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ORIGINAL ARTICLE

A multi-centre retrospective review of second-line therapy in advanced pancreatic adenocarcinoma

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Abstract
Introduction Limited information on second-line treatment in patients with pancreatic adenocarcinoma is available. At time of first-line treatment failure, approximately half of the patients are candidates for further treatment.
Material and methods A retrospective review of 183 patients submitted to second-line therapy has been performed to identify prognostic factors, provides useful information for patients counseling and generates hypotheses for future studies. Inclusion criteria were: cytological or histologic diagnosis of pancreatic adenocarcinoma and prior gemcitabine-including chemotherapy. Any age, performance status (PS) and chemotherapy regimen were considered.
Results One hundred and eighty-three patients (106 males; 168 metastatic; median age 62 years; median PS 1; 63 submitted to prior curative surgery, 32 to prior radiotherapy) with a median previous progression-free survival (PFS) of 6.7 months were included. Median and 6-month PFS after initiation of salvage therapy were 3.0 months and 20%. Median, 1 and 2 years, overall survival after initiation of salvage therapy were 6.2 months, 17 and 4%, respectively. Previous PFS, CA19.9 levels and age independently predicted OS.
Conclusion Re-challenge with gemcitabine and 5-fluorouracil administration may have a role in selected patients.

Keywords Chemotherapy · Pancreatic cancer · Second-line therapy · Gemcitabine-refractory cancer

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Introduction

Pancreatic adenocarcinoma has a dismal prognosis and progression typically occurs within 6 months from upfront treatment start in the majority of patients [1–7]. Approximately, half of the patients, failing previous treatment, present good performance status (PS) and are willing to undergo further treatment. However, due to the disappointing results of first-line treatment, limited investigation on second-line treatment after gemcitabine-based chemotherapy failure has been performed [8–23]. The sample size of most series was limited to <30 patients per treatment arm [10–12, 14, 17, 18, 21], thus producing data with very large confidence intervals. Furthermore, main patient and tumor characteristics consistently differed across series, thus hampering the drawing of any meaningful conclusion. On the other hand, salvage chemotherapy may improve survival when compared to best supportive care [17] and determine a clinically significant improvement in quality of life in several different domains [15].

The aim of treatment in advanced pancreatic adenocarcinoma is palliation, a fact that is even more evident in the case of salvage treatment. Administering an active and

effective regimen in a well-selected patient population may have a beneficial effect on quality of life, as a direct result of improvements in clinical outcome. Therefore, the knowledge of prognostic and predictive factors, which may contribute to the identification of the subset of patients with a greater likelihood of an outcome benefit from salvage therapy, could be useful. Given the scarcity of sound information from prospective series, the exploratory analysis of large series, reflecting different therapeutic trends in ordinary clinical practice, seems to be an important source of data to allow the definition of optimal treatment, enhance patient counseling and generate hypotheses for future studies.

The present report describes a large series of patients with progressive or recurrent pancreatic adenocarcinoma who received second-line treatment after gemcitabine-based chemotherapy.

Materials and methods

The study includes 183 patients with cytologically or histologically proven pancreatic cancer who received second-line therapy after gemcitabine-including chemotherapy at five Italian centers between January 2000 and January 2006. Data for patients considered in the analysis included patient and tumor characteristics as well as details regarding prior treatment and salvage therapy. Any age, PS and chemotherapy regimen were considered. Patients with ampullary tumors or other histologic variants of pancreatic carcinoma were not considered for this analysis.

Tumors were assessed every 2–3 months according to local policy. Tumor assessment was performed according to RECIST criteria [24]. Progression-free survival (PFS) was defined as the interval between the start of treatment and the occurrence of progressive disease (PD) or death. Prior PFS was defined as the interval between the start of first-line treatment and the occurrence of PD preceding second-line therapy. Overall survival (OS) was measured from the start of second-line treatment to date of death or to the last follow-up assessment.

Survival distribution was estimated by the Kaplan–Meier method. Significant differences in probability of surviving between the strata were evaluated by log-rank test. Binomial exact 95% confidence intervals (CIs) were calculated for percentages. Multivariate analysis by the Cox proportional hazard model was carried out to estimate independent risk factors that could affect OS. All probability values were from two-sided tests and p values of 0.05 were considered to indicate a statistical significance. Analyses were performed with the Statistica 4.0 statistical package for Microsoft Windows.

Results

Patient characteristics

Between January 2000 and January 2006, 183 patients with pancreatic adenocarcinoma received systemic ($n = 181$) or intra-arterial ($n = 2$) second-line treatment after previous gemcitabine-containing chemotherapy and were included in the current analysis. The characteristics of the patient population and previous treatment are summarized in Table 1. Twenty-three different combinations of 13 agents were used at salvage (Table 2). All patients had received a single prior systemic ($n = 181$) or intra-arterial ($n = 2$) chemotherapy line as adjuvant therapy after curative surgery or as therapeutic treatment for locally advanced or metastatic disease (Table 3).

Anti-tumor activity and survival

One complete (0.5%) and 25 partial responses (13.7%) for an overall response rate of 14.2% were observed. Median response duration was 6.1 months (interquartile range

Table 1 Patient characteristics at time of salvage therapy

Characteristic	*N* (%)
Patients enrolled	183
Median age (years)	62 (range 34–80)
Sex	
Male	106 (58)
Female	77 (42)
ECOG PS	
Median	1 (range 0–3)
Stage	
Local relapse or progression	15 (8)
Metastatic disease	168 (92)
Prior therapy	
Curative surgery	63 (34)
Radiotherapy	47 (26)
Chemotherapy	183 (100)
G	72 (39)
PEFG	55 (30)
G + *P*/*O*	24 (13)
G + celecoxib	17 (9)
GF	11 (6)
Others	4 (2)
Median previous PFS (months)	6.7 (range 1–46)
CA19.9 (UI)	
Normal/>ULN/unknown	29 (16)/148 (81)/6 (3)
Median 864	864
Range	1–160,000

PS performance status, *n* number, *P* cisplatin, *E* epirubicin, *F* 5-fluorouracil, *G* gemcitabine, *O* oxaliplatin, and *ULN* upper limit of laboratory normal

Table 2 Treatment summary

Regimen	No. of patients	CR/PR (%)	SD (%)	PFS-6 (%)	MOS	1-year-OS
PEFG	45	10 (22)	15 (33)	33	8.1	18
RO	35	9 (26)	10 (29)	17	5.4	11
G + O/P	21	4 (19)	7 (33)	29	8.2	24
OI	18	1 (6)	4 (22)	17	3.5	17
MDI	13	0	4 (31)	0	6.1	0
F/C + P/Ca/O	12	0	2 (17)	0	4.5	10
G	8	0	2 (29)	25	6.1	25
Others[a]	31	2 (6)	7 (23)	13	5.5	13

P cisplatin, *E* epirubicin, *F* 5-fluorouracil, *G* gemcitabine, *R* raltitrexed, *O* oxaliplatin, *M* mitomycin-C, *D* docetaxel, *I* irinotecan, *C* capecitabine, *Ca* carboplatin, *CR* complete response, *PR* partial response, *SD* stable disease, (*m*)*OS* (median) overall survival and *PFS-6* 6 months progression-free survival

[a] <7 patients per regimen

4.2–9.0 months). Stable disease was observed in 51 patients (27.9%) with a median duration of 4.7 months (interquartile range 3.6–7.9 months). Median and 6-month PFS (PFS-6) were 3.0 months and 20%, respectively. At the time of analysis, 179 patients had experienced PD, while four were PF at 6.0–8.0 months (median 7.0 months). One hundred and sixty-nine patients died of disease. Fourteen patients were alive with a median follow-up of 8.5 months (range 6.0–70.0 months). Median, 1-year and 2-year OS were 6.2 months, 17 and 4%, respectively (Fig. 1). Table 2 summarizes the main outcome measures based on chemotherapy regimen. Results of univariate and multivariate analyses of OS in the entire series are reported in Table 3.

Prognostic factors

Prior PFS, CA19.9 value and age were found to be independent prognostic factors in both univariate and multivariate analysis. Patients submitted to prior curative surgery did not have better survival compared with patients who had unresectable disease at first diagnosis. Similarly, patients receiving adjuvant first-line treatment did not have better survival when compared with patients who received first-line treatment for locally advanced or metastatic disease. The subsets of patients with early (i.e. with prior PFS < 6 month) or delayed failure were analysed separately, taking former treatment into account.

Outcome of patients with early failure

Among patients who had an early failure at first-line therapy, gemcitabine was included in salvage regimen in 24 of 50 patients formerly treated with single agent gemcitabine. A significant improvement of survival compared with 26 patients receiving combination chemotherapy without gemcitabine as second-line therapy was observed ($p = 0.002$). 5-FU including regimens were administered to 24 patients without any improvement of survival compared to 26 patients treated without 5-FU ($p = 0.15$). A platinum compound, consisting of cisplatin ($n = 24$), oxaliplatin ($n = 22$) or carboplatin ($n = 2$) was used in 48 out of 50 patients. The use of cisplatin was associated with longer survival compared with oxaliplatin ($p = 0.03$). Epirubicin use ($n = 17$; $p = 0.10$) did not significantly influence survival. The subgroups of patients treated with other agents included less than 15 patients.

Among 38 patients who had early (<6 months) progression while receiving upfront gemcitabine-based combinations, the administration of gemcitabine-including chemotherapy as second-line treatment ($N = 15$) was associated with longer survival when compared with the administration of regimens without gemcitabine ($N = 23$; $p = 0.04$). The use of 5-FU ($N = 15$; $p = 0.02$) was associated with better survival. The use of a platinum compound was not associated with better survival ($N = 21$; $p = 0.25$). The use of cisplatin was associated with longer survival compared with oxaliplatin ($p = 0.01$).

Outcome of patients with delayed failure

Among patients who had a prior PFS $\geq$ 6 months, 22 were previously submitted to single agent gemcitabine and 73 to gemcitabine-based combinations. Among patients of the former group, gemcitabine was resumed in six patients, obtaining a significant survival improvement ($p = 0.005$) when compared to 16 patients treated without gemcitabine at salvage. Neither platinum compounds ($N = 16$; $p = 0.13$) nor irinotecan ($N = 9$; $p = 0.35$) had a significant impact on survival. The other subsets of patients included six or less patients, thus not allowing any meaningful comparison.

Among patients who were submitted to a combination chemotherapy upfront, gemcitabine was resumed in 42 patients without achieving a better survival compared with other drugs ($p = 0.43$). Similarly, 5-FU ($N = 35$, 28 of those pre-treated with the same agent; $p = 0.21$), cisplatin ($N = 33$, 25 of those pre-treated with the same agent; $p = 0.26$), oxaliplatin ($N = 19$, 15 of those pre-treated with cisplatin; $p = 0.06$) and epirubicin ($N = 28$, 22 of those pre-treated with the same agent; $p = 0.21$) did not significantly influence survival in comparision with other drugs. The other subsets of patients included less than 15 patients.

Discussion

This multi-institutional retrospective series is an effort to identify patient- and disease-related prognostic factors for

Table 3 Impact on survival of patients and prior treatment related variables

Variable	Subgroups	No. of patients	Univariate			Multivariate	
			1-year OS	p^a	HR	95% CI	p
Prior surgery	Yes	64	21				
	No	119	16	0.13	1.02	0.57–1.84	0.95
Prior radiotherapy	Yes	47	22				
	No	136	17	0.11	0.90	0.57–1.43	0.66
First-line chemotherapy							
	Single agent	72	17				
	Combination	111	18	0.16	1.11	0.77–1.60	0.56
	Adjuvant aim	43	18				
	Therapeutic aim	140	18	0.24	0.76	0.40–1.43	0.39
Second-line chemotherapy							
	Single agent	16	20				
	Combination	167	18	0.25	0.91	0.50–1.64	0.75
PPFS	<6 mo.	88	11				
	>6 mo.	95	24	0.0005	0.56	0.39–0.79	0.001
Age	<60	84	26				
	>60	99	10	0.02	1.54	1.08–2.17	0.02
Gender	Male	106	15				
	female	77	22	0.24	1.09	0.78–1.54	0.61
PS	0	83	23				
	1–3	98	11	0.03	1.30	0.95–1.80	0.11
Stage	III	15	21				
	IV	168	17	0.01	1.97	0.78–4.93	0.15
Site:liver	Yes	95	16				
	No	65	16	0.25	0.84	0.52–1.38	0.50
Site: lung	Yes	30	19				
	No	130	16	0.44	1.04	0.64–1.70	0.87
Site: pancreas	Yes	116	14				
	No	44	22	0.11	1.31	0.74–2.33	0.35
Site: peritoneum	Yes	33	7				
	No	127	19	0.03	1.27	0.74–2.17	0.38
No. of sites	1	35	27				
	>1	125	13	0.002	1.10	0.58–2.08	0.78
CA19.9	<10 ULN	77	26				
	>10 ULN	100	12	0.02	1.45	1.02–2.07	0.04

Site of disease was unknown in 23 patients, PS was unknown in 2 cases, *pPFS* previous progression-free survival, *OS* overall survival, *PS* performance status, *HR* hazard ratio, *CI* confidence interval and *ULN* upper limit of laboratory normal

[a] log-rank test

second-line therapy of advanced pancreatic adenocarcinoma submitted to prior gemcitabine-containing chemotherapy. The present analysis shows that second-line chemotherapy could obtain interesting results. Our findings were comparable with those reported in another similar retrospective survey [25] in which 10% partial response, 25% stable disease and a median PFS of 2.65 months were observed [25]. While data on response rate and PFS may represent a rough estimate of treatment activity due to the retrospective and multi-centre nature of the analyses, implying the use of different chemotherapy regimens and timing of radiographic assessment, our survival datum, which is obviously more reliable, is similar to that achieved with upfront single agent gemcitabine [1–7]. Although it is likely that the subset of patients receiving salvage treatment is the result of a selection bias, as patients with very poor PS or with rapidly progressive disease are unlikely to receive further treatment, these data do suggest that patients with PD after upfront gemcitabine-containing chemotherapy may derive an indisputable survival benefit from second-line therapy. In fact, a randomized trial of salvage chemotherapy versus best supportive care showed that the expected median survival in patients who were assigned to the no-treatment arm was just 10 weeks [17]. Similarly, in a Japanese series of patients with gemcitabine-refractory pancreatic cancer who mainly

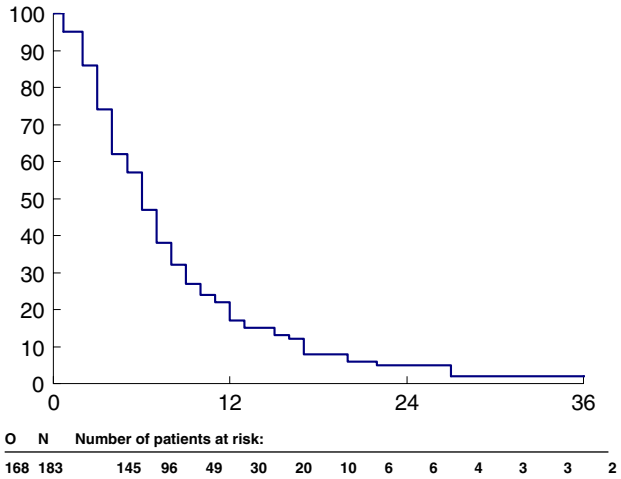

Fig. 1 Overall survival curve. *N* = number of eligible patients. *O* = total number of events at the final analysis. Subsequent numbers are the number of patients at risk

received best supportive care at time of progression, median survival was 2 months [26].

Prognostic factors at the time of upfront treatment failure are largely unknown, as they were rarely assessed in former series [14, 25, 26]. The current study suggests that second-line chemotherapy might be particularly worthwhile in younger patients with previous PFS $\geq$ 6 months and a CA19.9 value $\leq$ 10 upper limit of laboratory normal. The prognostic value of previous PFS $\geq$ 6 months was also suggested in a prospective series [14]. Since maximum duration of chemotherapy in the treatment policy of the centres involved in the current analysis was 6 months, this cut off value of PFS roughly separates patients with progressive disease during treatment from patients whose disease progressed after the conclusion of treatment, which is suggestive of partial chemosensitivity as a minimum. Another possible reason for our finding is that the lack of activity of upfront treatment in patients with early PD entails a greater disease burden with a lower chance of disease control at the time of salvage compared with patients with SD or PR. Other variables, such as PS, peritoneal disease, stage and number of involved organs, which had a significant impact on survival at univariate analysis, were not confirmed as independent prognostic factors in the multivariate analysis. The comparison of our results with those from other series is problematic, as previous PFS was never taken into account [25, 26]. Furthermore, results of an Italian/Swiss survey are available only in abstract form; this trial was still ongoing at the time of report and the impact of different variables on overall survival had not been assessed [25]. The Japanese series identified PS, peritoneal dissemination and C-reactive protein as predictors of survival [26]. However, the population included in this survey was mainly constituted of patients who did not receive any treatment at time of failure. This implies different selection criteria and underlying questions, while it does not provide any relevant information on the population who are more likely to derive some advantage from salvage therapy. Moreover, the multicentre and retrospective nature of all these studies does not allow the drawing of definitive conclusions, and a confirmatory analysis on a prospective series is thus warranted.

No clear guidelines driving second-line chemotherapy choice are available. Exploratory analyses to identify drugs yielding greater impact on survival were performed in the current study in order to provide helpful information for clinical practice. All of the current findings must be considered with caution, due to large number of statistical tests performed, and the consequent possibility of spurious associations, as well as to the heterogeneous regimens and schedules used and the small size of each subgroup. Nevertheless, they constitute a reasonable attempt to delineate several therapeutic indications for clinical practice in the absence of higher-level evidence. It is noteworthy that the use of a combination chemotherapy as second-line treatment did not improve survival when compared to single agent administration.

Among patients for whom gemcitabine-refractory disease could be arbitrarily assumed, based on PD experienced during the administration of upfront single-agent gemcitabine, the use of gemcitabine-based combinations obtained a significantly better survival when compared to other regimens. The time interval between treatment and progression after which a tumor may be defined as refractory to a given agent is somewhat arbitrary and differs in different tumor types. Current data suggest that despite tumor escape within 6 months of the initiation of treatment, gemcitabine may retain a residual synergistic activity when combined with appropriate agents. Another survey suggested that fluoropyrimidine-platinum doublets may have an impact on survival [25]. Platinum compounds were administered in 96% of our patients with early PD after upfront single-agent gemcitabine. Accordingly, no comparative information concerning the role of platinum compounds in comparison with other drugs is available. On the other hand, our findings suggest that cisplatin is preferable to oxaliplatin due to a possibly better impact on survival. No clear benefit was associated with the administration of epirubicin or 5-FU compared to other agents.

Among patients with early PD after upfront gemcitabine-based combinations, gemcitabine seems to maintain a role also when included in second-line combinations. Again, cisplatin appears to obtain a better survival impact than oxaliplatin. 5-FU seems to improve survival while the use of other drugs was infrequent.

With regard to patients with prior PFS $\geq$6 months, gemcitabine-based combinations confirmed their potential role, at least in patients who previously received single agent therapy, while no clear indication emerged for other agents.

In conclusion, our study suggests that patients with advanced pancreatic adenocarcinoma who experience PD after gemcitabine-based chemotherapy, and are willing to receive further treatment for their disease, may obtain some survival benefit from second-line chemotherapy. Re-challenge with gemcitabine and 5-FU administration may have a role in selected patients. Combination chemotherapy should be recommended with caution as a second-line treatment, due to the lack of data suggesting a relationship with improved survival. Previous PFS probably represents the main prognostic factor in this patient population, and may constitute a useful tool to inform discussion with patients and to drive therapeutic choices. This variable should be reported in prospective trials of second-line chemotherapy for advanced pancreatic adenocarcinoma to facilitate the comparative analysis of results and to favor adequate assessment of new therapeutic strategies deserving further evaluation.

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