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ORIGINAL ARTICLE

Second-line chemotherapy with Capecitabine (Xeloda) and Docetaxel (Taxotere) in previously treated, unresectable adenocarcinoma of pancreas: the final results of a phase II trial

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Abstract
Purpose To investigate the efficacy and toxicity of the docetaxel and capecitabine combination in patients with previously treated, unresectable adenocarcinoma of the pancreas.
Patients and Methods Patients with pancreatic adenocarcinoma, pre-treated with gemcitabine-based chemotherapy, were treated with capecitabine (800 mg/m^2 orally, twice a day for 14 days) and docetaxel (75 mg/m^2 i.v, on day1), every 3 weeks. The primary end-point was overall response rate (RR).
Results Thirty-one patients were enrolled in the study; 93.6% of them had a performance status (PS) of 0–1 and 96.8% had stage IV disease. Patients received a median of 4 cycles/patient, and the main reason for treatment discontinuation was disease progression. Partial response was observed in three (9.7%) patients, stable disease in seven (22.6%) (disease control rate: 32.3%, 95% CI: 15.80–48.71%) and disease progression in 21 (67.6%). The median progression-free survival (PFS) was 2.4 months (95% CI: 1.6–3.13) and the median overall survival (OS) was 6.3 months (95% CI: 3.38–9.23); the estimated 1-year survival rate was 14.7%. Grade III/IV neutropenia occurred in 10 (32.2%) patients and febrile neutropenia in one patient. Other severe non-hematologic toxicities were mild and manageable. After 2 chemotherapy cycles, pain control occurred in 20% of patients and stabilization of body weight in 40%.
Conclusion The combination of docetaxel/capecitabine may confer good disease control associated with improvement of quality of life as second-line chemotherapy in patients with metastatic pancreatic cancer.

Keywords Capecitabine · Docetaxel · Phase II trial · Pancreas

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Introduction

Adenocarcinoma of the pancreas is responsible for almost 6% of cancer-related deaths [1]. For all patients combined, the 1- and 5-year relative survival rates for this disease are only 24 and 5%, respectively. Up to 60% of patients have advanced pancreatic cancer at the time of diagnosis. The median survival of patients with locally advanced disease is 6–10 months, and for patients with metastatic disease, 3–6 months [2].

Fixed dose rate gemcitabine [3], or combination chemotherapy of gemcitabine with other cytotoxic agents such as oxaliplatin [4], or cisplatin [5], is currently used for first-line chemotherapy for locally advanced or metastatic disease.

Data for second-line chemotherapy in patients with advanced/metastatic pancreatic cancer are limited since the majority of progressing patients after first-line chemotherapy have poor performance status. Moreover, another reason that limits the therapeutic options for second-line treatment in these patients is the lack of active agents.

Nevertheless, there is some evidence from previous studies that some selected patients with adenocarcinoma of pancreas would benefit from more chemotherapy after failing single-agent gemcitabine or another first-line chemotherapy combination [6].

Capecitabine is an oral fluopyrimidine which offered a response rate of 24% when tested as first-line treatment [7, 8] for locally advanced or metastatic pancreatic cancer, suggesting a role in gemcitabine refractory disease. Capecitabine has also been combined with Oxaliplatin with encouraging results [9, 10]. Docetaxel is a semisynthetic taxane with a broad spectrum of antitumor activity. It has been previously investigated as single agent in phase II trials [11], with an objective response rate of 15% and stable disease rate of 38%.

The combination of docetaxel and capecitabine (DC regimen) was investigated in a phase I study in patients with various solid tumors [12]. The DC regimen has since been safely used in several disease settings, including gastric adenocarcinoma and breast cancer [13, 14]. Preliminary results of a phase II trial using the DC combination as second-line treatment for locally advanced and metastatic adenocarcinoma of pancreas were presented in the 2007 ASCO Annual Meeting [15]. The treatment was well tolerated and the response rate was 12.5%, while 70.8% of patients had stable disease for 2 or more cycles of treatment. The final results of this trial are pending.

The aim of the current phase II study, conducted by the Hellenic Oncology Research Group (HORG), was to evaluate the efficacy and tolerance of the DC regimen as second-line chemotherapy in patients with advanced/metastatic pancreatic cancer.

Patients and methods

Patient population

Eligible patients had to meet the following criteria: age >18 years, histologic confirmation of locally advanced or metastatic adenocarcinoma of the pancreas, one prior chemotherapeutic regimen with a gemcitabine-based combination, at least one bidimensionally measurable target lesion (i.e., lesions $\geq$2 cm other than the primary or $\geq$1.5 cm in case of lung metastasis, outside any previous eradicated area), WHO Performance Status (PS) of 0 to 2, recovery of the effects of previous chemotherapy, adequate hematologic function (defined as neutrophils >1,500/mm^3, platelets >100,000/mm^3, Hb > 10mgr/dl), adequate liver function (defined as bilirubin levels $\leq$1.5 times the institutional upper normal limit [ULN], after biliary drainage if previously abnormal, and as AST and alkaline phosphatase $\leq$2.5 times the UNL, or $\leq$5 times the UNL for patients with liver metastasis), normal renal function (defined as serum creatinine $\leq$1.5 times the UNL), absence of ascites. Patients with other primary tumors within the last 10 years were excluded from the study, except adequately treated in situ cervical carcinoma, and basal or squamous cell skin carcinoma.

Patients were also excluded from the study if they had symptomatic central nervous system metastasis or carcinomatous meningitis, a psychiatric disorder, active uncontrolled infection, a myocardial infarction within the last 12 months or congestive heart failure or cardiac arrhythmias not controlled on medication.

All patients have given their written informed consent before their enrollment to the study. The protocol has been approved by the Ethics and the Scientific Committees of the participating institutions.

Treatment plan

Docetaxel (Taxotere; Sanofi-Aventis, Bridgewater, NJ, USA) was given at a dose of 75 mg/m^2, on day 1 every 21 days, following pre-medication with dexamethasone 8 mg twice daily on days 0, 1, 2, for a total of 3 days. Capecitabine (Xeloda; Roche, Zurich, Switzerland) was given at a dose of 800 mg/m^2, orally, twice a day, from day 1 to day 14 of a 21-day cycle, starting the first dose at least 1 h after the first dose of Docetaxel. The chemotherapy regimen was continued for a total of 6 cycles, unless the patient suffered from an unacceptable chemotherapy adverse event or disease progression.

Patients with a PS $\geq$ 2 had the first cycle with a 20% dose reduction for both docetaxel and capecitabine; if the treatment was well tolerated, patients had to receive the subsequent chemotherapy cycles at the full protocol dose.

Response and toxicity evaluation

Response or progression were evaluated using the 2009, revised Response Evaluation Criteria in Solid Tumors (RECIST) [16]. Objective responses either complete (CR) or partial (PR) were to be confirmed at least 4 weeks later. Toxicities were graded according to the National Cancer Institute Common Toxicity Grading Criteria, version 2 [17] initially, and the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) after these were published (August, 2006).

Treatment was interrupted for $\geq$grade 2 toxicity (with the exception of alopecia, nausea or vomiting and anemia), and it was not restarted until improvement either complete or at least to a grade 1. Dose reduction for capecitabine or docetaxel was not necessary for the first occurence of a grade 2 toxicity. A second and a third occurence of a grade 2 event required a 20 and 40% dose reduction of both

drugs, respectively. The occurrence of ≥grade 3 toxicity required a 20% dose reduction of both drugs. In case of >grade 2 hand-foot syndrome, mucositis or diarrhea the dose of capecitabine had to be reduced by 25%. Patients who required more than two dose reductions as well as in the case of unresolved toxicity (>grade 1) 3 weeks after the last chemotherapy cycle had to be withdrawn from the study. Maximum delay for a chemotherapy cycle was up to 3 weeks. Granulocyte-Colony Stimulating Factor (G-CSF) could be administered for symptomatic neutropenia, but not prophylactically.

Pain assessment was made at baseline and every 6 weeks. Pain was assessed using the Memorial Pain Assessment Card. QoL was evaluated using the European Organisation for Research and Treatment of Cancer (EORTC) core QoL questionnaire (EORTC QLQ-C30) and European Study Group for Pancreatic cancer (ESPAC) QoL questionnaire pancreatic-specific module.

Statistics

This was a multicenter, single arm, open label, phase II study. The primary end-point of the study was the efficacy of the regimen in terms of objective response rate (CR, PR). Secondary end-points were the disease control rate, the progression-free survival, the overall survival and the toxicity profile of the regimen. Some investigators have used the cutoff of 5% response rate as significant [18]; others have used the 10% [19]. In any case, this assumption lacks any evidence and is based mainly on the RR that has already been achieved by other chemotherapy regimens in the past. We have decided that we would consider as significant any second-line regimen for metastatic pancreatic cancer associated with a ≥7% response rate, and any response rate equal or above that would be of further interest, but anything below would be unacceptable, as other regimens have been able to achieve better outcome. The study design employed a one-stage design with 31 eligible patients, with the assumption that if at least two of the 31 patients showed response, then the regimen would be considered to be of further interest for the patient population. Secondary end-points of this study included the duration of response, the progression-free survival, the overall survival, the toxicity profile and the quality of life of patients with locally advanced or metastatic adenocarcinoma of the pancreas previously treated with a gemcitabine-based chemotherapy combination.

Survival curves were estimated using the Kaplan–Meier method and Life tables. Safety analysis was carried out on the treated population using contingency tables and descriptive statistics. Statistical significance was set to be 0.05.

All clinical data were centrally collected and analyzed. Duration of tumor response is measured from the date the first objective response (complete or partial) was observed to the first date of tumor progression or death from any cause. The time to tumor progression (TTP) was measured from study entry until the day of the first evidence of disease progression whereas overall survival (OS) was measured from study entry to death or last contact. All patients who received at least 2 chemotherapy cycles were assessable for response, and all patients who received at least 1 cycle of chemotherapy were evaluated for toxicity.

Compliance with the EORTC QLQ-C30 was low, and QoL scores could not be calculated from all the patients, especially after the first two cycles of chemotherapy. We have decided that in the present study we could only present the percentage and number of patients experiencing disease-related symptoms that had an effect on the quality of their life, at baseline and after the first two cycles of chemotherapy without making specific statistical comparisons.

Results

Patient demographics

Between 08/05/2006 and 15/5/2009, 31 patients were enrolled in this study all over Greece. Baseline patient and disease characteristics are presented in Table 1. The patients' median age was 63 years and 19 (61.3%) were men. Most of the patients had a PS 0–1 (71.0%), all but one patients had stage IV disease and 26 (83.2%) had more than two organs involved. All patients had received first-line chemotherapy with gemcitabine either as a single agent or as combination treatment. Thirteen (41.9%) patients had previously received front-line treatment gemcitabine with erlotinib and 22 (71%) patients had previously been treated with a non-platinum-based regimen. The median interval from the previous treatment was 1.33 months (min–max: 0.23–8.87).

Compliance with treatment

The total number of chemotherapy cycles, median cumulative chemotherapy dose, dose intensity, reasons for treatment discontinuation are all summarized in Table 2. Overall, the DC regimen was found to be well tolerated, despite the fact that only 16.1% of patients managed to complete chemotherapy. There were two patients who discontinued treatment because of grade III neutropenia, grade I anemia, grade II diarrhea, and grade II mucositis ($n = 1$ patient) and consent withdrawn ($n = 1$ patient).

Table 1 Patient characteristics

	N (31)	%
Age		
Median (min–max)	63 (44–79)	
Sex		
Male	19	61.3
Female	12	38.7
Performance status		
0	7	22.6
1	22	71.0
2	2	6.5
Stage		
IIIB	1	3.2
IV	30	96.8
Anatomic cancer site		
Head of pancreas	15	48.8
Body of pancreas	7	22.6
Tail of pancreas	2	6.5
Ampulla of Vater	3	9.7
Head and ampulla of vater	1	3.2
Body and tail	2	6.5
Degree of differentiation		
Well differentiated	4	12.9
Moderately differentiated	7	22.6
Poorly differentiated	5	16.1
Unknown	15	48.4
Response to previous treatment		
PR	3	9.7
SD	7	22.6
PD	20	64.5
NE	1	3.2
Organs involved		
Pancreas	23	74.2
Liver	20	64.5
Nodes	14	45.2
Lung	11	35.5
Peritoneum	3	9.7
Bones	1	3.2
Other	6	19.4

Table 2 Compliance with the treatment

	N	%
Total no of cycles	123	
Median no of cycles/ patient (range)	4 (1–9)	
Treatment completed as per protocol	5	16.1
Actual dose intensity (mg/m^2/week)		
Capecitabine		
Median (range)	6222.22 (1239.32–7467.00)	
Docetaxel		
Median (range)	22.22 (10.77–25.00)	
Relative dose intensity* (%)		
Capecitabine		
Median (range)	83.33 (16.60–100.00)	
Docetaxel		
Median (range)	88.88 (43.08–100.00)	
Reason for treatment discontinuation		
Disease progression	20	64.5
Adverse event (treatment related)	1	3.2
Denial	2	6.5
Death	2	6.5
Ongoing	1	2.7
No of patients with dose reductions and delays		
≥1 cycle with dose reduction	13	41.9
≥1 cycle with delay	13	41.9

* Actual dose intensity/planned dose intensity

Eleven (35.48%) patients received the treatment without dose reductions or delays, whereas six (19.35%) had dose reductions and treatment delays.

Response and survival

All patients were evaluated for response in the context of an intention-to-treat analysis. A partial response was achieved in three (9.7%; 95% CI: 0–20.09%) patients and stable disease (SD) in seven; 21 (67.7%) patients had disease progression (PD). Treatment was not evaluated in one patient for logistical reasons and the patient was characterized as progressor. The overall disease control rate (DCR) was 32.2% (95% CI: 15.80–48.71%). Among the 22 patients who had previously been treated with a non-platinum-based regimen, seven (31.8%) experienced disease control (PR + SD group); the same was observed in three (33.3%) out of nine patients who had previously been treated with a platinum-based regimen ($P = 0.935$). There was no difference in terms of response rate according to PS (0–1 vs. 2; $P = 0.558$).

After a median follow-up period of 14.5 months (range: 1.33–23.60), 30 (6.8%) patients experienced disease progression. The median time to progression was 2.37 months (range, 0.90–7.43; 95% CI: 1.60–3.13). No evidence of disease progression for >6 months was documented in two (6.5%) patients. The estimated 1-year progression-free survival (PFS) rate was 3.2% (Fig. 1). PFS was 5.1 months for patients who experienced disease control (PR + SD) and 2.07 months for patients with PD ($P < 0.001$).

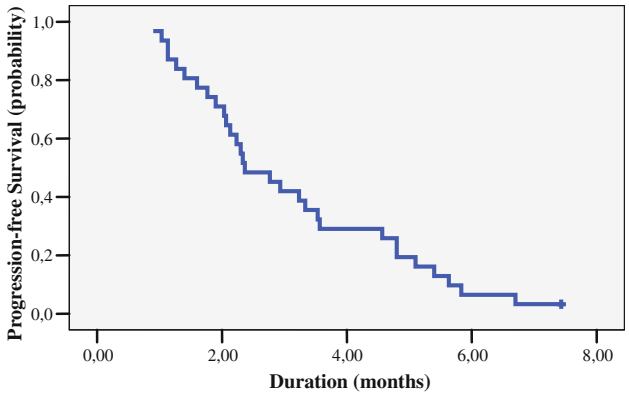

Fig. 1 Progression-free survival curve for patients treated with Docetaxel and Capecitabine

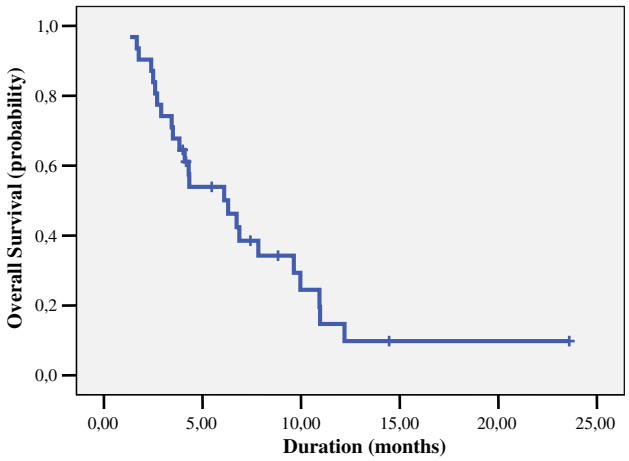

Fig. 2 Kaplan–Meier overall survival curve of patients treated with Docetaxel and Capecitabine

Twenty-four (77.4%) patients died due to disease progression during the follow-up period. The median overall survival (OS) was 6.3 months (range, 1.33–12.20; 95% CI: 3.38–9.23). Fourteen (45.2%) patients were alive for at least 6 months after enrollment. The estimated 1-year OS was 14.7% (Fig. 2).

Symptom control

All 31 patients completed QoL questionnaires at baseline and all but one, after 2 cycles of treatment. The number of patients available for QoL assessment decreased markedly after the second cycle of treatment, mainly because of symptom worsening and disease progression. The major benefit of chemotherapy was observed in patients after they had received 2 cycles of chemotherapy, and this effect was either maintained further (as observed in the very few patients that QoL was further assessed), or deteriorated toward the last period of treatment. Table 3 indicates the effect of treatment on the main disease-related symptoms. Pain was a major clinical problem in 58.1 and 38.7% of patients at enrollment and after 2 cycles of treatment, respectively. In addition, analgesia was used by 48.4 and 32.3% of patients at enrollment and after 2 chemotherapy cycles, respectively. Moreover, 32.3% of patients used opioids at baseline and this was reduced to 25.8%, after 2 cycles of treatment. In addition, 38.7% of the treated patients maintained their body weight.

Table 3 Incidence of disease-related symptoms at enrollment and after 2 cycles of chemotherapy

Disease-related symptoms	At baseline		After 2 cycles of treatment	
	N	%	*N*	%
Pain	18	58.1	10	32.3
Use of analgesics	15	48.4	10	32.3
Use of opiods	10	32.3	8	25.8
Fatigue	18	58.1	14	45.2
Weight loss	14	45.2	2	6.5

Table 4 Chemotherapy-induced adverse events

	GrI		*GrII*		*GrIII*		*GrIV*	
	N	%	*N*	%	*N*	%	*N*	%
Neutropenia	2	6.5	–	–	5	16.1	5	16.1
Febr./neutropenia	–	–	–	–	–	–	1	3.2
Anemia	14	45.2	11	35.5	–	–	1	3.2
Thrombocytopenia	8	25.8	–	–	–	–	1	3.2
Nausea	3	9.7	–	–	–	–	–	–
Vomiting	2	6.5	1	3.2	–	–	–	–
Constipation	2	6.5	1	3.2	–	–	–	–
Diarrhea	2	6.5	5	16.1	–	–	–	–
Stomatitis	1	3.2	2	6.5	1	3.2	–	–
Hand-Foot syndrome	2	6.5	–	–	–	–	–	–
Neurocensory	1	3.2	–	–	–	–	–	–
Neuromuscular	–	–	1	3.2	–	–	–	–
Allergy	–	–	1	3.2	–	–	–	–
Infection	–	–	–	–	–	–	–	–
Fatigue	5	16.1	7	22.6	2	6.5	–	–

Toxicity

The most common adverse event associated with the capecitabine/docetaxel combination chemotherapy was hematologic toxicity. Ten (32.3%) patients developed grade III–IV neutropenia but febrile neutropenia complicated treatment in only one patient (3.2%). All patients were treated with G-CSF support, and antibiotics were given prophylactically.

One patient developed grade IV thrombocytopenia without clinical evidence of bleeding; the patient had an uneventful recovery without necessitating hospitalization. There were no treatment-related deaths. Non-hematologic toxicity was mild (Table 4).

Discussion

Second-line chemotherapy for adenocarcinoma of the pancreas remains a major therapeutic challenge. Patients that have failed first-line chemotherapy, with a gemcitabine-based combination, are currently not able to be treated with an alternative chemotherapy that has proved as good as the first-line treatment. Standard of care needs to be established for this group of patients. There is evidence from previous studies that some of these patients may benefit from additional chemotherapy versus best supportive care (BSC) [6]. The NCCN Panel recommends that for patients with gemcitabine refractory disease, treatment should be delivered within a clinical trial [20].

The combination of capecitabine and docetaxel, which has been tested in the current study, was extremely well tolerated without major adverse events. However, only 16.1% of patients managed to complete the 6 chemotherapy cycles as per protocol. The main reason for treatment discontinuation was disease progression since only one patient, with febrile neutropenia, decided to stop treatment due to treatment-related toxicity. The main severe adverse event was grade III-IV neutropenia occurring in 32.3% of patients. Other severe toxicities were mild occurring in less than 5% of the treated patients. There were no documented treatment-related deaths.

Quality of life becomes extremely important when we deal with an aggressive and resistant to standard treatment disease, such as the adenocarcinoma of pancreas. This is even more important when we refer to second-line chemotherapy. In the present study, the DC regimen was associated with a clinical benefit, since almost half the patients that complained of some degree of pain at baseline had experienced good pain control (from 58.1% of patients initially to 32.3%) and 16.1% of patients, that used analgesia initially, stopped using it. An important proportion of patients (38.7%) maintained their body weight. Notably, this clinical benefit was observed without severe treatment-related adverse events. Unfortunately, we are not able to comment on QoL after the first two cycles of treatment (6 weeks), but we could assume that as disease control was gradually decreasing, symptom control was also deteriorating. With the DC regimen, patients have achieved a PFS of 2.4 months as described in detail above, and the fact is that most of them experienced good symptom control during this period.

The capecitabine/docetaxel combination resulted in a 9.7% objective response rate and a DCR of 32.2%. Moreover, 6.5% of patients did not have disease progression for at least 6 months whereas 53.9% of patients were alive for more than 6 months and 14.7% for more than 1 year. In addition, the data showed that patients achieving disease control have a significantly longer PFS compared to patients who failed to respond to treatment; for patients with a pancreatic cancer, it is important to achieve a delay to disease progression with a well-tolerated treatment that could at least partially explain the observed improvement of patients' quality of life. In any case, these results are in agreement with the reported preliminary data of a similar phase II trial of docetaxel/capecitabine as second-line chemotherapy for adenocarcinoma of the pancreas showing a PR rate of 12.5% [15]. Furthermore, the efficacy results of the DC regimen, reported in the current study, are practically similar to those reported in other studies, evaluating second-line treatment for pancreatic adenocarcinoma. However, most of these studies are small phase II trials with a limited number of patients [15, 21–23]. This is probably due to the patients' poor PS and, only few relapsing or progressing patients after first-line treatment preserve a PS good enough for second-line chemotherapy.

Several anticancer drugs used either as single agents or in combination regimens have been tested as second-line treatment for adenocarcinoma of the pancreas. Indeed, rubitecan has offered a 7% PR and 16% SD [24], whereas a 3.8% PR and 19.2% SD was achieved with pemetrexed [25]. In addition, paclitaxel was also found active with one patient from the 18 tested achieving CR and five patients SD [26]. Capecitabine was also found a safe and well-tolerated option with 39% of patients achieving SD [7] with a median survival of 7.6 months. More recently, S-1 resulted in a 15% PR and in a 43% SD as second-line chemotherapy in patients with a median survival of 4.5 months when tested in pre-treated patients with pancreatic cancer [27]. Combination chemotherapy based on oxaliplatin has also been tested, as second-line treatment for patients with advanced adenocarcinoma of the pancreas, that has failed single-agent gemcitabine. This agent has been combined with gemcitabine [28], capecitabine [10, 29], irinotecan [30], pemetrexed [31] or raltitrexed [32]. The results showed an overall response rate ranging from 3% for the oxaliplatin/capecitabine [10] to 24% for oxaliplatin/raltitrexed [32] and an OS ranging from 5.2 to 6 months, respectively. The CONKO-003 study has tested the Oxaliplatin, and 5FU/FA (OFF) combination versus the 5FU/FA as second-line treatment in patients with gemcitabine refractory pancreatic cancer. The authors conclude that treatment with OFF results in a significant improvement in PFS [13 weeks (95%CI 11.46–14.55) vs. 9 weeks (95% CI, 7.38–10.61),

$P = 0.012$] and OS [26 weeks (95% CI 19.56–32.41) vs. 13 weeks (95% CI 10.01–15.99) $P = 0.14$] [33].

Cis-platin-based chemotherapy has also been used in the second-line setting in patients with advanced adenocarcinoma of the pancreas. This agent when combined with gemcitabine [34] resulted to a PR rate of 8.3% and to SD rate of 58.3% of patients with a median OS of 4 months. Cisplatin was also used with gemcitabine, irinotecan and 5-FU/Leucovorin, in a very intense 2-day regimen [35]; the observed PR rate was 24% and the SD rate was 20.5% whereas the median OS was 10.3 months. More recently, the combination of cisplatin and S-1 resulted in a 29.4 and 11.8% of PR and SD, respectively, with a median OS of 10 months [33]. All these studies clearly indicate that despite the efficacy of the different regimens in terms of objective response rate the observed median OS is more or less similar and not more than 10 or 11 months.

A triple combination with docetaxel/gemcitabine/capecitabine resulted to an overall response rate of 29% with an OS of 11.2 months [36] whereas the combination of docetaxel/mitomycin-C/irinotecan was associated with a median OS of 6.1 months [34]. We can speculate that it is still unclear whether triple combinations in the second-line setting can offer substantial benefit to patients with pancreatic carcinoma.

In our study, previous treatments (both platinum-based or not) made no difference, to the final outcome. The same applies to PS. Obviously PS is essential, for patients to be able to have and complete any kind of treatment, but as long as patients have a PS ≤ 2, the combination of docetaxel and capecitabine is active and worth trying.

In conclusion, the results of the present study indicate that the combination of docetaxel and capecitabine is well tolerated and shows a degree of activity when used as second-line treatment for patients with advanced adenocarcinoma of the pancreas. Moreover, this regimen offers a benefit to the quality of life. Therefore, this combination merits to be used in the palliative setting in patients who progress under standard first-line chemotherapy. Further investigation is required to achieve a more satisfactory response for a second-line treatment in this disease setting.

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Conflict of interest statement None.

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