

Combining gemcitabine, oxaliplatin and capecitabine (GEMOXEL) for patients with advanced pancreatic carcinoma (APC): a phase I/II trial

V. Hess^{1*}, S. Pratsch¹, S. Potthast², L. Lee¹, R. Winterhalder³, L. Widmer⁴, C. Cescato⁵, A. Lohri⁶, L. Jost⁷, P. Stillhart¹, B. Pestalozzi⁸ & R. Herrmann¹

Departments of ¹Medical Oncology; ²Radiology, University Hospital Basel; ³Department of Medical Oncology, Cantonal Hospital Lucerne; ⁴Onkozentrum Hirslanden, Zurich; ⁵Department of Medical Oncology, St Clara Hospital Basel; ⁶Department of Medical Oncology, Cantonal Hospital Liestal; ⁷Department of Medical Oncology, Cantonal Hospital Bruderholz; ⁸Department of Medical Oncology, University Hospital Zurich, Switzerland

Received 11 March 2010; revised 25 March 2010; accepted 25 March 2010

Background: Gemcitabine remains the mainstay of palliative treatment of advanced pancreatic carcinoma (APC). Adding capecitabine or a platinum derivative each significantly prolonged survival in recent meta-analyses. The purpose of this study was to determine dose, safety and preliminary efficacy of a first-line regimen combining all three classes of active cytotoxic drugs in APC.

Patients and methods: Chemotherapy-naïve patients with locally advanced or metastatic, histologically proven adenocarcinoma of the pancreas were treated with a 21-day regimen of gemcitabine [1000 mg/m² day (d) 1, d8], escalating doses of oxaliplatin (80–130 mg/m² d1) and capecitabine (650–800 mg/m² b.i.d. d1–d14). The recommended dose (RD), determined in the phase I part of the study by interpatient dose escalation in cohorts of three to six patients, was further studied in a two-stage phase II part with the primary end point of response rate by RECIST criteria.

Results: Forty-five patients were treated with a total of 203 treatment cycles. Thrombocytopenia and diarrhea were the toxic effects limiting the dose to an RD of gemcitabine 1000 mg/m² d1, d8; oxaliplatin 130 mg/m² d1 and capecitabine 650 mg/m² b.i.d. d1–14. Central independent radiological review showed partial remissions in 41% [95% confidence interval (CI) 26% to 56%] of patients and disease stabilization in 37% (95% CI 22% to 52%) of patients.

Conclusion: This triple combination is feasible and, by far, met the predefined efficacy criteria warranting further investigations.

Key words: capecitabine, gemcitabine, oxaliplatin, pancreatic cancer

introduction

Gemcitabine remains the mainstay of medical treatment of advanced pancreatic carcinoma (APC), a disease with increasing incidence [1]. Disappointingly, results of the vast majority of large clinical trials studying gemcitabine-based combinations—including combinations with novel targeted drugs—did not meet expectations and survival for patients with APC remains short with a median survival time between 4 and 8 months [2, 3].

Yet, small but important progress has been made. For the first time since Burris' pivotal trial in 1997 [4], a significant survival gain for gemcitabine-based chemotherapy combinations as compared with gemcitabine monotherapy was shown in two meta-analyses. The combination of gemcitabine with either of two classes of cytotoxic drugs—capecitabine [5]

or a platinum derivative [6]—each resulted in lengthened overall survival.

Adding capecitabine, an oral fluoropyrimidine, to standard gemcitabine reduced the hazard of death by 14% [hazard ratio (HR) 0.86, 95% confidence interval (CI) 0.75–0.98, $P = 0.02$] in a pooled analysis of 935 patients from three randomized controlled trials (RCTs) [5, 7, 8]. The increase in toxicity for the doublet was manageable consisting mainly of neutropenia (not febrile) and hand-foot syndrome (HFS). Quality of life during chemotherapy—a secondary end point in the two larger RCTs [5, 7]—did not deteriorate in the combination arm [9].

Similarly, adding the platinum-derivative oxaliplatin to gemcitabine led to an increase in objective response rate (RR; 17.3% versus 26.8%, $P = 0.04$) and progression-free survival (3.7 versus 5.8 months, $P = 0.04$) but not to a significantly lengthened survival in any single RCT [10, 11]. However, in a large meta-analysis of 15 RCTs including 4465 patients, the hazard of death was reduced by 15% (HR 0.85, 95% CI 0.76–0.96, $P = 0.01$) for all platinum-based gemcitabine combinations [6]. Of note, clinical benefit ratio (CBR)

*Correspondence to: Dr V. Hess, Department of Medical Oncology, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland. Tel: +41-61-265-50-74; Fax: +41-61-265-53-16; E-mail: vhess@uhbs.ch

significantly improved by adding oxaliplatin to gemcitabine from 26.9% to 38.2% ($P = 0.03$) [10]. Gain in CBR was one of the hallmarks of gemcitabine monotherapy when introduced as a standard treatment in 1997 [4].

This prospective, multicenter phase I/II trial examines dose, safety and preliminary efficacy of a triple combination of the three most active cytotoxic drugs in APC—gemcitabine, oxaliplatin and capecitabine (GEMOXEL).

patients and methods

patients

Chemotherapy-naïve patients with histologically confirmed diagnosis of locally advanced inoperable and/or metastatic adenocarcinoma of the pancreas were eligible. Further inclusion criteria comprised a Karnofsky performance status (KPS) of at least 60%, either measurable disease on computed tomography (CT) scan or serum tumor marker CA 19-9 concentration $>1.5 \times$ the upper limit of laboratory normal (ULN) and age >18 years.

Patients were not eligible if they had received any prior chemotherapy for pancreatic cancer (including adjuvant chemotherapy). Prior adjuvant radiotherapy or concomitant radio-chemotherapy for pancreatic cancer was allowed if it was completed >12 months before study inclusion. Other exclusion criteria included known central nervous system metastases at the time of enrollment, clinically significant cardiac disease (New York Heart Association Class III–IV) or myocardial infarction within the previous 12 months, neurological disease with dys/paresthesia $>$ grade 1 according to National Cancer Institute—Common Toxicity Criteria (NCI–CTC), any serious concomitant disorder incompatible with trial participation (in the judgment of the investigator) or a psychiatric disability thought to be clinically significant in the opinion of the investigator precluding informed consent or interfering with compliance. Laboratory values that precluded trial participation were absolute neutrophil count $\leq 1.5 \times 10^9/l$, platelet count $\leq 100 \times 10^9/l$, hemoglobin ≤ 100 g/l, serum creatinine $>1.25 \times$ ULN, aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase >2.5 or >5 ULN in the presence of liver metastases and bilirubin >1.5 ULN (after treatment of obstructive jaundice, e.g. stent). Written informed consent was obtained from each patient.

treatment

Treatment consisted of six cycles of a 3-week regimen of gemcitabine (Gemzar®, Eli Lilly, Vernier, Switzerland) given at fixed doses of 1000 mg/m² i.v. over 30 min on d1 and d8, oxaliplatin (Eloxatin®, Sanofi Aventis, Meyrin, Switzerland) given in escalating doses i.v. over 120 min on d1 and capecitabine (Xeloda®, Roche, Pharma, Remach, Switzerland) given orally twice daily for 28 doses d1 through d14. After completing six cycles, treatment with this regimen was continued in responding patients at the discretion of the investigator. Dose was escalated in cohorts of three to six patients according to the following scheme:

Dose level	Oxaliplatin (mg/m ² d1)	Capecitabine (mg/m ² × 28 doses)
1	85	650
2	100	650
3	115	650
4	130	650
5	130	800
6	130	900

If one of three patients experienced dose-limiting toxicity (DLT) during the first two cycles, three more patients were included at the same dose level. If two or more patients experienced DLT, the previous dose level was considered the recommended dose (RD) and all patients of the phase II part of the study were treated at the RD.

DLTs were defined as any of the following: grade 4 neutropenia lasting ≥ 7 days or febrile neutropenia; grade 4 thrombocytopenia and grade 3/4 gastrointestinal symptoms (diarrhea, vomiting or mucositis), which were not reduced to grade 1 within 2 days of appropriate supportive care; grade 3/4 skin toxicity, e.g. palmo-plantar erythrodysesthesia (HFS); grade 3/4 neurological toxicity, e.g. cold paresthesia, which did not resolve to grade 1 within 3 days after chemotherapy and any grade 3/4 toxicity, which was considered to be dose limiting by the investigators.

Dose modifications for toxicity for each of the drugs were prespecified in the protocol. After the occurrence of a grade 3 hematologic toxicity, treatment was interrupted until the toxicity resolved to grade 0–1 and then reinstated at the same doses. After the occurrence of a grade 4 hematologic toxicity or a grade 3 non-hematologic toxicity, treatment was interrupted until resolution to grade 0–1 and then reintroduced at 75% of the doses of gemcitabine and capecitabine and at the next lower dose level of oxaliplatin. Treatment was discontinued after the occurrence of a grade 4 non-hematologic toxicity. Toxic effects clearly attributable to a specific drug (HFS to capecitabine; neuropathy to oxaliplatin) led to protocol-defined reductions of the causative drug only.

Response assessment by CT scan was done at baseline, every 6 weeks during active treatment and every 3 months during follow-up. An experienced radiologist (SP)—blinded to the clinical history—reviewed CT scans centrally and assessed the RR according to RECIST 1 criteria.

study design and statistics

This multicenter open-label phase I/II trial consisted of two parts: the phase I part was designed according to a modified Fibonacci design with interpatient dose escalation in cohorts of three to six patients with the primary end point of protocol-defined DLT.

The phase II part was designed in two stages (Simon two-stage optimal design) with an early stopping rule for safety: if one or fewer objective responses were to be observed with the first 13 patients treated at the RD, the trial was to be halted. Otherwise, 15 more patients were to be treated at the RD, for a total of 28 patients at the RD. Given that the ‘true’ response probability was 7.5%, there was a 74.55% probability of ending the trial during stage 1. However, if the ‘true’ response probability was 25%, then there was a 12.67% probability that the trial would have been stopped in stage 1. The alpha level was 0.04 and the power was 0.8.

Primary end point of the phase II part was objective RR according to RECIST criteria. Secondary end points were toxicity according to NCI–CTC v3.0, progression-free survival and overall survival.

The trial treatment was defined as worth of further investigation if four or more objective responses were observed by the end of the phase II part of the trial.

The study was conducted according to the ethical principles of the Declaration of Helsinki and Good Clinical Practice and was approved by health authorities and independent ethics committees for each participating center. Trial monitoring was carried out by an independent external clinical research organization (Pharma Brains AG, Basel, Switzerland).

The trial is registered on the USA NCI Web site www.ClinicalTrials.gov (NCT00744640).

results

Forty-seven patients with histologically confirmed APC were recruited from seven centers from November 2005 to

September 2008. Two patients were excluded from the analysis: One patient committed suicide after signing informed consent but before performing any study-specific intervention, whereas major violation of inclusion criteria (active life-threatening concomitant disease: gastrointestinal bleeding, not tumor-related) precluded trial participation of the second patient. Baseline characteristics of all 45 patients are summarized in Table 1.

dose escalation and DLT

Twenty patients were treated in the phase I part of this study. While escalating oxaliplatin from 85 to 130 mg/m², the maximum tolerated dose was not reached. However, when further escalating capecitabine in this combination (to 800 mg/m² twice daily) DLTs occurred in two patients: grade 3 diarrhea requiring hospitalization and grade 4 thrombocytopenia. The RD of this 3-week regimen was therefore defined as oxaliplatin 130 mg/m² d1, capecitabine 650 mg/m² b.i.d. d1–14 and gemcitabine 1000 mg/m² d1, d8.

safety and toxicity

Two hundred and three cycles of chemotherapy were administered to 45 patients. Grade 3/4 toxic effects are summarized in Table 2. Predominant adverse effects were neutropenia (33 patients; 30% of cycles), thrombocytopenia

(28 patients; 26% of cycles) and diarrhea (9 patients; 5% of cycles).

Twenty-eight patients were treated at the RD with a total of 111 cycles. Frequency of grade 3/4 neutropenia, thrombocytopenia and grade 3 diarrhea was similar in this group occurring in 33%, 32% and 7% of cycles, respectively.

Also, in the group of 30 patients with good baseline performance status (PS; 90%–100%), the percentage of cycles (*n* = 141) with grade 3/4 neutropenia, thrombocytopenia and grade 3 diarrhea was 32%, 30% and 5%, respectively.

One treatment-related death occurred in a 66-year-old man who was treated at the RD and died of diffuse intestinal bleeding from treatment-induced mucositis during the first cycle of chemotherapy. In two other patients, who both died after having completed three cycles of treatment, the relation between death and treatment was uncertain: The first patient died of tumor progression and gram-negative sepsis and the second died of intractable diarrhea, which occurred 1 week after active chemotherapy treatment had been stopped.

A median of six cycles (range 1–11) was administered per patient. The reason for stopping treatment was disease progression in 22 patients, completion of the planned six cycles in 14 patients, adverse events in 7 patients and patient’s wish in 2 patients. In one patient, trial treatment was stopped after four cycles because of an excellent tumor response allowing for a switch in therapeutic strategy to curative surgery.

At the RD, dose reductions of at least one of the three drugs—as prespecified in the protocol—were necessary in 56 (51%) of 111 cycles. For gemcitabine, capecitabine and oxaliplatin, 83% (range 50%–100%), 75% (range 9%–100%) and 91% (range 31%–100%), respectively, of the planned dose were administered at the RD (mean relative dose intensity per patient). Hematologic toxicity was the most common reason for dose reductions (Table 2). Diarrhea led to a dose reduction in 13 (12%), HFS in 3 (3%) and neurotoxicity in none of the 111 cycles at RD.

Figure 1 shows the percentage of patients who were treated with the planned full dose of each drug in each successive cycle.

Table 1. Patient characteristics

	<i>N</i> _{total} = 45	
	<i>n</i>	%
Median age, years (range)	63 (35–77)	
Sex		
Female	21	47
Male	24	53
Karnofsky performance status		
90%–100%	30	67
60%–80%	15	33
Extent of disease		
Locally advanced	11	24
Metastatic	34	76
Histology		
Well differentiated	–	–
Moderately differentiated	13	29
Poorly differentiated	7	16
Unknown	25	55
Prior surgery	9	20
Whipple procedure with R0-resection	1	2
Explorative surgery with biliodigestive anastomosis and/or gastroenterostomy	8	18
Prior radiotherapy	–	–
Part of the study		
Phase I (dose escalation)	20	44
Phase II (recommended dose)	25	56
Median baseline tumor marker CA 19-9 IU/ml (range)	1074 (<1–456 600)	

Table 2. Treatment-related toxicity according to NCI–CTC v3.0

	<i>n</i> = 203 cycles				<i>n</i> = 45 patients			
	Grade 3		Grade 4		Grade 3		Grade 4	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Hematologic toxicity								
Neutropenia	45	22	16	8	20	44	13	29
Febrile neutropenia	–	–	1	0.5	–	–	1	2
Thrombocytopenia	40	20	12	6	18	40	10	22
Non-hematologic toxicity								
Diarrhea	11	5	–	–	9	20	–	–
Infection	1	0.5	–	–	1	2	–	–
SIRS	1	0.5	–	–	1	2	–	–
Hand–foot syndrome	1	0.5	–	–	1	2	–	–

In addition, one treatment-related death occurred (grade 5 mucositis). For two other fatal adverse events (infection and diarrhea), association with treatment is uncertain (see text). No grade 3/4 paresthesia occurred. NCI–CTC v3.0: National Cancer Institute—Common Toxicity Criteria version 3.0; SIRS: systemic inflammatory response syndrome.

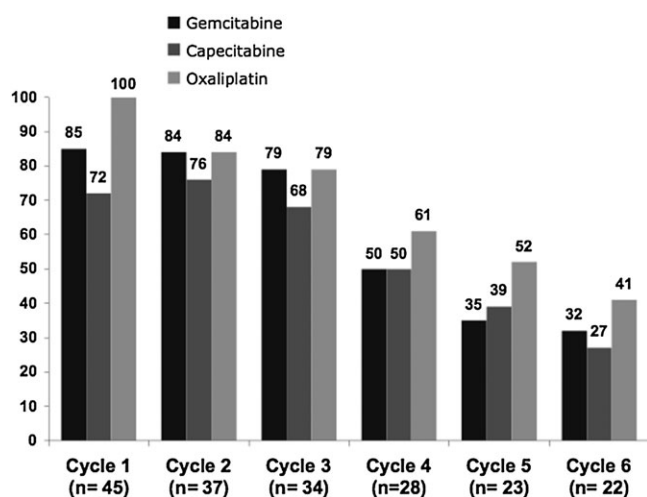


Figure 1. Percentage of patients treated at the full planned dose of each of the three drugs gemcitabine, capecitabine and oxaliplatin.

Of the 22 patients who underwent all six cycles, full doses of gemcitabine, capecitabine and oxaliplatin were given to 7, 6 and 9 patients, respectively.

After study treatment, 29 patients (64%) went on to a second line and 11 patients (24%) on to a third line of systemic treatment with various regimens including gemcitabine, capecitabine, erlotinib and experimental drugs in clinical trials.

efficacy and survival

CT scans of all 41 patients with measurable disease—centrally reviewed by an independent radiologist blinded to the clinical history of the patients—showed a partial response according to RECIST criteria in 17 patients (41%, 95% CI 26% to 56%). In 15 patients (37%, 95% CI 22% to 52%), imaging revealed stable disease, whereas the remaining 9 patients (22%, 95% CI 9% to 35%) progressed while on treatment. Fourteen of the 17 patients with partial remissions started chemotherapy in a good PS (KPS 90%–100%).

After a median follow-up of 27.2 months (95% CI 24.0–30.4 months), all 45 patients had experienced disease progression and 41 patients (91%) had died. Median progression-free survival time was 4.3 months (95% CI 3.3–5.4 months). Patients lived for a median time of 7.8 months (95% CI 5.3–10.3 months). Median survival time for the 30 patients with good PS was 8.9 months (95% CI 5.7–12.0 months) (Figure 2).

discussion

Progress in medical treatment of patients with APC comes in small steps. Out of an extensive body of clinical research data, three classes of cytotoxic drugs emerged as effective and life prolonging [4–6]. This is the first report of a chemotherapy regimen combining all three drugs in a first-line regimen. The RD of this 3-week regimen determined in the phase I part of this study consists of oxaliplatin (Ox) 130 mg/m² d1, capecitabine (Cap) 650 mg/m² b.i.d. d1–14 and gemcitabine (Gem) 1000 mg/m² d1, d8. This corresponds to full standard therapeutic doses in APC. Objective RR assessed by central radiological review, the primary end point of the phase II part

of this trial, was 41% (17 of 41 patients with measurable disease; 95% CI 26% to 56%) and—by far—met the protocol-defined precondition warranting further investigation of this regimen.

No DLTs occurred when escalating oxaliplatin up to 130 mg/m². Diarrhea and thrombocytopenia were dose limiting, when Cap was escalated from 650 to 800 mg/m² b.i.d. Interestingly, DLTs occurred at exactly the same dose escalation step in the similarly designed phase I trial of the GemCap doublet, where grade 4 neutropenia and thrombocytopenia and mucositis were dose limiting as well [12]. Taken aside a certain possibility of chance inherent to the phase I design, this implies that the addition of a full dose of Ox does not shift the limiting toxicity profile significantly, at least not during the first two cycles.

Tan et al. [13] studied a combination regimen of the same three drugs in 30 patients with advanced upper gastrointestinal malignancies including 15 patients with pancreatic cancer. In contrast to this study, the majority of patients were pretreated. The 29-day regimen consisted of oxaliplatin 100 mg/m² i.v. d1 and d15, gemcitabine 800 mg/m² i.v. as fixed dose rate infusion d1, d15 and capecitabine 800 mg/m² b.i.d. d1–d7 and d15–d21. Intriguingly, DLTs in their study included grade 3 fatigue and grade 3 dyspnea, none of which were dose limiting with any of the single drugs involved.

In our trial, most adverse events, including neutropenia, febrile neutropenia, HFS and peripheral polyneuropathy, occurred at or below the frequency expected from the GemCap [5, 7] and GemOx [10, 11] regimen in APC. However, thrombocytopenia (grade 3/4 in 28 of 45 patients) and diarrhea (grade 3 in 9 of 45 patients) were more common with the triple combination and the main reasons for dose adjustments. Thrombocytopenia was well manageable with dose reductions and/or delays and no platelet transfusions were required. Grade 3/4 diarrhea, consistently reported in ~5%–6% of patients treated for APC [5, 7, 10, 11], represents a serious clinical problem that needs careful monitoring when exposing these patients to any chemotherapy. One patient died of acute mucositis with diarrhea and intestinal bleeding during the first treatment cycle. It is well known that dihydropyrimidine dehydrogenase (DPD) deficiency, present in ~3%–5% of the population, renders some patients extremely prone to severe fluoropyrimidine toxicity [14]. DPD status in this patient was not known.

RR according to RECIST criteria, the primary efficacy end point of the phase II study, was 41% (95% CI 26% to 56%) for all patients and 50% (95% CI 31% to 69%) for patients with good PS, hence much higher than expected from previous studies using the doublet GemOx (10% to 27%) [10, 11] or GemCap (15%–19%) [5, 7]. Therefore, this regimen—in contrast to single-agent and doublet regimens—leads to a relevant tumor volume reduction in a substantial percentage of patients. In our series, a patient with primarily inoperable locally advanced disease was rendered eligible for resection following an excellent response to chemotherapy. The patient underwent complete R0-resection after four cycles of GEMOXEL and stayed disease free for 15 months.

In the majority of patients, however, response to chemotherapy was short lived with a median time to

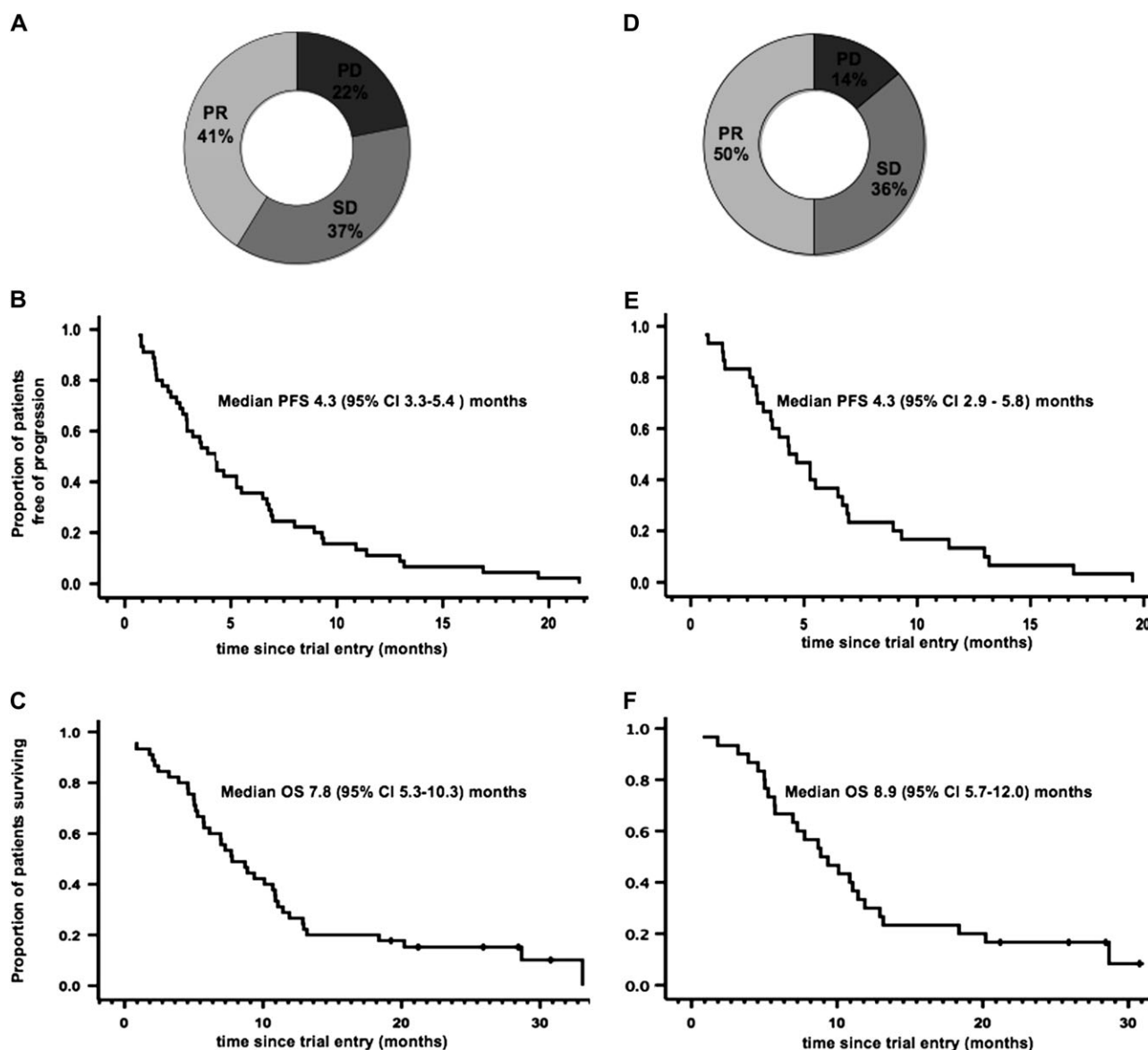


Figure 2. Best response according to RECIST criteria as assessed by independent central radiological review for all patients with measurable disease ($n = 41$; A) and patients with good Karnofsky performance status (90%–100%) ($n = 28$; D). Kaplan–Meier curves for progression-free survival (PFS) and overall survival (OS) for all 45 patients (B, C) and for the 30 patients with good performance status (E, F).

progression of 4.3 months (95% CI 3.3–5.4 months). This rapid development of chemotherapy resistance—even after initial susceptibility mirrored in the high RR—makes this regimen of limited value in the palliative setting of metastatic disease, where short-lived tumor volume reduction offers little clinical benefit.

PS is a prognostic factor of paramount importance in APC [6]. The decision to include patients with a relatively poor PS of 60%–80%, who, in general, are more susceptible to adverse events, might limit the ability of this trial to truly describe toxicity—and efficacy—of this triple combination for patients with good PS. Therefore, future studies of this combination regimen should focus on patients with good PS.

In summary, combining gemcitabine, oxaliplatin and capecitabine, three active cytotoxic drugs in APC, as a first-line regimen is feasible and the triplet clearly meets the prespecified

efficacy parameters. Given the high percentage of patients experiencing significant tumor volume reductions—a parameter most relevant in the preoperative setting—further investigation of this regimen in patients with locally advanced disease in the neoadjuvant setting is warranted.

funding

Swiss National Science Foundation (PMPDB-114392/1 to V.H.); Swiss Federation against Cancer, Oncosuisse (KLS—01881-04-2006 to V.H.).

acknowledgements

We thank Roche Pharma Schweiz, Switzerland, and Sanofi Aventis, Switzerland, for providing Xeloda® and Eloxatin®

free of charge for all study patients. Both companies were not involved in trial design, patient accrual, data collection, data analyses or manuscript writing.

disclosure

BP has occupied an advisory role toward Roche Pharma, Switzerland, and Sanofi Aventis, Switzerland. All other authors have no conflict of interest to declare.

references

1. Raimondi S, Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an overview. *Nat Rev Gastroenterol Hepatol* 2009; 6: 699–708.
2. Sultana A, Smith CT, Cunningham D et al. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. *J Clin Oncol* 2007; 25: 2607–2615.
3. Yip D, Karapetis C, Strickland A et al. Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer. *Cochrane Database Syst Rev* 2006; issue 3: CD002093.
4. Burris HA III, Moore MJ, Andersen J et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997; 15: 2403–2413.
5. Cunningham D, Chau I, Stocken DD et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol* 2009; 27: 5513–5518.
6. Heinemann V, Boeck S, Hinke A et al. Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. *BMC Cancer* 2008; 8: 82.
7. Herrmann R, Bodoky G, Ruhstaller T et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. *J Clin Oncol* 2007; 25: 2212–2217.
8. Scheithauer W, Schull B, Ulrich-Pur H et al. Biweekly high-dose gemcitabine alone or in combination with capecitabine in patients with metastatic pancreatic adenocarcinoma: a randomized phase II trial. *Ann Oncol* 2003; 14: 97–104.
9. Bernhard J, Dietrich D, Scheithauer W et al. Clinical benefit and quality of life in patients with advanced pancreatic cancer receiving gemcitabine plus capecitabine versus gemcitabine alone: a randomized multicenter phase III clinical trial—SAKK 44/00-CECOG/PAN.1.3.001. *J Clin Oncol* 2008; 26: 3695–3701.
10. Louvet C, Labianca R, Hammel P et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol* 2005; 23: 3509–3516.
11. Poplin E, Feng Y, Berlin J et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2009; 27: 3778–3785.
12. Hess V, Salzberg M, Borner M et al. Combining capecitabine and gemcitabine in patients with advanced pancreatic carcinoma: a phase I/II trial. *J Clin Oncol* 2003; 21: 66–68.
13. Tan BR, Brenner WS, Picus J et al. Phase I study of biweekly oxaliplatin, gemcitabine and capecitabine in patients with advanced upper gastrointestinal malignancies. *Ann Oncol* 2008; 19: 1742–1748.
14. Gross E, Busse B, Riemenschneider M et al. Strong association of a common dihydropyrimidine dehydrogenase gene polymorphism with fluoropyrimidine-related toxicity in cancer patients. *PLoS One* 2008; 3: e4003.