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Activity of raltitrexed and gemcitabine in advanced pancreatic cancer

E. Kralidis[1], S. Aebi[1], H. Friess[2], M. W. Büchler[2] & M. M. Borner[1]*

[1]*Institute of Medical Oncology,* [2]*Department of Visceral and Transplantation Surgery, University of Bern, Bern, Switzerland*

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Background: Gemcitabine has evolved as standard therapy in advanced pancreatic cancer since the demonstration of a significant clinical benefit. Phase II trials have shown that gemcitabine can be successfully combined with thymidylate synthase (TS) inhibitors such as continuous-infusion 5-fluorouracil (5-FU). However, continuous-infusion 5-FU is inconvenient because of the need for a central venous access. The aim of this study was to assess the efficacy and safety of gemcitabine in combination with raltitrexed (Tomudex), a novel and selective TS inhibitor that has the advantage of a 3-weekly treatment interval and manageable toxicity.

Patients and methods: Chemotherapy-naïve patients with measurable advanced pancreatic cancer were treated with raltitrexed 3 mg/m^2 as a 15-min infusion on day 1 and gemcitabine 1000 mg/m^2 on days 1 and 8, every 21 days.

Results: Twenty-five eligible patients (17 male, eight female) with metastatic (21 patients) or locally advanced (four patients) disease entered the study. The median number of courses per patient was four (range 1–14). One patient was not evaluable for response. There were three partial remissions [12%; 95% confidence interval (CI) 2.6% to 31.2%] and nine stable disease situations (36%; 95% CI 18.0% to 57.5%), while the tumours of 12 patients (48%; 95% CI 27.8% to 68.7%) showed progressive disease after three treatment cycles. WHO grade 3/4 toxicity was rare and symptomatic in only one patient, who experienced grade 4 diarrhoea and grade 3 nausea and vomiting. Symptomatic benefit was seen in 12 patients. Median survival was 185 days (95% CI 129–241) with six patients still alive.

Conclusions: The efficacy of raltitrexed plus gemcitabine is limited, but compares well with other chemotherapy treatment options in advanced pancreatic cancer. However, this combination is convenient and symptomatic toxicity is rare. Thus, raltitrexed and gemcitabine should be investigated further in combination with drugs interfering with specific molecular targets.

Key words: gemcitabine, pancreatic cancer, phase II, raltitrexed

Introduction

The study of Burris et al. [1] has established gemcitabine as standard treatment for advanced pancreatic cancer. Gemcitabine has not only shown a survival benefit but also an improvement of various disease-related symptoms over bolus 5-fluorouracil (5-FU). However, the effect of gemcitabine on measurable disease was rather limited since objective tumour responses were observed in only three out of 56 patients (5.4%). A beneficial effect of 5-FU *per se* cannot be excluded from this trial. The efficacy of fluoropyrimidines is highly schedule-dependent and weekly bolus administration might not be the optimal schedule. A phase II study with continuous-infusion 5-FU in advanced pancreatic cancer has shown an objective response rate of 19% and disease stabilisation in half of the patients [2]. Although different schedules of 5-FU administration have not been formally compared in pancreatic cancer, these results suggest that continuous infusion might be more effective than weekly bolus administration in this disease.

Two recently published studies in advanced pancreatic cancer have shown a 19–20% objective response rate and a clinical benefit in patients undergoing treatment with the combination gemcitabine plus continuous-infusion 5-FU [3, 4]. Despite a favourable toxicity profile, this treatment is not convenient, since continuous 5-FU necessitates the use of a permanent central venous access and a portable pump system. The major molecular target for the activity of 5-FU is thymidylate synthase (TS), which is inhibited by 5-FU alone and more efficiently by the combination 5-FU plus leucovorin [5]. Raltitrexed is a new selective TS inhibitor, which has the advantage of a 3-weekly treatment interval and low toxicity. Randomised phase III studies in advanced colorectal cancer have proven similar efficacy but significantly lower toxicity of raltitrexed compared with biomodulated 5-FU [6].

Given alone, raltitrexed has shown a response rate of 5% in pancreatic cancer [7], which compares well with the activity of

**Correspondence to:* Dr M. M. Borner, Institute of Medical Oncology, Inselspital, 3010 Bern, Switzerland. Tel: +41-31-632-84-42; Fax: +41-31-382-4-19; E-mail: markus.borner@insel.ch

gemcitabine in this disease [1]. Raltitrexed and gemcitabine are attractive partners for combination treatment because of the non-overlapping toxicity profile of the two drugs. The objective of this trial was to assess activity and tolerability of the combination raltitrexed and gemcitabine in chemotherapy-naïve patients with non-resectable, advanced or metastatic pancreatic cancer. Both drugs were administered at the doses used for single-agent treatment to allow for maximum dose intensity. This was a single-centre study and patients could be closely monitored for unforeseen toxicity.

Patients and methods

Patient eligibility

Chemotherapy-naïve patients with advanced non-resectable adenocarcinoma of the pancreas were entered into this single-centre phase II study between September 1999 and June 2001. Eligibility criteria included cytologically or histologically confirmed adenocarcinoma of the pancreas, two-dimensionally measurable disease by computed tomography (CT) scan, and a WHO performance status of two or less. Patients were older than 18 years of age and had an estimated life expectancy of at least 12 weeks. Adequate organ function was defined as white blood cell count ≥3500/μl, platelet count ≥100 000/μl, total bilirubin ≤35 μmol/l, and serum creatinine level ≤140 μmol/l. The study was submitted to the local ethics committee and written informed consent was obtained from all patients before study entry.

Treatment plan

Raltitrexed (Tomudex; AstraZeneca, Zug, Switzerland) was administered at a dose of 3 mg/m^2 over 15 min on day 1 of a 2-day treatment cycle. In cases of moderate renal dysfunction, the dose of raltitrexed was adapted. If the creatinine clearance was 55–65 ml/min, 75% of the planned dose was administered, and if the creatinine clearance was 25–54 ml/min only 50% of the dose was administered. In addition, the cycle duration was extended to 4 weeks in cases of moderate renal dysfunction. When the creatinine clearance was <25 ml/min, raltitrexed was stopped and the patient went off study.

Gemcitabine [Gemzar; Eli Lilly (Suisse) SA, Vernier, Switzerland] was administered at a dose of 1000 mg/m^2 over 30 min on days 1 and 8 of a 21-day treatment cycle. If the treatment cycle duration was extended because of renal dysfunction, gemcitabine was also given on day 15.

The start of a treatment cycle was postponed in case of WHO grade >1 toxicity. After a delay of more then 3 weeks, the patient went off study. The raltitrexed dose was reduced to 75 or 50%, respectively, if grade 3 (2) or grade 4 (3) (non)-haematological toxicity occurred in the previous treatment cycle. In the case of grade 4 non-haematological toxicity, the patient went off study. Gemcitabine was omitted in the case of grade ≥3 haematological and grade ≥2 non-haematological toxicity on day 8 (or 15). The gemcitabine dose was reduced to 75%, if grade 3 non-haematological or grade 4 haematological toxicity occurred in the previous treatment cycle.

Follow-up procedures and response evaluation

Blood counts were obtained weekly. Chemistry profiles including CA 19-9 antigen and physical examinations were done every 3 weeks. The first CT reassessment for response evaluation was performed at 9 weeks. Partial response (PR) was defined as ≥50% decrease in the sum of the products of two perpendicular diameters of all measurable lesions. In cases of responsive disease (PR or stable disease), the response had to be verified at least 4 weeks after the last CT scan.

Statistical methods

For the calculation of the required sample size, we used the MinMax two-stage design [8] with the following assumptions. A response rate of 15% was considered insufficient to allow further accrual into this study. A response rate of 30% was deemed interesting in view of the other treatment options in this disease stage. According to the Simon MinMax two-stage method with a type II error (1-β) of 80% and a type I error (α) of 5%, the combination of gemcitabine and raltitrexed was to be considered uninteresting in terms of efficacy if three responses or fewer were observed in the first 23 patients, or 11 responses or fewer in the first 48 patients.

Overall survival was determined as the time interval from day 1 of treatment until death. Survival was calculated by the Kaplan–Meier product-limit method [9].

Results

Twenty-six patients were entered in this study. One patient was considered ineligible because of the lack of measurable lesions and one patient did not receive any therapy because of fast clinical deterioration. The baseline characteristics of the 25 evaluable patients are summarised in Table 1. A total of 134 treatment cycles were administered (median four, range 1–14). Four patients received only one treatment cycle mainly because of early disease progression. One patient refused therapy after one cycle because of nausea and grade 2 anaemia. Over the first four treatment cycles, dose modifications for toxicity were performed in 12% of the patients. Raltitrexed dose reduction for renal impairment was necessary in four patients, whereas dose re-escalation was possible in two patients. In six patients, the raltitrexed dose was not adapted as detailed in the protocol for impaired renal

Table 1. Patient characteristics

Characteristic	*n*
Number of patients	25
Age (years)	
Median	63
Range	41–77
Female/male	8/17
WHO performance status	
0	5
1	18
2	2
WHO pain intensity	
0	7
1	17
2	1
>5% body weight loss pretreatment	16
Disease at presentation	
Locally advanced	4
Metastastic	21
More than one metastatic site	10

WHO, World Health Organization.

Table 2. Toxicity

Toxicity	WHO grade			
	1	2	3	4
Nausea	9 (19)	5 (6)	2 (2)	–
Diarrhoea	4 (8)	2 (2)	–	1 (1)
Cutaneous	4 (5)	–	–	–
Leukopenia	6 (9)	5 (14)	2 (4)	1 (1)
Anaemia	8 (58)	12 (22)	2 (2)	–
Thrombocytopenia	3 (3)	2 (3)	2 (2)	–
Elevated AST/ALT	3 (36)	3 (7)	8 (10)	1 (1)
Elevated alkaline phosphatase	12 (47)	3 (14)	5 (9)	–
Elevated bilirubin	3 (3)	–	1 (1)	–
Ankle oedema	7 (15)	–	–	–

Values are the number of patients with each toxicity (only highest toxicity grade per patient included) and in parentheses, the number of cycles with the toxicity (95 treatment cycles evaluated).
AST, aspartate aminotransferase; ALT, alanine aminotransferase; WHO, World Health Organization.

function at a creatinine clearance of 49–60 ml/min because of protocol violation. Four of these patients experienced grade 2 haematological toxicity, one patient in combination with grade 2 diarrhoea. One patient erroneously received raltitrexed on day 8 in addition to day 1. He was hospitalised immediately and treated prophylactically with intravenous leucovorin and subcutaneous granulocyte colony-stimulating factor. After eventless recovery, the protocol treatment was continued.

Toxicity

For all patients, toxicity of up to six treatment cycles was evaluated and the results are summarised in Table 2. The most important toxicity was anaemia. However, grade 1/2 anaemia was pre-existing in 70% of the patients. Six patients required blood transfusions. In 85% of cycles the haemoglobin remained stable at day 1 of the treatment cycles or rose during treatment. Grade 3/4 leukopenia was rare and was not complicated by fever and infections in any patient. Thrombocytopenia was also a rare side-effect and occurred only in cases where the raltitrexed dose was not adapted according to the reduced creatinine clearance.

Elevated transaminases and alkaline phosphatase were frequently observed in these patients. However, these abnormalities were pre-existing in most of the cases and more probably disease-associated than treatment-related. Grade 1/2 nausea occurred in 26% of the treatment cycles, whereas vomiting was observed in only 12% of the cycles. Diarrhoea emerged in 10% of all cycles. Grade 4 diarrhoea occurred in one patient, leading to hospitalisation at the end of the second cycle. The recovery was uneventful. However, treatment had to be stopped because of tumour progression.

Efficacy

Three of the 25 chemotherapy-treated patients achieved a lasting PR for a response rate of 12% [95% confidence interval (CI) 2.6% to 31.2%]. All these responses were radiologically verified after at least 1 month of continuing treatment. One additional patient with liver metastases experienced a radiological PR and a drop of the marker CA 19-9 from 250 to 74 kU/l. However, this response was not radiologically confirmed, since the clinical status of the patient deteriorated rapidly within 6 weeks. Thirty-six percent (95% CI 18.0% to 57.5%) of the patients experienced disease stabilisation or a minor response lasting 3–10 months. In 48% (95% CI 27.8% to 68.7%) of the patients the tumour was progressive despite treatment.

Results of CA 19-9 measurements were available in 23 patients. This tumour marker decreased in all of the responding patients and began to increase as a reflection of disease progression one or two cycles before radiological documentation of progression or clinical deterioration in all cases. In only one patient did the marker decrease despite radiological disease progression (Figure 1).

Eighteen patients reported pain and 20 patients had a reduced performance status at study entry. Pain could be reduced in 77% of the patients for at least one cycle on study treatment without intensification of the pain medication. In 38% of these patients, the pain medication could be reduced without pain intensification. Five patients could stabilise their weight, seven continued loosing weight and seven gained a median of 2 kg on study. Most of these clinical improvements occurred after two or three treatment cycles. Of patients receiving more than one treatment cycle, 64% improved or stabilised their performance status.

The median follow-up for the patients still alive was 353 days (range 270–675). The median overall survival from study entry for all eligible patients was 185 days (95% CI 129–241) (Figure 2). Six patients are still alive at 270, 295, 338, 368, 590 and 675 days follow-up. Six-month survival was 50%, 9-month survival 23% and 1-year survival 12%. Three patients are still on trial.

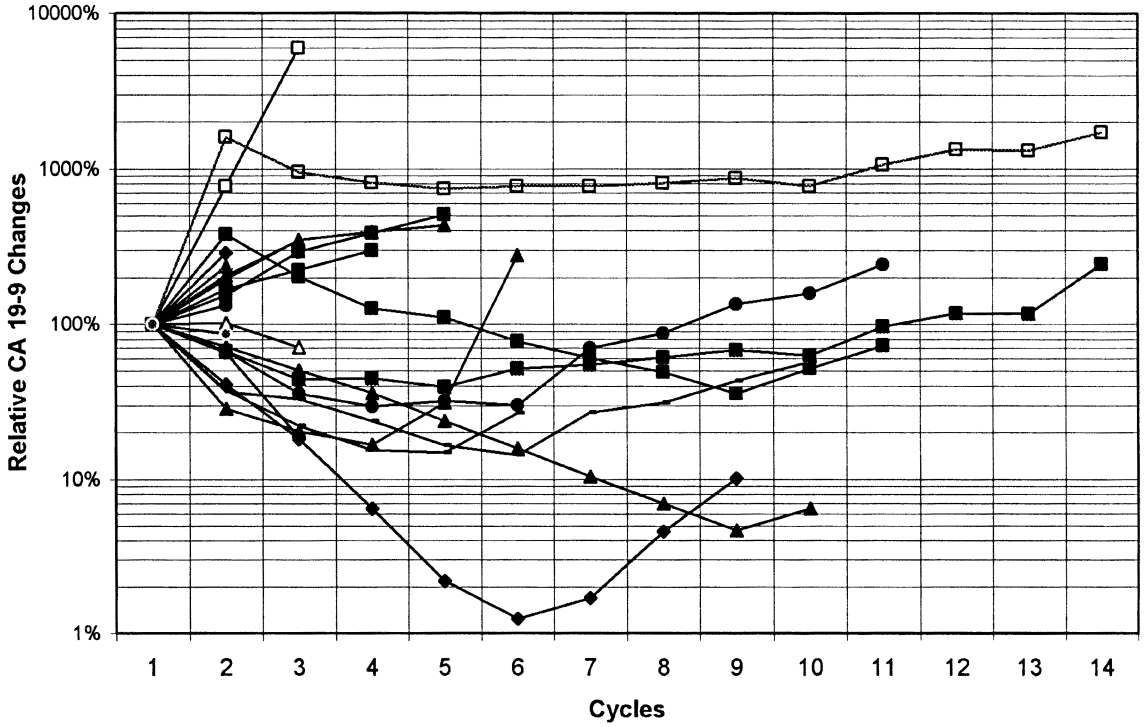

Figure 1. CA 19-9 evolution during trial treatment.

Discussion

Progress in the treatment of advanced pancreatic cancer has been slow. The only study to demonstrate a clinical benefit of one chemotherapy over another has established gemcitabine as the standard single-agent treatment in this disease [1]. However, a non-optimal 5-FU schedule was used in the comparator arm of the trial and a 5% response rate and 23-week survival duration with gemcitabine alone leave much room for improvement. Other modern anticancer drugs such as paclitaxel, docetaxel, topotecan or irinotecan seem not to have major single-agent activity, based on the results of well-conducted phase II studies [10–14]. Disappointingly, median survival duration has generally remained below 6 months with all available agents.

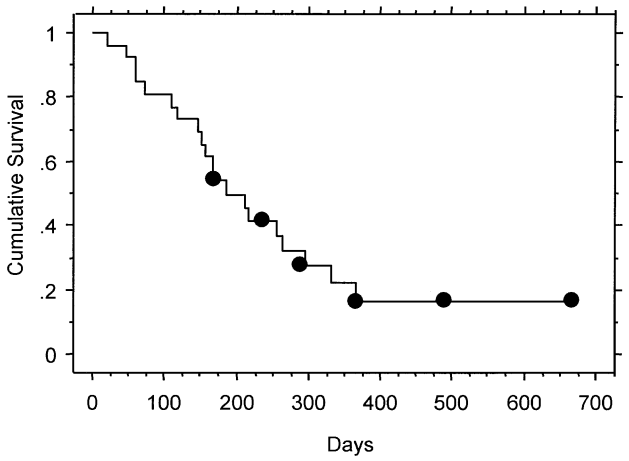

Figure 2. Overall survival.

Considering the clinically most relevant median survival end point, various chemotherapy combinations have suggested a slight improvement compared with single-agent treatment. Combining gemcitabine with cisplatin or oxaliplatin has translated into a median survival duration of 7.4–9+ months [15–18]. However, this apparent superiority of combination treatment has been derived from the results of non-comparative trials and it is possible that the slight improvement seen with combination treatment is mainly because of better patient selection. It is well known that extent of disease and performance status are major prognostic factors for survival, even in the absence of treatment [19]. Thus, until the results of well-performed randomised trials comparing single-agent with combination treatment are available, it is not clear whether the additional costs and toxicity of combinations are outweighed by significant clinical benefit. This is even more true in the light of recent results with novel drug combinations such as docetaxel plus cisplatin, docetaxel plus gemcitabine, pemetrexed plus gemcitabine or oxaliplatin plus gemcitabine [20–22]. Even in probably highly selected phase II study populations, these combinations have resulted in disappointing median survival durations of 5.7–7.6 months.

So far, no randomised study has proven a clear advantage of combination chemotherapy over single-agent treatment in advanced pancreatic cancer. Adding mitomycin C to protracted venous infusion 5-FU has led to a significantly improved response rate without translating into a survival benefit. No symptomatic and quality-of-life improvement was observed with the combination treatment. Two recently reported studies have investigated the impact of combining 5-FU with standard gem-

citabine. A randomised phase II study from an Italian group found no survival benefit if gemcitabine was combined with continuous-infusion 5-FU. The study was presented after 89 evaluable patients had been entered. A more mature trial of the Eastern Cooperative Oncology Group has randomised 327 patients. The results of this trial favour combination treatment, although the survival difference is not statistically significant ($P = 0.11$). Again, 5-FU has not been used in the most promising continuous-infusion schedule.

Two phase II studies have shown a median survival of 6.7–7.2 months and a clinical benefit in patients undergoing treatment with the combination gemcitabine plus continuous-infusion 5-FU [3, 4]. Although the toxicity profile was favourable, this treatment is not convenient since continuous 5-FU necessitates the use of a permanent central venous access and a portable pump system. The recent availability of oral fluoropyrimidine drugs such as uracil/tegafur or capecitabine has helped to circumvent this problem. A phase I study by Herrmann et al. [23] has tested the combination of capecitabine and gemcitabine in advanced pancreatic cancer. The recommended dose for capecitabine from this trial was 1300 mg/m^2 daily for 14 days every 3 weeks, which is nearly half of the recommended single-agent dose for this drug. Thus, there are considerations that capecitabine was underdosed in this study [24]. Currently, this regimen is being compared with gemcitabine alone in an international randomised phase III study (R. Herrmann, personal communication). Scheithauer et al. [25] have recently presented the preliminary results of a similar study suggesting no efficacy benefit of the capecitabine plus gemcitabine combination over gemcitabine alone. Again, the chosen dose regimen for the fluoropyrimidine drug was not standard, since capecitabine was only given for 7 days per cycle instead of the more common 14-day or continuous administration schedule.

In terms of survival and clinical benefit, the combination raltitrexed and gemcitabine compares well with other combinations of gemcitabine and TS inhibitors in the treatment of advanced pancreatic cancer. Our study population was not a good-prognosis selection, as most patients had metastatic as compared with locally advanced disease. This is an important issue in assessing clinical studies of advanced pancreatic cancer, since the overall survival in metastatic disease is significantly worse than in locally advanced disease [19]. In our study, a significant proportion of patients reported decreasing pain intensity and analgesic consumption, a better performance status and increasing weight with protocol treatment. Quality-of-life issues are very important in chemotherapy treatment of advanced pancreatic cancer in view of the fact that even new agents and drug combinations have not yet translated into better median survival results than 6–8 months. Thus, the major advantage of the combination raltitrexed and gemcitabine is its favourable toxicity profile and the convenience of administration. Symptomatic side-effects are very rare, with a minority of patients experiencing nausea or diarrhoea. Stomatitis or the hand–foot syndrome have not been observed in our study population. The TS inhibitor raltitrexed can be given as a short infusion once every 3 weeks and the use of infusion pumps or the prolonged intake of several tablets per day is not necessary.

Clearly, the efficacy of the gemcitabine and raltitrexed combination leaves much room for improvement. This combination should not be routinely used outside clinical trials until it has been formally tested against other therapeutic options in advanced pancreatic cancer. However, because of its convenience and favourable toxicity profile, it is an eligible combination partner for other active agents. As novel compounds interfering with specific biological targets such as the epidermal growth factor signalling pathway, angiogenesis or apoptosis regulation enter the clinic, it will be advantageous to combine these agents with minimally toxic chemotherapy drug partners.

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