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A phase II study of raltitrexed and gemcitabine in patients with advanced pancreatic carcinoma

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Advanced adenocarcinoma of the pancreas has a very poor prognosis. The aim of this study was to assess the efficacy and tolerability of a combination of the chemotherapeutic agents gemcitabine and raltitrexed. Chemonaïve patients with advanced adenocarcinoma of the pancreas were treated with a combination of raltitrexed (3.5 mg m^{-2} on day 1 of a 21-day treatment cycle) and gemcitabine (800 mg m^{-2} intravenously (i.v.) on days 1 and 8 of a 21-day cycle). Between April 2000 and February 2003, 27 patients were enrolled onto the study. The mean duration of treatment was 11 weeks. Four of 27 patients experienced at least one episode of grade 3 or 4 neutropenia. One patient with grade 4 neutropenia died due to sepsis. Four of 27 patients experienced grade 4 diarrhoea. There was one partial remission (4%) and 12 patients experienced disease stabilisation (44%). The 6-month and 1-year survival rates were 37 and 11%, respectively. Symptomatic benefit occurred in seven (26%) patients. We conclude that a combination of raltitrexed and gemcitabine, using the schedule and doses in this study, cannot be recommended for patients with advanced pancreatic cancer.

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Adenocarcinoma of the pancreas is a disease that rapidly leads to fatality, which causes annually over 40 000 deaths in Europe (Pisani *et al*, 1999) and more than 210 000 world wide (Parkin *et al*, 2001). The median survival of untreated patients is 3 months (Palmer *et al*, 1994; Glimelius *et al*, 1996). A median survival of up to 14.3 months can be achieved with radical surgery, but this is possible in less than 20% of patients, as pancreatic carcinoma tends to present late in its course (Conlon *et al*, 1996; Haycox *et al*, 1998).

All other patients, with unresectable disease, are potential candidates for systemic treatment, although unfortunately, pancreatic carcinomas are rather chemoinsensitive (Kornmann *et al*, 1999). In a study of patients with advanced pancreatic cancer by Burris *et al*, gemcitabine provided clinical benefit to 24% of patients compared to 5% with 5-fluoruracil (5-FU), and the survival rate at 12 months was 18% for gemcitibine patients compared to 2% for 5-FU patients (Burris *et al*, 1997). No single agent or combination of agents has been proven superior to gemcitabine alone, and although the objective response is low (below 10%), gemcitabine is the drug of choice for patients with advanced pancreatic cancer (Burris *et al*, 1997; Shore *et al*, 2003).

Recent advances in cancer genetics have led to the development of novel rationally designed chemotherapeutic agents. A promising target for pancreatic cancer therapy is the K-Ras oncogene product and its signalling pathway. K-Ras mutations that encode for activated proteins are found in more than 90% of all pancreatic cancers (Jaffee *et al*, 2002; Shore *et al*, 2003). In order to bind to the cell membrane, Ras protein has an additional farnesyl group. Raltitrexed (Tomudex®; AstraZeneca Pharmaceuticals, Holland) is a quinazoline folate analogue, which acts as a pure and specific thymidylate synthetase (TS) inhibitor, designed to inhibit K-ras protein farnesylation. *In vitro* single dosing has shown a similar duration of inhibition of TS as bolus 5-FU (Ford *et al*, 2002). Large randomised studies of raltitrexed have demonstrated equivalent response rates and reduced toxicity compared to the combination of 5-FU and leucovorin in colorectal cancer (Cunningham, 1998). A phase II study with raltitrexed in patients with pretreated pancreatic cancer showed a response rate of 5% (Pazdur *et al*, 1995).

Owing to some single agent efficacy, a nonoverlapping toxicity profile and a difference in mechanism of action, raltitrexed is an interesting agent to combine with gemcitabine. In order to assess the efficacy and tolerability of the combination of raltitrexed and gemcitabine in patients with nonresectable advanced pancreatic cancer, a multicentre phase II trial was started in April 2000.

PATIENTS AND METHODS

Study design objectives

The primary objective of this phase II study was to determine the efficacy of a combination of gemcitabine and raltitrexed in

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advanced or metastatic adenocarcinoma of the pancreas. Secondary objectives were to determine the duration of objective response and to evaluate the toxicity profile of this treatment.

Patient eligibility

Patients with inoperable advanced or metastatic adenocarcinoma of the pancreas had to be chemonaïve. Further inclusion criteria consisted of histologically or cytologically proven pancreatic adenocarcinoma, a World Health Organization (WHO) status of two or less and the presence of a two-dimensional measurable lesion of at least 1 cm. Patients had to be older than 18 years with an estimated life expectancy of at least 8 weeks. Adequate organ function was defined as: a haemoglobin level $\geqslant 6.5\,\mathrm{mmol\,l^{-1}}$, a white blood cell count $\geqslant 4000\,\mu\mathrm{l}^{-1}$, a platelet count $\geqslant 100\,000\,\mu\mathrm{l}^{-1}$, a creatinine clearance of $\geqslant 65\,\mathrm{ml\,min^{-1}}$ (calculated according to the formula of Cockcroft and Gault, 1976), bilirubin levels $\leqslant 3$ times the upper normal laboratory value, serum transaminase levels <2.5 times the normal laboratory values without known liver involvement or <5 times the normal laboratory values with known liver involvement. Patients who had been treated with radiotherapy for pancreatic cancer, and patients with symptomatic cerebral or leptomeningeal metastases were excluded. The local ethics committees approved this study and written informed consent was obtained from all patients before entry to the study.

Treatment protocol

Raltitrexed (Tomudex®) was administered intravenously (i.v.) at a dose of $3.5\,\mathrm{mg\,m^{-2}}$ over 15 min on day 1 of a 21-day treatment cycle. Gemcitabine (Gemzar®; Eli Lilly, Indianapolis, USA) was administered at a dose of $800\,\mathrm{mg\,m^{-2}}$ i.v. over 30 min on days 1 and 8 of a 21-day cycle. Courses were administered every 3 weeks, as long as patients benefited, and there was no evidence of progressive disease (PD).

Adverse reactions were evaluated according to Common Toxicity Criteria of the National Cancer Institute of Canada (NCI – CTC). In the event of clinically relevant toxicity during the first cycle of treatment, dosing was delayed until all signs of toxicity had resolved or at least improved. Any patient who required more than 14 days for recovery was removed from the study. For all further cycles, administered doses were based on toxic effects observed during the previous cycle. In the case of grade 3 or 4 haematological toxicity requiring more than 1 week delay of the next treatment cycle, or febrile neutropenia, both drug doses were reduced by 25% for subsequent cycles. The raltitrexed dose was reduced to 75 or 50%, respectively, if grade 3 or 4 nonhaematological toxicity occurred during the previous treatment cycle. Doses of both chemotherapeutic agents were reduced in the case of grade 2 or 3 diarrhoea and discontinued in the case of grade 4 diarrhoea. In the event of renal function impairment, raltitrexed was reduced to 75 or 50%, if creatinine clearance was 55–65 or $25–54\,\mathrm{ml\,min^{-1}}$, respectively. In both cases cycle duration was extended to 28 days. When creatinine clearance was less than $25\,\mathrm{ml\,min^{-1}}$, raltitrexed treatment was terminated. In the case of grade 3 or 4 toxicity after a dose reduction, patients were removed from the study.

Clinical evaluation

Toxicity analyses were applied to patients who received at least one course of chemotherapy, while response evaluation was assessed after every two cycles of chemotherapy, either using a CT scan or clinically according to WHO standard criteria (Miller *et al*, 1981). Subjective symptoms (pain score, analgesic use and performance status), serious adverse reactions, physical examination, performance status and other clinical benefit response parameters were recorded before each treatment cycle.

Statistics

According to the optimal two-stage design, for a target activity level of at least 20% response rate, two objective responses had to be observed in the first 21 assessable patients (alpha and beta error probabilities 0.005 and 0.01, respectively), otherwise this trial would be terminated. Time-related parameters were analysed using Kaplan–Meier on an intention-to-treat analysis.

RESULTS

Between April 2000 and February 2003, 27 patients from six institutions were enrolled onto the study. All patients were eligible. The main clinical characteristics at study entry are listed in Table 1. The median age was 59 years (range 42–74 years) and the performance status was 44, 44 and 11% for WHO 0, 1 and 2, respectively. No patients had received radiotherapy or chemotherapy prior to the study. In all, 16 (59%) patients had metastatic disease at the time of registration. A total of 95 cycles were administered (mean four cycles per patients, range 1–14). The mean duration of treatment was 11 weeks.

Six patients (22%) did not start with the second course of chemotherapy due to objective or subjective toxicity and were not assessable for efficacy (Table 2). One (4%) patient showed a partial response (95% CI-3–11%). A total of 12 (44%) patients showed disease stabilisation or a minor response with a median duration of 3 months (range 2–7 months). In eight patients (30%), the tumour was progressive despite treatment. The overall median survival was 5.5 months (range 1–16 months). The median time to progression was 3.4 months (range 0–12 months). At the time of study evaluation, two patients were still alive at 99 and 106 days of follow-up. The 6-month and 1-year survival was 37 and 11%, respectively.

The toxicity for up to six treatment cycles was evaluated for all patients and results are summarised in Table 3. Four patients were unwilling to undergo further treatment because of subjective toxicity. Haematological toxicities were grades 3–4 in four patients with leucopoenia and in three patients with thrombocytopenia. One patient with grade 4 leucopoenia died due to septicaemia. Elevated transaminases and alkaline phosphatase were frequently observed in the patients. However, these abnormalities were

Table 1 Patient characteristics

Characteristic	*n*
Number of patients	27
Age (years)	
Median	59
Range	42–74
Female/male	13/14
Disease at presentation	
Locally advanced	11
Metastatic	16
WHO performance status	
0	12
1	12
2	3
WHO pain intensity	
0	6
1	6
2	6
3	8
4	1
Weight loss >5% pretreatment	13

WHO = World Health Organization.

Table 2 Overall objective response

	No. of patients ($n = 27$)	%
PR	1	4
SD	12	44
PD	8	30
Not assessable	6	22

PR = partial response; SD = stable disease; PD = progressive disease.

Table 3 Toxicity

	WHO grade			
Toxicity	**1**	**2**	**3**	**4**
Anaemia	9 (19)	4 (5)	—	1 (1)
Leucopoenia	3 (9)	4 (6)	0 (1)	4 (4)
Thrombocytopenia	0 (2)	—	3 (3)	—
Elevated ASAT	10 (30)	5 (7)	4 (5)	1 (1)
Elevated ALAT	9 (23)	6 (12)	8 (10)	—
Elevated alkaline phosphatase	7 (23)	9 (12)	2 (2)	—
Elevated bilirubin	2 (2)	1 (1)	2 (2)	4 (4)
Nausea	8 (29)	7 (12)	7 (7)	—
Vomiting	9 (16)	8 (10)	2 (2)	—
Diarrhoea	6 (8)	0 (2)	2 (3)	4 (4)
Mucositis	4 (5)	—	2 (2)	—
Cutaneous	2 (6)	2 (3)	—	—
Flu-like symptoms	4 (9)	5 (7)	—	—

ASAT = serum glutamic oxaloacetic transaminase; ALAT = serum glutamic pyruvic transaminase; WHO = World Health Organization.

self-limiting. In eight patients, transaminases were elevated before entry to the study and were therefore most probably disease related. Grade 1–2 nausea occurred in 41% of the treatment cycles. Grade 1–3 diarrhoea occurred in 17% of cycles, leading to hospitalisation in four (15%) patients. In two patients, with grade 2 and 3 diarrhoea, respectively, the doses of gemcitabine and ralitrexed were not reduced according to the protocol. Both patients experienced grade 4 diarrhoea in the following treatment cycle. No dose modifications for renal impairment needed to be performed over the first six treatment cycles.

Five of the 27 patients who reported pain at study entry reported less pain after treatment and two patients experienced weight gain. Therefore, seven patients (26%) were classified as clinical benefit responders. Four patients (15%) were stable in both primary (ie pain intensity and WHO performance status) and secondary (weight) parameters.

DISCUSSION

The effects of 5-FU in pancreatic carcinoma have been extensively studied and reported response rates for single agent 5-FU treatment in patients with pancreatic cancer range from 0 to 19% (Warshaw and Fernandezdelcastillo, 1992; Haller, 2003). Although gemcitabine is generally approved as a first-line treatment for advanced pancreatic cancer, the objective responses are low and the median survival benefit is modest in comparison with 5-FU alone (Burris *et al*, 1997). Owing to disappointing results from chemotherapy in pancreatic cancer, combination regimens have now been developed. Combinations of 5-FU-like drugs and gemcitabine show synergistic antitumour activity *in vitro* (Ren *et al*, 1998; Peters *et al*, 2000). In patients with advanced cancer, it has been shown that gemcitabine increases systemic 5-FU exposure (Correale *et al*, 2003a), and several studies have tested the combination of these two drugs in pancreatic cancer with response rates of up to 31% and median survival rates of up to more than 1 year (Correale *et al*, 2003b; Lee *et al*, 2004). One randomised phase III study with gemcitabine in combination with 5-FU *vs* gemcitabine alone did not demonstrate any improvement in median survival (Berlin *et al*, 2002). However, 5-FU was given as a bolus infusion and there is evidence that continuous infusion might be superior to bolus administrations (Hansen *et al*, 1988; Aschele *et al*, 1992; Hidalgo *et al*, 1999). Thus, the method of administration may have influenced the outcome of the study by Berlin *et al* and so the combination of these two drugs remained attractive.

A full paper was published on one study by Kralidis *et al* (2003) involving the combination of raltitrexed and gemcitabine in patients with locally advanced and metastatic pancreatic cancer. In this study, the patients were treated with raltitrexed ($3\,mg\,m^{-2}$ in 15 min infusion) on day 1 and gemcitabine ($1000\,mg\,m^{-2}$) on days 1 and 8. In comparison to our study, patients had worse prognostic factors (Cubiella *et al*, 1999), that is, 20% of patients had a WHO score of 0 compared to 44% in our study and 84% of patients had metastatic disease compared to 59% in our study. The reported 1-year survival (11%) and tumour growth stabilisation rate (overall response + stable disease) are more or less equal in both studies, but the reported response rates differ (12% compared to 4% in our study). We used a relatively high dose of bolus raltitrexed in combination with a lower dose of gemcitabine. Laboratory research on the effects of raltitrexed on elevation of plasma 2′ deoxyuridine as a marker for TS inhibition suggests that there is a plasma drug level above which no further TS inhibition is accomplished (Ford *et al*, 2002). Thus, high plasma concentrations of raltitrexed after bolus infusion might be responsible for the increased amount of gastrointestinal toxicity in our patients, without an increase in therapeutic effect. In our study, seven patients stopped further chemotherapy due to subjective or objective toxicity. One of these patients had a potential partial response, but this could not be confirmed objectively. The difference observed between these studies may also be caused by the relatively low dose of gemcitabine administered to our patients. Preclinical data using human tumour cell lines indicated a possible dose–response relationship, suggesting that exposure to a higher concentration of gemcitabine might correlate with improved clinical effectiveness (Von Hoff, 1996).

The reported 1-year survival and clinical benefit ratios in our study and the study of Kradalis *et al* are not better than the results reported with gemcitabine as a single agent (Burris *et al*, 1997). One reason for this could be related to the design of both studies. Preclinical data suggest that gemcitabine given before 5-FU produces more synergistic antitumour activity in pancreas carcinoma cell lines (Correale *et al*, 2000). In our study and the study of Kradalis *et al*, gemcitabine was administered after the raltitrexed. In our study, gemcitabine was administered as a 30 min infusion and not as a fixed dose rate (FDR). In a randomised phase II study by Tempero *et al* (2003) comparing gemcitabine treatment as a standard 30 min infusion to administration at an FDR of $10\,mg\,m^{-2}\,min^{-1}$ over 150 min, the 1- to 2- and even 3-year survival rates were in favour of the FDR. This was also seen in a phase II study in which patients with advanced pancreatic cancer given FDR gemcitabine in combination with an oral fluoropyrimidine had a median survival of almost 1 year (Feliu *et al*, 2002).

We conclude that this combination of raltitrexed and gemcitabine given in a sequential schedule has a moderate activity. There is no evidence suggesting that this combination is advantageous over gemcitabine or 5-FU alone in the treatment of advanced pancreatic cancer.

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