Original Article

Phase II trial of capecitabine plus nab-paclitaxel in patients with metastatic pancreatic adenocarcinoma

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Background: Combination chemotherapy regimens including fluoropyrimidines as well as albumin-bound paclitaxel have shown promising results in patients with metastatic pancreatic adenocarcinoma (mPC). Based on the recently described excellent therapeutic index of capecitabine plus nab-paclitaxel in metastatic breast cancer, the present phase II trial was initiated.

Methods: Patients with previously untreated mPC were treated with capecitabine (825 mg/m^2 orally bid on days 1-15) and nab-paclitaxel (125 mg/m^2 intravenously on days 1 and 8) every 3 weeks. In patients without clinically relevant adverse reactions after the 1st treatment course (≤ grade 2 toxicities according to NCI-CTC *vs.* 4.0, exuding alopecia and fatigue of any degree) and adequate bone marrow function, the nab-paclitaxel dose was escalated to 100 mg/m^2 on days 1, 8 and 15 of each cycle; this intra-individual dose escalation was maintained during subsequent treatment courses if tolerated. The primary endpoint was objective response rate (ORR) according to RECIST criteria, assessed by an independent radiological review committee with evaluation performed every 2 months.

Results: Between 12/2013 and 01/2015, 30 patients were entered in this monocentric academic phase II trial. All patients had an ECOG performance status of 0-1, 80% had liver metastases and 23% had biliary stents in place at time of study initiation. Median CA19-9 was 1,004 U/mL (0.9-100.000 U/mL). In all patients except 2, a dose escalation of nab-paclitaxel after the 1st treatment course could be accomplished. The most common grade 3 adverse events (AEs) included transient sensory neuropathy (23%), (afebrile) neutropenia (17%), hand-foot-syndrome (13%) and phototoxic skin reaction (10%). Among 29 RECIST-response assessable patients, the ORR was 41.4% and stable disease (SD) was noted in 34.5%, resulting in a disease control rate (DCR) of 76%. After a median follow-up duration of 10.3 months (range, 1.9-19.0 months), 13/30 patients (43.3%) are presently being alive.

Conclusions: The combination of capecitabine + nab-paclitaxel at these doses and scheduling was well tolerated and showed substantial antitumor efficacy.

Keywords: Pancreatic cancer; nab-paclitaxel; capecitabine

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Introduction

Metastatic pancreatic adenocarcinoma (mPC) is a lethal disease with a median survival of approximately 6-7 months in the gemcitabine ± erlotinib era (1). Introduction of the combination of 5-fluorouracil (5-FU), leucovorin, oxaliplatin, and irinotecan (FOLFIRINOX), as well as the better tolerated nab-paclitaxel plus gemcitabine regimen, represented a significant advance in the treatment of mPC (2,3).

Apart from the principial antitumor potential of capecitabine in advanced pancreatic cancer when given as a radiosensitizer (4) or in combination with gemcitabine (5,6) or gemcitabine + oxaliplatin (7,8), this oral 5-FU prodrug seems to represent a particularly attractive combination partner for nab-paclitaxel: taxanes upregulate thymidine phosphorylase in liver tissue, potentially increasing the tumor concentration and efficacy of capecitabine (9).

In view of the recently described excellent therapeutic index of capecitabine plus nab-paclitaxel in metastatic breast cancer (10), we initiated the present phase II trial to evaluate this combination as first-line therapy in mPC. The primary objective of the trial was to determine the objective response rate (ORR), secondary objectives included determination of the disease control rate (DCR), progression-free survival (PFS), and overall survival (OS), as well as evaluation of the safety and tolerability of this combination when administered according to an intra-individual dose escalation schedule.

The trial is registered with the European Medicines Agency as EudraCT 2013-001714-15.

Patients and methods

Patient population

Adults (≥18 years of age) with histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 were enrolled. Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 was required (11). Additional eligibility criteria included adequate hepatic, hematologic, and renal function. No previous chemotherapy for metastatic disease was allowed. Adjuvant gemcitabine was permitted if the last cycle was completed ≥6 months prior to trial entry.

Trial medication

Patients received capecitabine (825 mg/m^2 orally twice daily on days 1-15) and nab-paclitaxel (125 mg/m^2 intravenously on days 1 and 8) every 3 weeks. In patients with adequate bone marrow function (neutrophils ≥1,500/μL, thrombocytes ≥100,000/μL) and with no clinically relevant adverse reactions [defined as adverse events (AEs), other than alopecia or fatigue, that were of ≤ grade 2 severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0] after the first cycle of treatment (11), the nab-paclitaxel dose was escalated to 100 mg/m^2 on days 1, 8, and 15 of each subsequent cycle, and was maintained at this level if tolerated.

Granulocyte-colony stimulating factor (G-CSF) was recommended in case of neutropenia of grade >2. In patients with an objective treatment response or with stable disease (SD), treatment was continued until the development of progressive disease (PD). In patients who derived a clinical benefit, and in whom either capecitabine or nab-paclitaxel had to be discontinued for toxicity reasons (for example, hand-foot syndrome associated with capecitabine, or neuropathy associated with nab-paclitaxel), continuation with the non-dose-limiting component of the combination as monotherapy was recommended.

Trial design and statistical considerations

The study was conducted in accordance with the International Conference on Harmonization E6 requirements for Good Clinical Practice and with the ethical principles outlined in the Declaration of Helsinki (12).

This was a single-center, open-label, phase II clinical trial. The primary endpoint of the trial was the ORR according to RECIST version 1.1 criteria. This was evaluated at baseline and every 2 months thereafter, with assessments carried out by an independent radiological review committee. Secondary endpoints included DCR (abrogation of PD), PFS, and OS, in addition to evaluations of the safety and tolerability of capecitabine plus nab-paclitaxel in mPC. The latter was assessed by the incidence of treatment-related AEs according to NCI-CTCAE version 4.0.

In order to demonstrate that capecitabine plus nab-paclitaxel administered according to an intra-individual dose-escalation schedule would yield an ORR of ≥30% with 80% power, it was estimated that we needed to enrol 32 patients to obtain a sample size of 29 evaluable patients.

Results

Between December 2013 and January 2015, 30 patients were enrolled into this single-center, phase II clinical

Table 1 Baseline characteristics

Characteristics	n [%]
Age	
Median, years [range]	63 [37-79]
≥65 years	14 [47]
Sex	
Male	16 [53]
ECOG PS	
0	27 [90]
1	3 [10]
International Staging System stage IV disease at primary diagnosis	
Yes	30 [100]
Pancreatic primary tumor location	
Head ± body	24 [80]
Tail	6 [20]
Current site(s) of metastasis	
Lung	3 [10]
Liver	24 [80]
Peritoneum	3 [10]
Number of metastatic sites	
1	2 [7]
2	11 [37]
≥3	17 [56]
Previous surgery	
Yes	2 [7]
Biliary stent	
Yes	7 [23]
CA19-9	
Normal	4 [13]
Median, U/mL (range)	1,004 (0.9-100,000)

Table 2 Treatment response rates

Best response (N=29)	Number of patients, n (%)
Objective response	12 (41.4)
SD	10 (34.5)
PD	7 (23.1)

SD, stable disease; PD, progressive disease.

trial. Patients' median age was 63 years. All patients had an ECOG PS of 0-1, most patients (93%) had multiple metastatic sites, 80% had liver metastases, and 23% had biliary stents in place at the time of trial entry. Median CA19-9 was 1,004 U/mL (0.9-100,000 U/mL). Patients' baseline characteristics are shown in *Table 1*.

Treatment efficacy

Among the 29 RECIST response-assessable patients, the ORR was 41.4%, and SD was noted in 34.5% (*Table 2*). This gave a DCR of 76%. As shown in *Figures 1* and *2*, after a median follow-up of 10.3 months (range, 1.9-19.0 months), the median PFS is 5.6 months (range, 1.9-16.0 months), and median OS is 10.3 months (range, 2.0-19.0+ months), with 13/30 (43.3%) patients remaining alive at present.

Rapid decreases in CA-19/9 levels were observed. Among patients with pathologically elevated baseline values, 24/30 (92%) had a >20% decrease, 18/30 had a >50% decrease (60%), and 9 had a >90% decrease. CA-19/9 levels were correlated with increased survival. Patients with a >90% decrease in CA-19/9 levels had a 62% ORR, and 6.7 and 11 months of PFS and OS respectively.

It should be mentioned that 2nd-line chemotherapy with gemcitabine + oxaliplatin + erlotinib (n=18) was effected upon PD in 18 (60%) of our patients. In agreement with our and others' previous experience (13-15), half of them benefited by achieving ≥SD. Third-line treatment with FOLFIRI was given to 4 patients (13%).

Safety

All 30 evaluable patients were included in the safety analysis. In all except two of these patients, it was possible to escalate the nab-paclitaxel dose after the first treatment cycle. A total of 180 cycles of nab-paclitaxel and 193 cycles of capecitabine were administered per protocol. A summary of treatment-related AEs by severity is presented in *Table 3*.

The only AEs of grade 3 severity were peripheral neuropathy (23.3%), afebrile neutropenia (16.7%), hand-foot syndrome (13%), and phototoxic skin reaction (10%). No grade 4 AEs occurred.

Table 4 shows the number of patients who required capecitabine or nab-paclitaxel dose modifications during the course of the trial. Two patients required capecitabine dose reductions. In each of the six patients who required nab-paclitaxel dose reductions, the dose was reduced to the starting level of 125 mg/m^2 on days 1 and 8 every 3 weeks. nab-paclitaxel and capecitabine dosing delays were required by 19 and eight patients, respectively. Three patients had to discontinue nab-paclitaxel, while all 29 evaluable patients were able to remain on capecitabine for the duration of the trial.

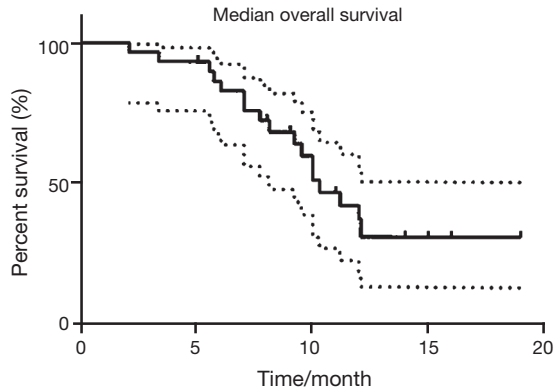

Figure 1 Kaplan-Meier estimates of OS in patients with mPC treated with capecitabine + nab-paclitaxel. OS, overall survival; mPC, metastatic pancreatic adenocarcinoma.

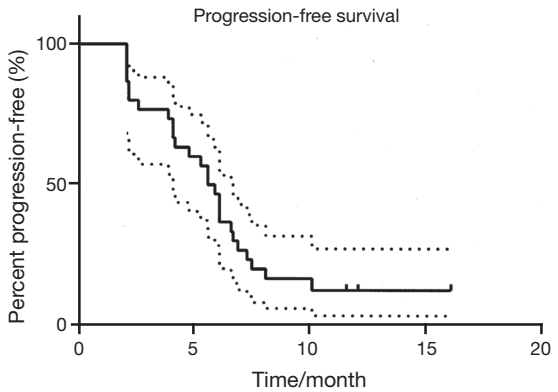

Figure 2 Kaplan-Meier estimates of PFS in patients with mPC treated with capecitabine plus nab-paclitaxel. PFS, progression-free survival; mPC, metastatic pancreatic adenocarcinoma.

Conclusions

The combination of capecitabine plus nab-paclitaxel shows substantial antitumor activity when administered as first-line chemotherapy in mPC: The ORR according to RECIST criteria was 41%, and the DCR (objective response + SD) was 76% After a median follow-up of 10.3 months, median PFS and median OS are 5.6 and 10.3 months, respectively with 13 patients (43%) remaining alive. The described dose regimen of capecitabine plus nab-paclitaxel can be administered safely: Intra-individual dose escalations were feasible in 28/30 patients, and could be maintained in the large majority of cases (93%). The only AEs of grade 3 severity were transient peripheral neuropathy (23%), afebrile neutropenia (17%), hand-foot syndrome (13%) and phototoxic skin reaction (10%). No grade 4 AEs occurred.

Table 3 Treatment-related AEs

AE	Incidence, n (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Afebrile neutropenia	9 (30.0)	4 (13.3)	5 (16.7)	0 (0.0)
Febrile neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anemia	3 (10.0)	2 (6.7)	0 (0.0)	0 (0.0)
Thrombocytopenia	4 (13.3)	2 (6.7)	0 (0.0)	0 (0.0)
Alopecia	8 (26.7)	16 (53.3)	–	–
Fatigue	6(20.0)	5 (16.7)	0 (0.0)	0 (0.0)
Hand-foot syndrome	3 (10.0)	2 (6.7)	4 (13.3)	0 (0.0)
Peripheral neuropathy	6 (20.0)	10 (33.3)	7 (23.3)	0 (0.0)
Phototoxic skin reaction	0 (0.0)	2 (6.7)	3 (10.0)	0 (0.0)
Anorexia	4 (13.3)	1 (3.3)	0 (0.0)	0 (0.0)
Nausea/vomiting	4 (13.3)	1 (3.3)	0 (0.0)	0 (0.0)
Stomatitis	2 (6.7)	2 (6.7)	0 (0.0)	0 (0.0)
Constipation	0 (0.0)	2 (6.7)	0 (0.0)	0 (0.0)
Diarrhoea	7 (23.3)	3 (10.0)	0 (0.0)	0 (0.0)

AEs, adverse events.

Table 4 Dose modifications

Modification required	Drug	No. of patients	No. of cycles with dose modifications
Dose reduction	nab-paclitaxel	6	13
	Capecitabine	2	2
Dose withdrawal	nab-paclitaxel	3	2
	Capecitabine	0	0
Dose delay	nab-paclitaxel	19	36
	Capecitabine	8	10

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Footnote

Conflicts of Interest: W Scheithauer—Consultant & advisory

role, honoraria and research funding, Celgene Corporation; G Kornek and G Prager—honoraria as invited speakers, Celgene Corporation; S Schindl—advisory role, Celgene Corporation.

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