Phase I/II Study to Investigate the Use of Gemcitabine in Combination with Raltitrexed in Locally Advanced or Metastatic Pancreatic Adenocarcinoma

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Citation

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Abstract

Adenocarcinoma of the pancreas remains one of the most difficult cancers to treat. Raltitrexed, a novel quinazoline analogue, combined with gemcitabine is likely to potentate the anti-cancer effect, as both of those drugs inhibit DNA synthesis via separate metabolic pathway. We report a phase I/II study of increasing dose of gemcitabine with raltitrexed in patients with advanced adenocarcinoma of the pancreas. The study was conducted at three different dose levels with raltitrexed at 3mg/m2 and increasing gemcitabine levels. 24 patients were recruited. Cohort 2 patient developed unexpected toxicity with 58% of patients experiencing haematological toxicity and 29% nausea and vomiting. The majority of patients complained of lethargy and 5 patients reached dose-limiting toxicity. Partial responses were documented in two out of 24 patients (8%), 25% had stable disease and 50% developed progressive disease. We found the combination of raltitrexed and gemcitabine active but poorly tolerated in pancreatic cancer.

INTRODUCTION

Adenocarcinoma of the pancreas remains one of the most difficult cancers to treat. Despite progress in diagnosis and improvement in surgical techniques the 5- year survival rate for pancreatic cancer is approximately 3%. Patients with advanced cancer are often cachectic and experience many disease related symptoms such as weight loss, pain and anorexia. Use of median survival alone as the primary endpoint for assessment of chemotherapy efficacy is felt to be inadequate and therefore the majority of new therapeutic trials use clinical benefit response (CBR) as a more relevant assessment of efficacy [1].

The most accepted and least toxic chemotherapy agent currently used for pancreatic cancer is gemcitabine, with a radiological response rate of 5.4%, median survival of 5.65 months and clinical benefit response of 28% [1], compared to bolus 5-FU where median survival is in the range of 4.4 months . Raltitrexed is a novel quinazoline analogue, specific thymidylate synthase (TS) inhibitor that has a similar mechanism of action to 5FU. Raltitrexed is a substrate for the enzyme folylpolyglutamate synthetase (FPGS) which converts raltitrexed to its polyglutamate forms. These are retained within the cells for long periods and are a lot more potent inhibitors of TS than the parent compound.

Raltitrexed has been extensively used in the treatment of colorectal cancer but also in treatment of other malignancies such as non-small cell lung cancer, mesothelioma, head and neck malignancies and sarcoma [2]. Raltitrexed, as a single agent in pancreatic cancer has been evaluated in only one study, published in 1996 [3]. It was shown to have acceptable safety profile but limited activity in patients with advanced pancreatic cancer. Raltitrexed selectively inhibits thymidylate synthase and therefore prevents DNA replication. Gemcitabine inhibits DNA synthesis by incorporating CTP; therefore combining the two drugs is likely to potentate the anti-cancer effect by affecting two separate metabolic pathways.

Combination of gemcitabine with raltitrexed has been previously evaluated in a phase I trial of solid tumour treatment [4]. The maximum tolerated dose was 3.5mg/m² raltitrexed and 1000mg/m² gemcitabine. The recommended dose level was gemcitabine 800mg/m² day 1 and 8 with raltitrexed 3.5mg/m² on day 1 of a 21-day cycle. The use of raltitrexed at 3.5mg/m² on a 21-day cycle is the recommended dose for single agent use. Gemcitabine dose

of 800mg/m² for 2 weeks out of 3 (dose intensity of 533mg/m²/week) is considerably less than the recommended single agent dose of 1000mg/m² for 3 weeks out of 4 (dose intensity of 750mg/m²/week).

We have performed a phase I/II study of increasing dose of gemcitabine with raltitrexed in patients with advanced adenocarcinoma of the pancreas in order to define maximal tolerated dose (MTD) and clinical benefit response (CBR) for the combination. The gemcitabine dose was escalated to a maximum of 1400mg/m ^{2} (dose intensity 933mg/m ^{2}) to meet the recommended single agent dose and then to test it at a higher level, the raltitrexed dose was set at 3mg/m ^{2} , to limit the potential toxicity of the combination regimen.

PATIENTS AND METHODS

Patients with histologically or cytologically confirmed inoperable adenocarcinoma of the pancreas were recruited from four Oncology Departments. All patients were required to have an adequate organ function, defined as WBC count of 3.0 x 10 ^{9} /l with absolute neutrophil count of 2.0 x 10 ^{9} /l, a platelet count of 100 x 10 ^{9} /l, adequate renal function with creatinine clearance of more than 65ml/min (calculated by Cockroft and Gault formula) and adequate hepatic function with bilirubin level of less than 1,5 times the upper limit of normal range, serum transaminase level of less than 5 times the upper limit of normal were necessary; Karnofsky performance status of more than 60% and life expectancy over 12 weeks. A complete medical history, physical examination, performance status assessment, vital signs and pain score were obtained at baseline for each patient. Baseline investigations included full blood count, biochemistry including urea and electrolytes, ALT, AST, alkaline phosphatase, albumin, bilirubin, CA19-9, CEA and LDH, chest X-ray, ECG and CT scan. Full blood count was repeated weekly and physical examination, recording of toxicity, analgesic score, serum biochemistry, CA19-9 and calculated creatinine clearance at three weekly intervals, prior to each cycle and post treatment. Disease status was evaluated prior to starting chemotherapy, after the third and the sixth cycle of treatment. The treatment consisted of raltitrexed given at 3 mg/m ^{2} with gemcitabine dose escalating by 200mg/m ^{2} from 1000mg/m ^{2} in cohort 1 to 1400mg/m ^{2} in cohort 3, given on day 1 and 8 of 21-day cycle. Doses were assigned at registration and no dose escalation was permitted in individual patients. Cohorts of at least three patients were treated at each dose level. Dose escalation proceeded if no patients had dose-limiting toxicity (DLT). Haematological DLT was defined as persistent neutropaenia (less than 0.5 x 10 ^{9} /L for 7 days or more), platelet count of less than 50 x 10 ^{9} /L or haemorrhage secondary to thrombocytopaenia requiring transfusion and febrile neutropaenia. Non-haematologic DLT was defined as any grade 3 or 4 NCIC-CTC toxicity with the exception of nausea, vomiting, alopecia and transaminitis. The time period of defining DLT was 21 days from the start of treatment. If the toxicity did not reverse within 21 days (after a 3 week treatment delay) the patient was withdrawn from the study, for patients who recovered fully a dose modification was required. The subsequent cycle of treatment was administered so long as neutropaenia and/or thrombocytopenia had resolved after up to a maximum of 3 weeks delay. If the delay was greater than 2 weeks then both drugs were administered at 75% of dose for the next and all subsequent cycles. Day 8 gemcitabine was administered so long as the neutrophil count was 1.0 x 10 ^{9} /L and platelets ≥ 100 x 10 ^{9} /L on that day. If either count was below that level then the infusion was delayed by one week. In case of grade 3 diarrhoea or mucositis in any one cycle, the dose was reduced to 75% for all subsequent cycles.

If one or more patients had DLT, three more patients were enrolled at that level.

If 2 patients experienced similar DLT the maximum tolerated dose was defined and the recommended therapeutic dose was established at the next lower dose level. Patients were evaluated at the study entry and later at 3-weekly intervals to assess for disease progress and presence of treatment related toxicities, the full blood count was repeated at weekly intervals. Response was classified as per the WHO criteria and in addition patients were assessed for the Clinical Benefit Response as defined by Burris et al [Burris, 1997 #21]. Clinical Benefit Response (CBR) was defined as a sustained improvement for a minimum of 4 weeks in at least one of the primary parameters, i.e. pain, analgesic consumption or Karnofsky performance status, without any sustained worsening in any other (weight), or stability in all the primary parameters with a sustained weight gain (more than 7% for at least 4 weeks), not due to fluid accumulation. The study and subsequent amendments to the protocol were approved by the ethics committees of participating centres and written informed consent was required from each patient.

The sample size for the phase II study has been determined using the Simon two stage minimax design (1989). This

design allows for early termination of the study should the treatment show insufficient activity. For the phase II of the study, 30 patients eligible for clinical benefit response were required for the stage 1, if 4 or less responses were observed in these patients the trial would have been stopped due to the treatment having insufficient activity, otherwise it would continue into stage 2, until a total of 41 patients, eligible for objective response were recruited.

RESULTS

PATIENT CHARACTERISTICS AND DOSE ESCALATION

Twenty-four patients were registered on the study over a period of 21 months (Table 1). Eighteen patients were male and six female. Age varied between 35 and 78 with a median of 60 years old. Mean Karnofsky performance status was 84% and varied from 70 to 100%. Six patients were recruited in cohort 1, at the initial dose level of ralitrexed 3,0mg/m ^{2} with gemcitabine 1000mg/m ^{2} . The gemcitabine dose was escalated to 1200mg/m ^{2} in cohort 2 and remained the same for 12 patients. Cohort 2 patients experienced unexpected toxicity (see below) and the protocol was amended for the remaining 6 patients. The ralitrexed dose was reduced to 2mg/m ^{2} with gemcitabine dose remaining at 1200mg/m ^{2} .

Figure 1

Table 1: Patients characteristics.

No of Patients		
Total patients		
24		
Sex		
	Male	18
	Female	
6		
Age, years		
	Median	60
	Range	35-78
Karnofsky Performance status		
	100	1
	90	13
	80	6
	70	4
Locally advanced tumours		**Metastatic tumours**
8		16

24 patients received the total of 93 cycles (mean 3.87; range one to six cycles per patient) and all cycles were assessable for toxicity. Cohort 1 patients received 27 cycles (median 4.5), cohort 2 patients received 43 cycles (mean 3.58) and remaining six patients received 23 cycles (mean 3.83). Seven patients completed all six cycles of treatment, one in cohort 1, four in cohort 2 and two patients in the last group (with reduced dose of raltitrexed).

TOXICITY

In cohort 1, three patients stopped prematurely. Two developed progressive disease and the third patient was admitted with an extensive bullous rash over the chest, abdomen, arms and upper legs. Blood analysis revealed neutropaenia, anaemia and thrombocytopaenia. One case of neutropaenic fever, was recorded, which resolved with intravenous antibiotics, and one patient developed grade 3 diarrhoea warranting admission for intravenous fluids and antibiotics. Thus one dose limiting toxicity and one case of idiosyncratic skin rash were seen in six patients and the dose was escalated.

Cohort 2 patients experienced unexpected toxicity (table2). Eight out of twelve patients did not complete six cycles of treatment. Six patients had progressive disease, one withdrew consent, and one patient was withdrawn from the study following two hospital admissions. Both admissions were due to fever associated with grade 2-anaemia and grade 2-nausea and vomiting. Although the fever was not associated with neutropaenia, the patient was found to be thrombocytopaenic (grade 3) and was severely lethargic (grade 3).

Figure 2

Table 2: Toxicity profile

Haematological toxicity									
Cohort	Haemoglobin			White cell count (ANC)			Platelets		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Cohort 1	5	0	0	0	1	0	0	0	1
Cohort 2	15	0	0	5	1	1	2	0	1
Cohort 3	0	0	0	0	0	0	0	0	0
Non-haematological toxicity									
	Lethargy			Gastro-Intestinal			Other		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Cohort 1	0	0	0	0	1	0	Rash-1		
Cohort 2	5	0	0	4	4	1	Neuropathy-1 DVT-1		
Cohort 3	0	0	0	0	0	0	DVT-1		

In total there were fifteen serious adverse events recorded. Haematological toxicity included seven cases (58%) of anaemia, six requiring blood transfusion, one case of febrile neutropaenia and two patients developed thrombocytopaenia, warranting delay of treatment. Non-haematological toxicity included lethargy with the majority of patients affected (grade 1-2). Seven patients experienced nausea and vomiting (three cases of grade 3 and four of grade 2), in two cases associated with diarrhoea, four of the affected patients required in-patient rehydration with intravenous fluids. Thus in total 8 patients experienced grade 3 toxicity and 5 patients had DLT. The latter were attributed to be probably caused by ralitrexed. In view of above toxicities the protocol was amended as above.

In the final group that received reduced dose of raltitrexed, four out of six patients did not complete treatment, three due to progressive disease and one withdrew consent. Although the treatment was better tolerated the investigators concluded that the level of toxicity experienced, limited the potential application of the combination and the study was discontinued without fulfilling the phase II design.

EFFICACY

Partial radiological responses were documented in two out of twenty four patients-8%. Six patients had stable disease (25%) and twelve had progressive disease (50%). Four patients could not be evaluated (2 patients withdrew consent and 2 stopped the study due to associated toxicities). Within the first cohort there was one recorded PR and one SD, three patients progressed and one was withdrawn. At the second dose level, one patient had a PR, three-SD, six had PD and 1 withdrew consent. Within the last cohort there were 2 cases of SD and 3-PD, one patient withdrew consent.

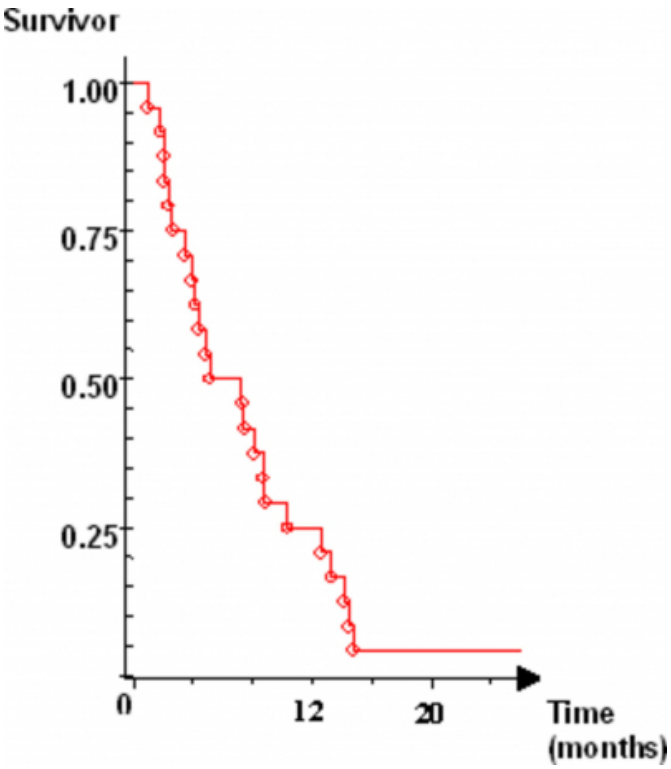
Marker reduction of more than 50% was seen in seven (29%) patients whose CA19-9 was significantly elevated at study entry, in 4 cases the results correlated with radiological findings.

Six patients (25%) had clinical benefit response, two of them in cohort 1, three in -2 and four in the final group, nine patients were non-responders and nine were non-evaluable.

Survival rate at the time of analysis was estimated at 5.14 months (95% CI 3,93-8,78) (Figure 1).

Figure 3

Figure 1: Median survival



DISCUSSION

Despite improvement in survival and sustained clinical benefit response the activity of Gemcitabine as single agent is modest. One of the most important factors when considering new combinations of chemotherapeutic agents is a careful assessment of potential toxicity. Tolerability of Gemcitabine is very good with main side effects being myelosupression. Raltitrexed as a single agent has manageable toxicity. Several studies in colorectal cancer proved it to have comparable efficacy to 5FU but with more convenient dosing on 3-weekly basis. The main side effects of raltitrexed as single agent at recommended dose of 3,5mg/m ^{2} are asthenia, myelosupression and gastrointestinal side effects. Phase II and phase III studies using raltitrexed at 3,0mg/m ^{2} reported incidence of grade 3 /4 diarrhoea and grade 3 /4 nausea/ vomiting in the range of 10-14% and 9-13% respectively [$_5$]. Grade 3 /4 leucopaenia and thrombocytopaenia was noted in 14-18% and 1-6% of patients respectively. Grade 3 /4 anaemia was reported in 2-9% of patients.

The efficacy of gemcitabine and raltitrexed in pancreatic cancer has been reported by Kralidis et al [$_6$] and more recently by Arends et al [$_7$]. Both studies used different doses of drugs and reported a different level of toxicity. Kralidis et al used 3mg/m ^{2} of raltitrexed with 1000mg/m ^{2} gemcitabine. The reported toxicities were manageable but the activity of the combination was not superior to the gemcitabine alone [$_2$]. Arends et al used higher dose of raltitrexed (3.5mg/m ^{2}) with low dose gemcitabine (800mg/m ^{2}). The reported toxicity profile was a lot higher with many patients withdrawing from the study due to side effects. Our study used 3mg/m ^{2} of raltitrexed and a higher - escalating dose of gemcitabine, closer to the recommended single agent intensity. Cohort one patients received the same treatment as in study by Kralidis et al and tolerated it well. Cohort two patients had a gemcitabine dose intensity of 800m/m ^{2} /week and experienced the most toxicity. The reported side effects were most likely due to combination with raltitrexed treatment as cohort three patients received the same dose of gemcitabine with a lower dose of raltitrexed and the treatment was much better tolerated. None of the above combinations had a higher efficacy.

The explanation of the toxicity seen in this study is not clear. It is not the first trial to be terminated early due to unexpected toxicity of raltitrexed. The Pan-European Trial in Adjuvant Colon Cancer-1 (PETACC-1) was stopped prematurely due to the number of drug related deaths in raltitrexed group, which was double to that in the controls-17 (1,9%) of 911 patients vs 7 (0,8%) of 927 respectively [$_8$]. Our study does not report any terminal events directly related to the study drugs; however associated toxicity was felt to be too high. Mackay reported another study, which found raltitrexed in combination with epirubicin and cisplatin to have unacceptable toxicity [$_9$]. In view of our finding together with the already reported studies using the combination of gemcitabine and raltitrexed we feel that further evaluation of combination of raltitrexed and gemcitabine in pancreatic adenocarcinoma is not warranted.

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