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A phase II study: docetaxel as first-line chemotherapy for advanced pancreatic adenocarcinoma

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Abstract

The aim of this study was to evaluate the efficacy of docetaxel as first-line chemotherapy in patients with unresectable metastatic or locally advanced pancreatic adenocarcinoma and to further characterise the safety and pharmacokinetic profiles of docetaxel. 43 patients were enrolled into this phase II study. Treatment consisted of a 1-h infusion of docetaxel 100 mg/m^2 every 3 weeks without premedication with corticosteroids until progression or unacceptable toxicity occurred. Dose modifications were planned for adverse events. Patients were observed for 1 month after the last docetaxel infusion, to document any late adverse events, with a follow-up every 3 months until death. Response rate and duration were the major efficacy endpoints. Response status was reviewed by an external independent panel. Pharmacokinetic analysis was performed during the first treatment cycle. 40 patients were evaluable for response, and all were evaluable for safety. After independent review, partial response was recorded in 6 patients (overall response rate, 15%; 95% confidence limit (CI), 7.7–29.8%) and stable disease was recorded in 15 patients (38%). The median duration of response was 5.1 months (range: 3.1–7.2). The median pain control time was 4.5 months (range: 0–8) and the median time to performance status worsening was 2.3 months (range: 0–4.5). Most patients 40 (93.0%) received a relative dose intensity of more than 70% of the planned dose. The incidence and severity of adverse events reflected the known safety profile for docetaxel. Docetaxel clearance was reduced in patients with elevated concentrations of hepatic enzymes or bilirubin. Docetaxel is an active agent for unresectable metastatic or locally advanced pancreatic adenocarcinoma.

Keywords: Pancreatic adenocarcinoma; Cancer of the pancreas; Phase II trial; Chemotherapy; Docetaxel; Taxotere®

1. Introduction

Existing chemotherapeutic options for patients with unresectable metastatic or locally advanced adenocarcinoma of the exocrine pancreas are of limited value. In general, monotherapy with traditional agents such as 5-fluorouracil (5-FU) has resulted in variable response rates (usually less than 10%) and short response durations, and there is scant evidence to suggest that conventional combination therapy offers additional benefit [1–12]. Similarly, modulation of 5-FU with agents such as leucovorin and interferon-α seems to offer little therapeutic advantage over 5-FU alone (although a response rate of 38% was reported recently for the combination of 5-FU, leucovorin, interferon-α-2b and cisplatin) and is associated with considerable toxicity [13–18].

Despite the discouraging results achieved with existing therapies, trials comparing best supportive care and chemotherapy suggest that chemotherapy does have a positive effect on survival and quality of life [19,20]. Recent research has continued to focus therefore on the development of new active drugs suitable for use as first-line single agents in the treatment of metastatic or locally advanced pancreatic cancer.

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One new agent of interest is docetaxel (Taxotere®; Rhône-Poulenc Rorer, Antony, France), a taxoid obtained by hemisynthesis from an inactive precursor extracted from the needles of the European yew, *Taxus baccata*. Taxoids enhance microtubule assembly and inhibit the depolymerisation of tubulin, thereby promoting the formation of stable, intracellular bundles of microtubules, which disrupt cell replication [21–24]. This mode of action contrasts with those of other spindle poisons in clinical use, such as the vinca alkaloids, which inhibit the polymerisation of tubulin into functional microtubules [25].

This study was performed to evaluate the efficacy of docetaxel as first-line chemotherapy for patients with unresectable metastatic or locally advanced adenocarcinoma of the pancreas, as part of a phase II clinical trial programme. The study also aimed to further characterise the safety and pharmacokinetic profiles of docetaxel in this group of patients.

2. Patients and methods

2.1. Eligibility

Men and women aged 18–75 years, with histologically or cytologically proven metastatic or locally advanced pancreatic adenocarcinoma, at least one bidimensionally measurable target lesion, a World Health Organization (WHO) performance status of 0–2, adequate haematological and renal functions, a total bilirubin of $\leqslant 1.25\times$upper normal limit, aspartate aminotransferase $\leqslant 2\times$upper normal limit and a life expectancy of at least 12 weeks, were eligible for recruitment into the study.

Specific criteria for exclusion were current biliary dilation; islet, ampullary or epidermoid carcinoma; cystadenocarcinoma; pancreatic lymphoma or sarcoma; a history of malignancy (other than curatively treated *in situ* carcinoma of the cervix or basocellular skin carcinoma); brain or leptomeningeal metastases; symptomatic peripheral neuropathy of at least grade 2 according to National Cancer Institute (NCI) Common Toxicity Criteria; any other serious illness or medical condition.

Patients were also excluded if they had previously received immunotherapy or chemotherapy. Previous treatment with radiotherapy was permitted if at least 4 weeks had elapsed between the end of radiotherapy and entry into the study, and if the radiotherapy had not been applied to the only site available for assessing response. Women were excluded if they were pregnant, lactating or of childbearing potential and not using effective contraception.

Ethical committee approval was obtained before the start of the trial and all patients gave their written informed consent to participate.

2.2. Study design

This was an open, non-randomised, phase II study conducted at two centres in France. Patients were scheduled to receive an intravenous infusion of docetaxel 100 mg/m^2 over 1 h every 3 weeks, with no routine premedication with corticosteroids. The planned duration of treatment was dependent on response: patients with partial or complete responses continued until the occurrence of disease progression or excessive toxicity; patients with stable disease continued for a maximum of six cycles. Once withdrawn from study medication, patients could receive second-line treatment at the investigator's discretion. Patients were observed for 1 month after the last docetaxel infusion, to document any late adverse events, with a follow-up every 3 months until death, to document time to progression and duration of survival.

Although each cycle was to be given at the same dose, dose and schedule modifications were permitted for myelosuppression, anaphylactoid or hypersensitivity reactions, cutaneous reactions, peripheral neurotoxicity, nausea, vomiting and toxicities of grade 3 or more, other than alopecia and anaemia. In the case of several toxicities leading to conflicting recommendations, the most conservative dose adjustment was to be made. A maximum of two 25% dose reductions were allowed per patient, i.e. from 100 to 75 mg/m^2 and from 75 to 55 mg/m^2. Doses reduced for toxicity could not be re-escalated to the starting level.

2.3. Concomitant therapy

At the time of this study, the following concomitant medications and therapeutic measures were not permitted: refrigerated helmet; steroids; preventive oral or intravenous antibiotics in the case of neutropenia without fever; other investigational drugs and anticancer treatments; colony stimulating factors, unless indicated medically; concomitant radiotherapy, unless for local control of bone pain.

Preventive anti-allergic measures (antihistamine and steroids) were not allowed, but symptomatic treatment with oral antihistamine (dexchlorpheniramine) was permitted for late occurrence of hypersensitivity symptoms, and oral or intravenous antihistamine premedication could then be given before the next cycle of treatment. No prophylactic use of antiemetics, including steroids, was planned during the first course. However, when nausea and vomiting were reported, curative treatment was given and prophylactic measures taken for the subsequent cycles.

2.4. Study assessments

A pretreatment evaluation, comprising disease history, physical examination (including WHO performance

status, tumour measurement, assessment of vital signs and neurological examination), haematological and biochemical tests, tumour marker measurement, radiological tests, electrocardiography and assessment of baseline symptoms and toxicity, was performed in the 3 days before the first infusion of study medication. Radiological tests could be performed up to 2 weeks before the first infusion of study medication.

Tumour measurements were made every two cycles to determine response. Patients with disease progression before the end of the second treatment cycle were considered to have early progression, whereas patients who received at least two cycles of therapy had their response to treatment classified as follows: complete response, partial response, stable disease or progressive disease, according to the WHO response criteria. Response status was reviewed by an external, international and independent panel. The tumour marker CA19-9 was measured every treatment cycle.

Regular safety evaluations, including haematological and biochemical tests, vital signs assessments, chest X-rays and electrocardiograms, were performed to identify adverse events and haematological and biochemical laboratory abnormalities. Toxicities were graded using the NCI Common Toxicity Criteria.

Pharmacokinetics of docetaxel were planned by the protocol due to the incomplete data available at this stage of development. During the first cycle of therapy, three blood samples were collected according to one of four population pharmacokinetic protocols assigned randomly at the time of registration in the study [26]. Plasma docetaxel concentrations were measured by high performance liquid chromatography after a solid phase extraction [27].

Pharmacokinetic parameters were determined by Bayesian estimation using concentration–time data for each patient and data from a previously defined population model [28,29] and the non-linear mixed effect modelling programme (double precision, version IV, level 2.0) [30]. A three-compartment structural model with first-order elimination was used. The analysis focused on docetaxel plasma clearance and area under the curve (AUC).

2.5. Statistical analyses

A modified two-stage Fleming study design was used with between 15 and 25 evaluable patients [31,32]. The study design allowed for the termination of patient recruitment after the first 15 evaluable patients were treated if no objective response occurred. If at least one response was observed, an additional 10 evaluable patients could be recruited, enabling a response rate to be determined.

Patients had to have received at least two cycles of treatment and to have had all baseline lesions assessed at least once after the second treatment cycle to be evaluable for efficacy. All patients who had received at least one docetaxel infusion were evaluable for safety.

The primary efficacy variables were overall response rate (defined as the percentage of patients who achieved a complete or partial response) and duration of response (calculated from first administration of docetaxel to first progression). Additional efficacy variables were time to progression, duration of survival (calculated from first administration of docetaxel to death), time to pain intensity increase or analgesic consumption increase, time to performance status worsening, time to weight loss and the relationship between tumour marker evolution and response.

Categorical data were presented in contingency tables and continuous data were summarised with at least median, minimum and maximum values. Time-to-event variables were analysed by the Kaplan–Meier method. Patients were censored on the date of their last assessment if there was no documentation on progression or death, on the cut-off date if neither progression or death occurred before that time point or on the start date of further anticancer therapy.

3. Results

3.1. Patient disposition and characteristics

All 43 patients (26 males, 17 females) enrolled in the study received at least one docetaxel infusion: 1 patient was not eligible due to active uncontrolled infection at study entry. All patients were evaluable for safety. Baseline elevated concentrations of hepatic enzymes and/or bilirubin above the cut-off defined by the protocol were reported in 5 patients. However, as these abnormalities could be related to the disease, all these patients were included and considered eligible. 3 patients were not evaluable for response: 1 patient was not eligible because of the presence of active uncontrolled infection at study entry, 1 patient received only one cycle of treatment and did not have further tumour assessment after baseline to evaluate tumour response, and 1 patient received two cycles of treatment and died from toxicity before a tumour assessment could be repeated, this patient with portal hypertension due to pancreatic carcinoma experienced during the second course uncontrollable vomiting leading to dehydration, worsening of the general status and cardiorespiratory arrest. Although the underlying medical history contributed to this toxicity, the death was considered as drug-related. The reasons for the withdrawal of the other 42 patients were as follows: disease progression ($n=31$); adverse events ($n=4$); completed as per protocol ($n=3$); withdrawal of consent ($n=2$); other reasons ($n=2$).

Table 1
Tumour characteristics at baseline

Median interval diagnosis — first cycle (range), months	0.7 (0.1–20.0) *n* (%)
Histological subtypes	
Adenocarcinoma	42 (98)
Infiltrating duct carcinoma	1 (2)
Extent of disease	
Local	3 (7)
Locoregional/locally recurrent	6 (14)
Metastatic only	2 (5)
Primary not excised and metastatic	30 (70)
Locoregional/locally recurrent and metastatic	2 (5)
Number of organs involved	
1	15 (35)
2	20 (47)
⩾3	8 (19)
Site of involvement	
Visceral only	37 (86)
Liver	33 (77)
Soft tissue + visceral	6 (14)

The median age of the patients was 57 years (range, 36–76) and the median WHO performance status was 1 (range: 0–2). No patient had received previous chemotherapy or radiotherapy, 4 (9%) of patients had undergone surgery and 2 (5%) of patients had received previous hormonal therapy. Tumour characteristics at baseline are presented in Table 1.

3.2. Exposure to study medication

A total of 173 treatment cycles were administered: 29 (67%) patients received at least three treatment cycles, and the median number of treatment cycles was 4 (range: 1–10). Overall, 23 treatment cycles (13%) were delayed; of these, nine cycles were delayed by more than 7 days.

Most cycles 147 (85%) were administered at the initial scheduled dose (100 mg/m^2). The study medication dose was decreased from 100 to 75 mg/m^2 in nine cycles (5%) and from 75 to 55 mg/m^2 in two cycles (1%), mostly because of non-haematological adverse events. The median actual dose of docetaxel was 99.0 mg/m^2 (range: 65.1–109.3; this dose is due to a calculation error and considered as a minor violation) and the median cumulative dose was 351.1 mg/m^2 (range: 98.1–976.0). The median relative dose intensity was 0.96 (range: 0.58–1.09); 40 patients (93.0%) received a relative dose intensity of more than 70% of the planned dose.

3.3. Response to treatment

Response to treatment is shown in Table 2. No complete responses were recorded. The nine patients with locally advanced disease were considered retrospectively evaluable but not measurable for response due to difficulties of separating the tumour mass from the surrounding pancreatic reaction. For this reason, partial response could not be reported in patients with locally advanced disease. One patient was censored for analysis of response duration because of a lack of documentation of progression before the last contact. After independent review, 6 patients out of 40 evaluable patients were in partial response. The response rate was 15% (95% confidence interval (CI), 7.7–29.8%) in the population evaluable for response and with intent-to-treat basis, 14% considering all the patients entered in the study whilst 15 patients (38% for evaluable patients; 35% for all patients) were in stable disease corresponding to a tumour growth control of 49%. Taking into account only the evaluable metastatic population, the response rate was 6/31 (19%). No objective response was seen in locally advanced disease, but 6 out of 9 were

Table 2
Response to treatment

	Overall		Metastatic disease						Locally advanced
	Intent-to-treat	Evaluable	Intent-to-treat			Evaluable			
			All patients	PS = 0	PS = 1 or 2	All patients	PS = 0	PS = 1 or 2	
	n	*n* (%)	*n*	*n* (%)	*n*	*n*	*n* (%)	*n* (%)	*n* (%)
No. of patients	43	40 (93)	34	9 (26)[a]	24 (71)[a]	31	9[a] (29)	21[a] (68)	9 (100)
Response to treatment, *n* (% of patients)[b]									
Partial response	6 (14)	6 (15)	6 (18)	3 (33)	3 (13)	6 (19)	3 (33)	3 (14)	NA
Overall response [95% CI]	6 (14) [5.3; 27.9]	6 (15) [7.7; 29.8]	6 (18) [6.8; 34.5]	–	–	6 (19) [7.5; 37.5]	–	–	NA
Stable disease	15 (35)	15 (38)	9 (26)	2 (22)	7 (29)	9 (29)	2 (22)	7 (33)	6 (67)
Progressive disease	20 (47)	19 (48)	17 (50)	4 (44)	12 (50)	16 (52)	4 (44)	11 (52)	3 (33)
Median duration of response, months (range)	5.1 (3.1+; 7.2)	5.1 (3.1+; 7.2)	5.1 (3.1+; 7.2)	–	–	5.1 (3.1+; 7.2)	–	–	NA

PS, performance status; CI, confidence interval; NA, ?.

[a] PS missing for one patient.

[b] After independent, external, international review panel assessment.

stabilised or had a minor response for a median duration of 4.4 months.

3.4. Secondary efficacy measures

The median time to progression was 2.1 months in the overall population (95% CI, 1.4–3.4 months), 1.5 months (95% CI, 1.3–3.4 months) in the metastatic population and 3.9 months (95% CI, 1.3–7.5 months) in the locally advanced population, as shown in Fig 1. 3 patients were censored for the analysis of time to progression: 1 patient required further chemotherapy and 2 patients lacked documentation of progression before the last contact.

The median duration of survival was 7 months (95% CI, 5–8 months) in the overall population, 6 months (95% CI, 4–7 months) in the metastatic population and 9 months (95% CI, 7–15 months; range: 4–26 months) in the locally advanced population as shown in Fig. 2; 1 patient was censored for the analysis of survival duration.

The median time to pain intensity increase or analgesic consumption increase (pain control time) was 4.5 months (range: 0–8 months), the median time to performance status worsening was 2.3 months (range: 0–4.5 months), the median time to weight loss in the absence of fluid retention was 2.5 months (range: 0.5–4.5 months) and if one considers the time to benefit decrease as the worsening of at least one of the above criteria it was 1.7 months (range: 0–4.5 months).

A 50% decrease in the tumour marker CA 19-9 of at least 4 weeks' duration was observed in 8 (20%) of the 39 patients evaluable for biological response. In the metastatic population, the biological response rate was 5/30 (17%) and 4 of the 6 patients in partial response had a biological response. In the locally advanced population, the biological response was 2/9 (22%) with all patients in stable disease.

3.5. Adverse events

The incidence of adverse events related to study medication is shown in Table 3; the most frequently reported adverse events were neutropenia grade 3–4: 96% of the patients and grade 1–4 anaemia: 98% of the patients. The other adverse events were asthenia (58%), skin toxicity (53%) and nausea (44%). The most frequently occurring serious adverse events were febrile neutropenia (9%) and infection (23%). Non-haematological adverse events requiring dose adjustments were moderate skin reactions ($n=3$) or moderate to severe asthenia ($n=3$).The adverse events that led to the withdrawal of 4 patients were fluid retention ($n=3$), with a

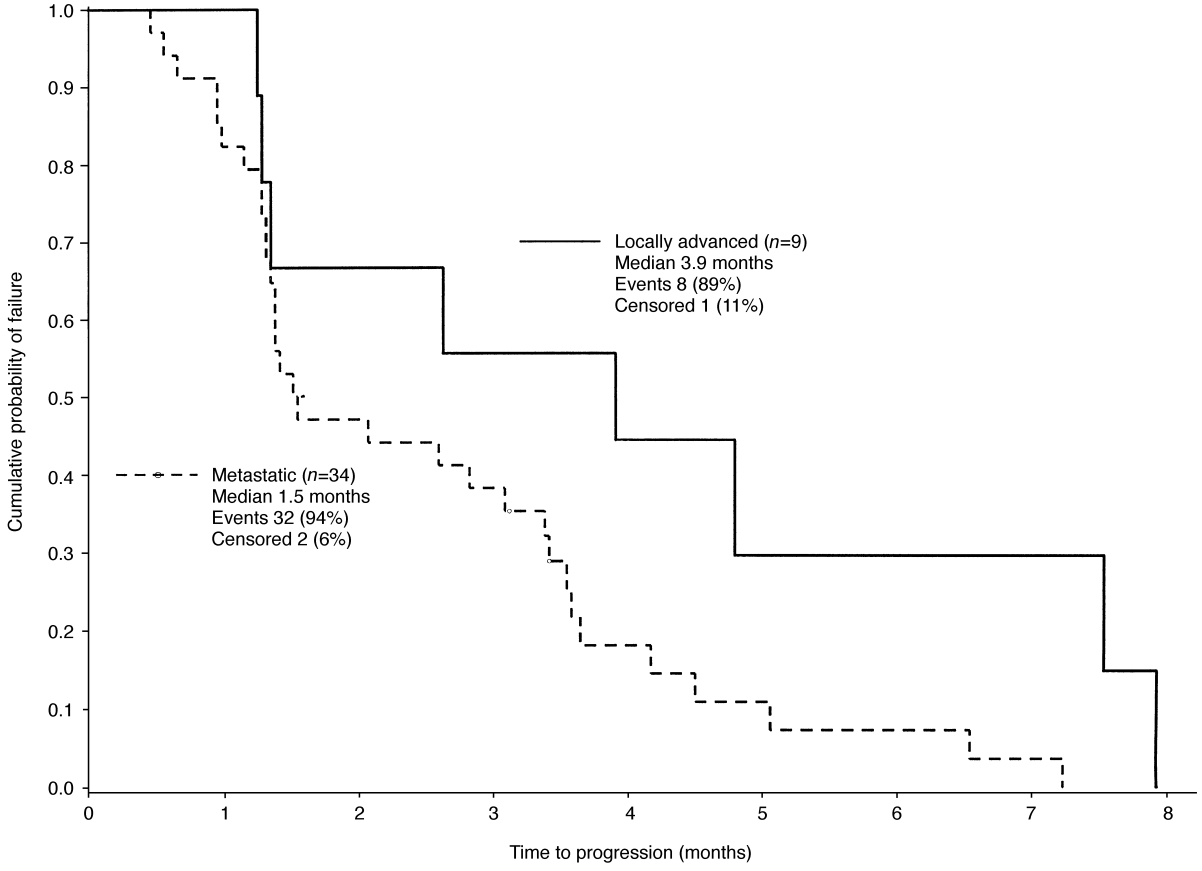

Fig. 1. Time to progression (months).

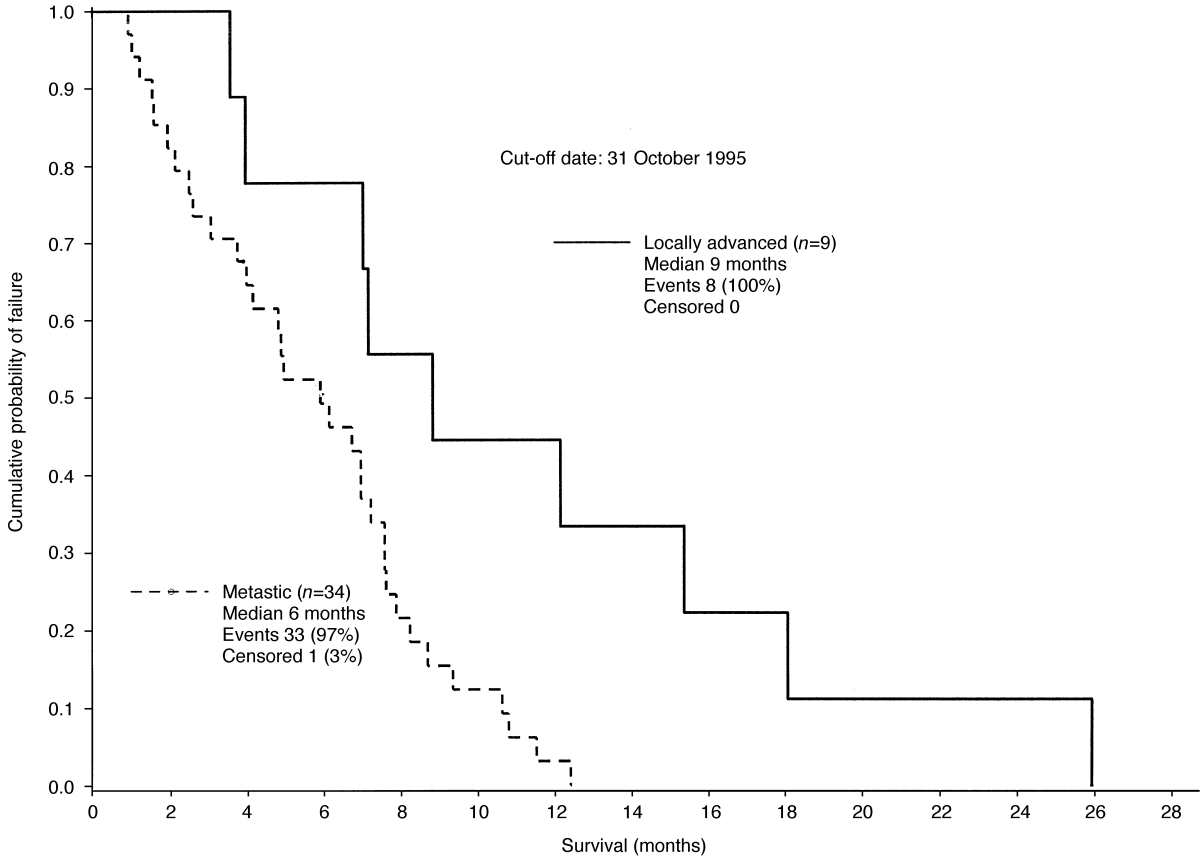

Fig. 2. Survival (months).

Table 3
Adverse events probably/possibly related to study medication

Adverse events (NCI or non-NCI)	Patients (%) ($n=43$)			Cycles (%) ($n=173$)		
	Overall *n* (%)	Grade 3 (NCI) or severe non-NCI *n* (%)	Grade 4 (NCI) *n* (%)	Overall *n* (%)	Grade 3 (NCI) or severe non-NCI *n* (%)	Grade 4 *n* (%)
Neutropenia	43 (100)	11 (26)	30 (70)	169 (98)	50 (30)	91 (52)
Febrile neutropenia[a]	4 (9)	NA	NA	4 (2)	NA	NA
Anaemia	42 (98)	5 (12)	2 (5)	151 (87)	8 (5)	4 (2)
Thrombocytopenia	6 (14)	0	0	13 (7)	0	0
Infection	10 (23)	1 (2)	1 (2)	17 (10)	1 (1)	1 (1)
Asthenia	25 (58)	10 (23)	–	54 (31)	19 (11)	0
Oedema/effusion[b,c] (including weight gain)	12 (28)	3 (7)[c]	–	53 (31)	11 (6)	–
Stomatitis	12 (28)	1 (2)	1 (2)	19 (11)	1 (1)	1 (1)
Nausea[b]	19 (44)	1 (2)	0	34 (20)	1 (1)	–
Vomiting[b]	16 (37)	2 (5)	1 (2)	22 (13)	2 (1)	1 (1)
Diarrhoea[b]	18 (42)	0	0	22 (13)	0	0
Skin toxicity	23 (53)	1 (2)	2 (5)	66 (38)	3 (2)	4 (2)
Neuromotor	3 (7)	0	0	4 (2)	0	0
Neurosensory	16 (37)	0	0	38 (22)	0	0
Hypersensitivity reaction[b]	11 (26)	2 (5)	0	13 (8)	2 (1)	0

NA, not available/applicable; NCI, National Cancer Institute.
[a] Fever grade 2 with concomitant neutropenia grade 4 and serious fever and/or intravenous (i.v.) antibiotics.
[b] No premedication.
[c] After cycle 4 or 5.

cumulative docetaxel dose to treatment discontinuation from 586 to 745 mg/m^2, and skin disorder ($n=1$).

Fluid retention was defined as one or more of the following symptoms: oedema/peripheral oedema, effusion (pleural effusion, ascites, pericardial effusion) and weight gain. The median cumulative dose to onset of fluid retention was 515 mg/m^2 (range 98+–707+ mg/m^2). Severe fluid retention was observed in only 3 patients (7%).

Amongst the 10 patients who had baseline elevated concentrations of either hepatic enzymes; concomitant elevations of transaminases (>1.5×upper limit of normal) and alkaline phosphatase (>2.5×upper limit of normal) as defined in a previous population pharmacokinetic/pharmacodynamic study [26,28] and/or bilirubin (between 1 and 3×upper limit of normal), the following related adverse events were observed: toxic death ($n=1$, previously described), infection grade 3/4 ($n=2$), febrile neutropenia ($n=2$), fluid retention ($n=2$).

3 patients died within 30 days of the last docetaxel infusion: 1 patient from a toxic death (previously described) and 2 patients from malignant disease. The remaining 40 patients died at least 30 days after the last docetaxel infusion due to disease progression.

3.6. Laboratory abnormalities

The incidence of haematological toxicities is shown in Table 3 by patient. Grade 4 neutropenia was observed in 91 (52%) of cycles, with a median duration of 7 days (1–17 days). Fourteen episodes of infection were associated with neutropenia.

Grade 3/4 increases of alkaline phosphatase and/or aspartate aminotransferase and/or alanine aminotransferase and/or total bilirubin were observed in 11 patients during the study. However, 6 out of them had abnormal liver function tests at baseline, the other 5 patients were in progressive disease when abnormal liver tests were observed.

One patient had an increase in the level of creatinine (grade 1), 1 patient had grade 3 hypocalcaemia, and 1 patient had grade 3 hypercalcaemia.

3.7. Pharmacokinetics

The pharmacokinetic analysis was performed on 28 evaluable patients. Two or three quantifiable concentrations with actual sampling times ranging from 0.37 to 7.63 h were available. Plasma clearances and AUC are summarised in Table 4, according to liver function tests. 9 patients had elevated concentrations of either hepatic enzymes and/or bilirubin (as previously described). Clearance was decreased by 28% in 2 patients with elevated hepatic enzyme concentrations only, by 25% in 4 patients with an elevated bilirubin concentration only, and by 57% in 3 patients with elevated concentrations of both hepatic enzymes and bilirubin.

4. Discussion

This multicentre, phase II study has shown that docetaxel (100 mg/m^2/3 weeks) is an active agent for the

Table 4
Plasma clearance and AUC estimates ($n=28$ patients)

Parameter	Mean (CV%)	Median (range)
Patients with normal hepatic enzymes[a] and bilirubin ($n=19$)		
Plasma clearance (l/h)	37.2 (41.5)	33.2 (19.6–86.5)
Plasma clearance (l/h/m^2)	21.8 (40.2)	19.8 (11.9–47.8)
AUC (μg/ml·h)	5.08 (32.09)	5.04 (2.08–8.16)
Patients with elevated hepatic enzymes only[b] ($n=2$)		
Plasma clearance (l/h)	26.8 (7.4)	26.8 (25.4–28.2)
Plasma clearance (l/h/m^2)	16.5 (7.2)	16.5 (15.6–17.3)
AUC (μg/ml·h)	6.14 (5.48)	6.14 (5.90–6.37)
Patients with elevated bilirubin only ($n=4$)		
Plasma clearance (l/h)	28.1 (46.0)	25.4 (16.4–45.1)
Plasma clearance (l/h/m^2)	16.3 (45.3)	14.1 (10.5–26.4)
AUC (μg/ml·h)	7.08 (39.28)	7.40 (3.77–9.75)
Patients with elevated hepatic enzymes and bilirubin ($n=3$)		
Plasma clearance (l/h)	16.1 (25.3)	15.8 (12.1–20.3)
Plasma clearance (l/h/m^2)	9.6 (33.5)	10.4 (6.0–12.3)
AUC (μg/ml·h)	11.97 (44.77)	9.51 (8.29–18.12)

AUC, area under the curve.

[a] Patients without concomitant elevations of transaminases (>1.5×upper limit of normal) and alkaline phosphatase (>2.5×upper limit of normal).

[b] Patients with concomitant elevations of transaminases (>1.5×upper limit of normal) and alkaline phosphatase (>2.5×upper limit of normal).

treatment of patients with pancreatic adenocarcinoma. Docetaxel produced an encouragingly high response rate of 19% in evaluable patients with metastatic disease and a response rate of 15% in the overall population with a median duration of response of 5.1 (range 3.1–7.2) months. Docetaxel also controlled tumour growth for a median duration of 4.4 months in 6 out of the 9 patients with locally advanced disease. The quality of these data is strengthened by the fact that response was classified using WHO response criteria (with confirmation of the response at 4 weeks) and reviewed by an independent panel.

The most extensively studied monotherapy for pancreatic adenocarcinoma is 5-FU, for which response rates of approximately 10% in randomised studies and between 5 and 52% in non-randomised studies have been reported [2,3,5–7]. The wide range in response rates for 5-FU may reflect differences in patient selection factors or response criteria or statistical variations in relatively small sample sizes, but it also emphasises the role of external review of these responses and the inherent difficulty in assessing objective tumour response accurately in patients with advanced pancreatic cancers, particularly in the case of pancreatic mass related to locally advanced disease without metastasis. In those cases, it is quite impossible to separate the tumour mass from the surrounding pancreatic reaction.

The results for docetaxel in this study compare favourably with those reported for other new first-line agents currently under investigation for metastatic or locally advanced pancreatic cancer. For example, response rates of 5–11% have been reported for ZD1694 (raltitrexed) [33], the topoisomerase inhibitor irinotecan (CPT-11) [34,35], and the nucleoside analogue gemcitabine hydrochloride [36]. Gemcitabine has also been shown to provide clinical benefit (a novel non-validated outcome measure based mainly on marked, sustained improvement in pain intensity, analgesic consumption and performance status) in 24–27% of patients [37,38] and to prolong survival slightly compared with 5-FU (median survival 5.6 months versus 4.4 months, respectively) [38]. We did not analyse the clinical benefit as described above because this criterion was not defined when we initiated this study and because not all the patients experienced pain at the initial work-up. However, we have determined that the median pain control time was 4.5 months (range: 0–8) and the median time to performance status worsening was 2.3 months (range: 0–4.5) which reflected a positive effect of docetaxel on tumour-induced symptoms in a very aggressive cancer. In our study, the median duration of survival for patients receiving docetaxel was 7 months (95% CI 5–8 months). The modest impact on survival is balanced by the significant and documented response rate (19%) in the metastatic population and the biological responses on CA 19-9 (20%).

Our results allow comparison with reference treatments. The only drug which had the same range of response is cisplatin which had a 21% response rate in an European Organization for Research and Treatment of Cancer (EORTC) study [39], but was also more toxic and less convenient. Recently, two studies with docetaxel have been reported with minimal activity. One Japanese study used low-dose of docetaxel (60 mg/m^2 every 3–4 weeks) and reported no objective response with a median survival time of 3.8 months, underlying the importance of the dose/intensity for this drug [40]. The second study [41] using usual dose (100 mg/m^2 every 3 weeks) reported only one complete response and one partial response (6%) in 33 evaluable patients. However, only 50% of the patients had distant measurable metastases and were truly evaluable. 19 (58%) had stable disease. In this trial, the median survival of the entire group was longer than usual (8.5 months) and the 1-year survival was 36.4%; 27% of the assessable patients had a performance status (PS) improvement, 67% of the assessable patients had pain improvement and the tolerance was good. These results, like this study, suggest this drug may have some efficacy supporting the development of further clinical trials investigating this drug.

The incidence and severity of adverse events in our study reflect the known safety profile for docetaxel. Nausea, vomiting, diarrhoea, hypersensitivity and fluid retention can be managed effectively with the appropriate premedication. This premedication was not permitted in this study and one can imagine that the tolerance would have been better and comparable with that observed for breast cancer [42]. Grade 3 and 4 hepatotoxicity was observed in 11 patients: 6 of them had abnormal liver function tests at baseline and 5 patients had progressed with liver metastases.

Plasma clearance of docetaxel in patients with normal concentrations of hepatic enzymes and bilirubin in this study was similar to that estimated in a previous population pharmacokinetic study performed on 640 patients with various tumour types (mean standard deviation, S.D. 37.1 [12.3] l/h, i.e.20.9 [6.6] l/h/m^2) [26]. In addition, the decrease in plasma clearance in patients with elevated hepatic enzyme concentrations only was similar to that estimated in a previous population pharmacokinetic/pharmacodynamic study (27% decrease) [26,28]. The influence of bilirubin on docetaxel clearance could not be evaluated in the previous population study because no patient had an elevated bilirubin concentration; in this study, the influence of bilirubin was illustrated by the reduction in clearance by 25% in patients with an elevated bilirubin concentration and by 57% in patients with elevated concentrations of both hepatic enzymes and bilirubin. The population pharmacokinetic model will be revised according to this new information. This clearance reduction should

explain some of the grade 3–4 toxicities observed in that study.

The response rate and favourable side-effect profile for single-agent docetaxel in this study suggest that patients with pancreatic cancer may gain additional benefit from the combination of docetaxel with other active agents such as cisplatin, gemcitabine, 5-FU and CPT11. In particular, the absence of grade 3/4 neurotoxicity indicates that docetaxel may be more suitable for combination with platinum-based compounds. In addition, the simple dosing regimen for docetaxel (1-h infusion every 3 weeks) facilitates both combination with other agents and outpatient administration, with potential positive implications for resource utilisation.

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