combined surgical resection of a primary tumor.[92] Tipton et al[93] reported a PR associated with an OS of 2 years in a patient who received a combination of VP-16, cisplatin, cyclophosphamide, doxorubicin, and vincristine. A locally advanced tumor was treated with 5-FU plus concomitant radiation, achieving clinical progression. He received gemcitabine alone with a PR, which allowed pancreatoduodenectomy.[94] The low aggressive biology of the tumor is confirmed by the history of a patient who underwent several lines of treatment: gemcitabine alone (6 cycles), gemcitabine plus irinotecan (3 cycles), oxaliplatin plus irinotecan and capecitabine (8 cycles), gemcitabine plus capecitabine (6 cycles), and weekly 5-FU. Finally, in the last 2 years until publication of the data, the patient received capecitabine alone.[95] All patients considered in our study received gemcitabine alone or in combination with oxaliplatin or 5-FU with only SD.

Pancreatoblastoma

Pancreatoblastoma typically mainly occurs in the pediatric population, with approximately only 40 cases described in adults.[96,97] Prognosis in this small group of patients is dismal, with an mOS of 5 months in the advanced stages.[98] In children, PLADO regimen represents the criterion standard in the first-line setting.[99] Very limited information regarding adult patients is available. Rajpal et al[100] reported the history of a subject who received a first-line therapy with cisplatin plus doxorubicin, with a mixed radiographic response and a TTP of 3 months. After progression, the administration of docetaxel plus gemcitabine resulted ineffective. The combination of capecitabine plus oxaliplatin third-line therapy was associated to a TTP of 4 months.[100] Salman et al[101] reported the history of a patient with metastatic disease who received a first-line therapy with streptozocin, doxorubicin, and gemcitabine in conjunction with chemoembolization using radiolabeled somatostatin, with a TTP of 51 months. Zouros et al[96] unsuccessfully treated a recurrent pancreatoblastoma with PLADO regimen with an OS after recurrence of less than 10 months. We reported a very short TTP-1 and OS concerning the first patients treated with PEXG as first-line therapy.

Pancreatic Carcinosarcoma

Pancreatic carcinosarcoma is a very rare histotype of pancreatic cancer with approximately only 20 cases reported in the literature.[102,103] Gelos et al[104] reviewed 7 cases, with an OS after surgery of 6 months. Jia et al[103] considered 19 cases and calculated an mOS of 9 months using the Kaplan-Meier method including cases of all stages. Herein, we reported one of the more significant series of advanced pancreatic carcinosarcoma, whose mOS was 5 months. Despite several available data reporting pathological[105] and radiological[102] features, only few authors reported data concerning systemic therapies. Gemcitabine alone resulted ineffective in 2 advanced cases.[103,106]

Among 4 of our 5 patients, 2 were treated with gemcitabine plus nab-paclitaxel, and 2 were treated with gemcitabine plus FU. All of them showed a PD with an OS equal to or shorter than 5 months. Our fifth patient was treated with adriamycin plus ifosfamide with a TTP-1 of 8 months and an OS of 10 months.

CONCLUSIONS

The very low incidence of these malignancies and the lack of knowledge concerning their biological features represent the main obstacles in the definition of a chemotherapy regimen that can be recommended in these patients. In this retrospective analysis of chemotherapeutic approaches in advanced rare exocrine pancreatic histotype, we tried to answer to the clinical needs in treatments of these patients with locally advanced or metastatic disease. Nevertheless, the heterogeneity of the reported data in combination with the revision of the literature (Table 3) allowed us to suggest, in some cases, possible therapeutic options.

Because of the lack of the possibility to perform clinical trials in patients affected by rare pancreatic malignancies, we believe that only their molecular classification could help clinicians in their therapeutic choice.

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