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ORIGINAL ARTICLE

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A phase 1 and pharmacokinetic study of gemcitabine and oxaliplatin in patients with solid tumors

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Abstract *Purpose*: This dose escalation study aimed to determine the recommended doses, toxicity and pharmacokinetics of oxaliplatin and gemcitabine given on days 1 and 8 every 21 days. This schedule may maximize dose intensity of both drugs with acceptable or reduced toxicity. *Patient and methods*: Eligible patients had solid malignancies, no more than two prior courses of chemotherapy, ECOG performance status 0–2, neurotoxicity ≤ NCI-CTC grade 1 and adequate organ function. Dose escalation commenced at oxaliplatin 40 mg/m^2 and gemcitabine 750 mg/m^2, both given on days 1 and 8 every 21 days, and reached oxaliplatin 80 mg/m^2 and gemcitabine 1,500 mg/m^2. The two highest dose levels were each expanded to six patients to gain additional toxicity data. *Results*: There were no dose limiting toxicities related to treatment and an MTD was not reached. Five patients (24%) had grade 3 neutropenia, without associated infection, and seven patients (33%) had grade 3/4 thrombocytopenia. Neurotoxicity was mild and no worse than grade 1. Two patients with mesothelioma (10%) had partial responses and 11 patients (52%) had disease stabilization. No pharmacokinetic interaction between oxaliplatin and gemcitabine was detected. Dose intensity was maximal at level 4 (oxaliplatin 70 mg/m^2 and gemcitabine 1,250 mg/m^2). *Conclusions*: This schedule allows oxaliplatin and gemcitabine to be delivered at the full dose intensity of each drug with excellent tolerability and predictable pharmacokinetics. The recommended doses for phase II studies are oxaliplatin 70 mg/m^2 and gemcitabine 1,250 mg/m^2 on days 1 and 8 every 21 days.

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Introduction

Gemcitabine is an anti-metabolite that causes DNA chain termination in S-phase. Gemcitabine has activity in non-small cell lung cancer (NSCLC) [36], pancreatic cancer [6], bladder cancer [1], breast cancer [3] and mesothelioma [33]. It is well tolerated, with the dose-limiting toxicity being myelosuppression. Standard regimens of single-agent gemcitabine are 1,250 mg/m^2 on days 1 and 8 of a 21-day cycle [1] or days 1, 8 and 15 of a 28-day cycle [36].

Oxaliplatin is a diaminocyclohexane platinum compound that interferes with DNA replication by forming platinum-DNA adducts between adjacent guanine-guanine or guanine-adenine base pairs. Unlike cisplatin, it has no significant nephrotoxicity or ototoxicity [11]. Oxaliplatin has been widely used in the treatment of colorectal cancer [4, 29] and also in the treatment of pancreatic [10] and ovarian cancer [9]. The dose limiting toxicity (DLT) is peripheral neurosensory toxicity [5, 11] and standard regimens of oxaliplatin are 130 mg/m^2 every 21-days as a single agent [22] or 85–100 mg/m^2 every 14 days in combination with 5-fluorouracil and leucovorin [23, 19].

Combination therapy with oxaliplatin and gemcitabine has been described in pancreatic [21], germ cell [28], NSCLC [13], biliary tract [2], ovarian [13] and a number of other epithelial tumours. The majority of these have administered the oxaliplatin on day 1 and the gemcitabine on days 1 and 8 every 21 days [28], or the oxaliplatin on days 1 or 2 and the gemcitabine on day 1 every 14 days [13, 2, 21]. This Phase 1 study aimed to investigate combination therapy with oxaliplatin and gemcitabine both administered on days 1 and 8 every 21 days to determine if dose intensity of both drugs could be maintained with reduced or acceptable toxicity.

Patients and methods

The primary objective was to determine the maximum tolerated dose (MTD) of this combination, while secondary objectives were to obtain toxicity and pharmacokinetic data.

Patients

Eligible patients were aged at least 18 years, with histological or cytological evidence of solid malignancy for which there was no standard treatment. Up to two prior chemotherapy regimens were allowed but chemotherapy must have been completed at least 4 weeks prior to enrolment (6 weeks for mitomycin or nitrosureas). Prior radiotherapy was allowed to ≤30% of bone marrow but must have been completed at least 2 weeks prior to enrolment. Other eligibility requirements were ECOG performance status 0–2, life expectancy ≥12 weeks, adequate hematological function (absolute neutrophil count (ANC) $\geq 1.5\times10^9$/l, platelet count $\geq 100\times10^9$/l and hemoglobin ≥90 g/l), adequate renal function (serum creatinine ≤0.16 mmol/l), adequate liver function (bilirubin ≤1.5 times upper limit of normal (×ULN); alkaline phosphatase (ALP), aspartate transaminase (AST) and alanine transaminase (ALT) ≤3×ULN; in the presence of liver metastases, ALP, AST and ALT ≤5×ULN was acceptable), baseline neurosensory toxicity ≤NCI-CTC grade 1, and written informed consent. Measurable disease was not required for study entry. Patients with controlled brain metastases were eligible but patients with meningeal metastases were excluded. The Institutional Ethics Committees of participating hospitals approved the study.

Treatment and monitoring

Patients received gemcitabine as a 30-min infusion given prior to a 2-h infusion of oxaliplatin on days 1 and 8 every 21 days. Dose levels are shown in Table 1. Three patients were entered at each level but if a DLT occurred, that cohort would be expanded to six patients. If ≥2 of these six patients experienced a DLT, this level would be considered the MTD level. Patients could receive a maximum of eight cycles.

Baseline assessment included history and physical examination, chest radiograph and CT scan of disease sites within 3 weeks of treatment, and baseline blood tests within 7 days of treatment. Patients were reviewed weekly for toxicity. A full blood count (FBC) was performed weekly and biochemical evaluation—electrolytes, urea, creatinine, liver function test (LFTs)—was performed 3-weekly. Radiological imaging was repeated every three cycles and at the end of treatment for patients who had measurable disease. For responders (World Health Organization criteria), confirmatory imaging at least 4 weeks later was required.

DLT was defined as any of the following occurring during cycle 1 and attributed to study drugs: grade 4 neutropenia (neutrophil count $<0.5\times10^9$/l) for >5 days; febrile neutropenia (neutrophil count $<1.0\times10^9$/l with fever ≥38.5°C); platelet count $<25\times10^9$/l; grade 3 or 4 neurosensory toxicity; grade 3 or 4 non-hematological toxicity (excluding alopecia, nausea, emesis and isolated grade 3 ALT/AST elevations that returned to grade 1 or pre-treatment value within 3 weeks).

Toxicity was graded using the NCI-CTC criteria (Version 2.0, 1998), except for neurosensory toxicity, which was assessed using the following modified toxicity scale [30]: grade 0, No symptoms; grade 1, Paresthesiae/dysaesthesiae that resolve and do not interfere with function; grade 2, Paresthesiae/dysaesthesiae interfering with function, but not activities of daily living (ADL); grade 3, Paresthesiae/dysaesthesiae with pain or with functional impairment that also interfere with ADL; grade 4, Persistent paresthesiae/dysaesthesiae that is disabling or life-threatening.

Patients experiencing DLT were permitted to continue in the study with appropriate dose modification if investigators felt that they were benefiting from treatment despite toxicity.

Dose modifications on day 1 and 8

Treatment on day 1 was delayed until ANC was $>1.5\times10^9$/l and platelets $>100\times10^9$/l. Dose modifications on Day 1 were based on the worst toxicity during the previous cycle as shown in Table 2. Dose modifica-

Table 1 Dose levels of gemcitabine and oxaliplatin

Dose level	Gemcitabine day 1 and 8 (mg/m^2)	Oxaliplatin day 1 and 8 (mg/m^2)	No. of patients (*n*)	Total cycles	Patients receiving ≥80% of planned gemcitabine dose *n* (%)	Patients receiving ≥80% of planned oxaliplatin dose *n* (%)	Median dose of oxaliplatin received (mg/m^2)
1	750	40	3	13	3 (100%)	3 (100%)	320
2	1,000	50	3	20	3 (100%)	3 (100%)	588
3	1,250	60	3	18	2 (67%)	2 (67%)	682
4	1,250	70	6	23	4 (67%)	4 (67%)	445
5	1,500	80	6	23	3 (50%)	3 (50%)	389

Table 2 Dose reductions

	Severity	Gemcitabine	Oxaliplatin
Day 1			
Haematological toxicity in preceding cycle			
Neutropenia	ANC $<0.5\times10^9$/l	↓ 25%	No change
Thrombocytopenia	Platelets $<50\times10^9$/l	↓ 25%	No change
	Platelets $<25\times10^9$/l	↓ 25%	↓ 25%
Febrile neutropenia	Not applicable	↓ 25%	↓ 25%
Treatment delay of more than 1 week because of ANC $<1.5\times10^9$/l or platelets $<100\times10^9$/l	Not applicable	↓ 25%	↓ 25%
Non-haematological toxicity in preceding cycle			
Peripheral neuropathy	Grade 2+	No change	Delay until < grade 2 then ↓ 25%
Laryngo-pharyngeal dysaesthesia	Any	No change	↑ Infusion time to 6 h
Others (exclude alopecia, anaemia and transient LFT rises which have returned to < grade 2 or to baseline on day 1)	Grade 3+	Delay until < grade 2 then ↓ 25%[a]	Delay until < grade 2 then ↓ 25% [a]
Day 8			
Haematological			
Neutropenia	ANC $<1.5\times10^9$/l	↓ 25%	↓ 25%
	ANC $<1.0\times10^9$/l	↓ 50%	↓ 50%
	ANC $<0.5\times10^9$/l	Withhold	Withhold
Thrombocytopenia	Platelets $<100\times10^9$/l	↓ 25%	↓ 25%
	Platelets $<50\times10^9$/l	↓ 50%	↓ 50%
	Platelets $<25\times10^9$/l	Withhold	Withhold
Febrile neutropenia	Not applicable	↓ 50%	↓ 50%
Non-haematological			
Peripheral neuropathy	Grade 2+	No change	Withhold
Laryngo-pharyngeal dysaesthesia	Any	No change	↑Infusion time to 6 h
Mucositis	Grade 2	↓ 25%	No change
	Grade 3+	Withhold	↓ 25%
Nausea or vomiting	Grade 3+	Symptomatic management and ↓ 25%	Symptomatic management and ↓ 25%
Diarrhoea	Grade 3+	Symptomatic management and ↓ 25%	Symptomatic management and ↓ 25%
Others (excluding anaemia)	Grade 3+	Withhold	Withhold

[a] At investigator's discretion

tions on Day 8 were based on toxicities occurring during the first week of the cycle, as shown in Table 2.

Pharmacokinetics

Pharmacokinetic specimens were collected on day 1 of Cycle 1. Gemcitabine samples were collected in lithium heparin tubes containing tetrahydrouridine at 0, 10, 25, 40, 60, 90, 120, 155, 240, 420 min and 24 h from the commencement of the gemcitabine infusion. Plasma gemcitabine was analyzed using an isocratic high pressure liquid chromatography system, containing a UV detector at 272 nm, a normal phase (amino) column and a mobile phase of cyclohexane:1,2-dichloroethane:methanol:water:aceticacid:triethylamine (630:150:220:1:0.5:1) at a flow rate of 1.5 ml/min [17].

Oxaliplatin samples were collected in lithium heparin tubes at 0, 10, 115, 140, 200, 320, 380 min and 24, 48 and 168 h from the start of the oxaliplatin infusion. Total plasma platinum (Pt) concentrations were measured by inductively coupled plasma mass spectrometry(ICPMS) [32]. Pharmacokinetic parameters were determined using non-compartmental analysis (WinNonlin, Pharsight Corporation, NC).

Statistical methods

To summarise the dose reductions and delays, the relative dose intensity of each drug was calculated by dividing the total given dose as a proportion of the planned protocol dose by the total number of days of treatment relative to the protocol time. The protocol time was 21 days for each cycle given. The total number of days on treatment was calculated from day 1 of the first cycle to 14 days after the second dose of gemcitabine and oxaliplatin on the last cycle. Dose propor-

Table 3 Patient characteristics ($n = 21$)

	No. of patients (%)[a]
Male/Female	15/6
Age	Median 60 years (43–72)
Histology	
Mesothelioma	7 (33%)
Colorectal cancer	3 (14%)
Pancreatic cancer	2 (10%)
Soft tissue sarcoma	2 (10%)
Renal cell cancer	2 (10%)
Non-small cell lung cancer	2 (10%)
Other	3 (14%)
Performance status	
0	3 (14%)
1	15 (71%)
2	3 (14%)
No of prior chemotherapy regimens	
0	5 (24%)
1	9 (43%)
2	7 (33%)
Prior radiotherapy	10 (48%)

[a] Total may not add up to 100% because of rounding

tionality for area under the curve (AUC) versus dose was examined using the Power Test, with a β value of 1 supportive of dose proportionality [35].

Results

Twenty-one patients were enrolled and their characteristics are summarized in Table 3. All 21 patients were evaluable for toxicity and 20 patients were evaluable for response. One patient was not evaluable for response as he withdrew from study after only one cycle of treatment because of the need to resect bleeding metastases. A total of 97 cycles were administered, with a median of six cycles per patient. The median cumulative dose of gemcitabine was 9,093 mg/m^2 (range 2,469–16,147 mg/m^2) and of oxaliplatin was 520 mg/m^2 (140–927 mg/m^2).

Dose limiting toxicity and the maximum tolerated dose

Three patients per cohort were treated up to dose level 5 (oxaliplatin 80 mg/m^2 and gemcitabine 1,500 mg/m^2) with no DLT attributable to study drugs during the first cycle. There was no further dose escalation as the drug intensities achieved in levels 4 and 5 were equivalent to those found in the monotherapy setting and it was considered that additional clinical benefit from higher doses was unlikely. Therefore, an MTD was not defined. The cohorts at level 4 and 5 were expanded to six patients each to obtain further toxicity data. No DLT occurred in the expanded cohorts. Dose level 4 (oxaliplatin 70 mg/m^2 and gemcitabine 1,250 mg/m^2) is recommended for Phase 2 studies as a higher proportion of the planned dose intensity was delivered at this dose level compared with dose level 5 (see below).

Toxicity

Myelosuppression was mild, with no grade 4 neutropenia or febrile neutropenia (Table 4). Five patients (24%) experienced grade 3 neutropenia. One patient was removed from study at dose level 5 because of recurrent neutropenia despite dose reductions. Five patients (24%) experienced grade 3 thrombocytopenia and two patients (10%) grade 4 thrombocytopenia. One of the patients who experienced grade 4 thrombocytopenia had an associated gastrointestinal hemorrhage during cycle 4, requiring platelet and red cell transfusion. This patient had peritoneal mesothelioma and had achieved disease stabilization after the initial three cycles of treatment. Haemorrhage was considered most likely to be of upper gastrointestinal origin as there was a prior history of esophageal strictures. The patient withdrew from study at this time but had not progressed when last reviewed (22 months after cessation of treatment).

Two other episodes of bleeding were noted during the trial, both without associated thrombocytopenia or coagulopathy, and these were thought to be unrelated to treatment. The first patient, who was on dose level 4, had bleeding metastases after one cycle of treatment and required surgery. The patient subsequently withdrew from the study. The second patient, treated on dose level 5, experienced malaena during cycle 1 related to pre-existing gastritis. Treatment was continued without dose reduction for a total of three cycles and without any further bleeding problems.

Neurosensory toxicity was very mild. Two patients (10%) had no neurosensory symptoms while 19 patients

Table 4 Grade 3–4 toxicities

	Level 1 ($n = 3$)		Level 2 ($n = 3$)		Level 3 ($n = 3$)		Level 4 ($n = 6$)		Level 5 ($n = 6$)		Total no. (%)	
Grade	3	4	3	4	3	4	3	4	3	4	3	4
Haemoglobin	1	0	0	0	0	0	1	0	1	0	3(14%)	0(0%)
Neutrophils	1	0	0	0	0	0	2	0	2	0	5(24%)	0(0%)
Platelets	1	0	1	0	1	0	1	1	1	1	5(24%)	2(10%)
LFT's	1	0	1	0	0	0	2	0	3	0	7(33%)	0(0%)
Bleeding with thrombocytopenia	0	0	0	0	0	0	1	0	0	0	1(5%)	0(0%)
Nausea and vomiting (treatment related)	0	0	0	0	1	0	0	0	0	0	1(5%)	0(0%)

(90%) described grade 1 toxicity only. Grade 2 neurosensory toxicity was not seen. There were no dose reductions or delays required for neurosensory toxicity. Fatigue was reported as grade 2 in six patients (29%) and grade 3 in two patients (10%).

Dose reductions, dose delays and dose intensity

Eight patients required no dose reductions (total 40 cycles). Of the 13 patients who required dose reductions, one was on dose level 1, two on level 3, and five each on levels 4 and 5. One patient required the first dose reduction during the first cycle, seven patients required their first dose reduction during the second cycle, three patients during the third cycle, one patient during the fourth cycle and one patient during the fifth cycle. Once reduced, the doses were not re-escalated. Seven patients required more then one dose reduction (all on dose levels 3, 4 and 5). The reasons for dose reductions were neutropenia (5 patients), thrombocytopenia (1 patient), neutropenia and thrombocytopenia (4 patients), abnormal LFTs and neutropenia (1 patient), emesis (1 patient), non-neutropenic fever and declining performance status (1 patient).

Of 20 patients who received more then 1 cycle of treatment, 13 (65%) experienced no treatment delays. Nine cycles (9%) in seven patients (33%) were delayed for 7 or more days: two on dose level 1, one on level 2 and two each on dose levels 4 and 5. The causes of treatment delays were neutropenia (2 cycles), thrombocytopenia (2 cycles), abnormal LFTs (1 cycle), patient request (1 cycle) and other reasons unrelated to treatment (3 cycles).

At dose level 4, the recommended Phase 2 dose level, four patients received at least 80% of the protocol dose intensity of each drug and the remaining two received 60–65%. At dose level 5, three patients received at least 80% of the protocol dose intensity, two received 60–65% and one received 50–55%.

Anti-tumor efficacy

There were no complete responses and two partial responses (10%). Eleven patients (52%) experienced disease stabilization for ≥3 months. Of note, all seven patients with mesothelioma experienced a clinical benefit: two patients with partial responses lasting 6 and 12 months respectively, and five patients with disease stabilization for a median of 6.1 months (range 5–22 months). One patient with stable disease at 22 months remains alive without disease progression at latest follow up.

Withdrawal from study

Seven patients (33%) were withdrawn from study because of progressive disease. Two patients (10%) were withdrawn because of toxicity (one for recurrent neutropenia and one for persistent liver function abnormalities). One patient was withdrawn because of the need for surgery. Two patients (10%) withdrew consent for further participation: following gastrointestinal haemorrhage and thrombocytopenia during cycle 4, and at patient request, respectively. The remainder was taken off study at the completion of six or eight cycles of treatment.

Pharmacokinetics

The pharmacokinetic data is summarized in Table 5 and Figs. 1, 2 and 3. The AUC of gemcitabine increased in linear relationship to dose, as expressed by the equation $\mathrm{AUC} = 0.8(\mathrm{dose}) - 38$ ($r^2 = 0.75$) with a β value of 1.05 (0.44–1.66). The maximum concentration ($C_{\max}$) was reached at the end of the infusion (30 min) and the mean volume of distribution was 36 l. The relationship between gemcitabine AUC and $C_{\max}$ is described by the equation $\mathrm{AUC} = 18(C_{\max}) - 20$ ($r^2 = 0.75$). Gemcitabine was rapidly eliminated, with a mean clearance rate (CL) of 165 l/h and a mean plasma half-life ($t_{1/2}$) of 13 min. This is similar to pharmacokinetic data from a study where gemcitabine was administered as monotherapy [18], suggesting no interaction with oxaliplatin.

The AUC of platinum increased in linear relationship to the dose of oxaliplatin and was expressed by the equation $\mathrm{AUC} = 1.6(\mathrm{dose}) - 16$ ($r^2 = 0.80$) with a β value of 1.21 (0.72–1.70). The $C_{\max}$ was reached at the end of the infusion (at 120 min) and the mean volume of distribution was 138 l. The elimination of oxaliplatin was slow, with a CL of 1 l/h and a mean $t_{1/2}$ of 112 h. This is similar to pharmacokinetic data of oxaliplatin as a single agent [12, 24] suggesting no interaction with gemcitabine.

Discussion

This phase 1 study showed that this schedule of gemcitabine and oxaliplatin was well tolerated. At levels 4 and 5, dose intensity equivalent to that used in the monotherapy setting was achieved without excessive toxicity. No DLT was seen and a MTD was not defined. The recommended doses for phase II studies are those employed at dose level 4 (oxaliplatin 70 mg/m^2 and gemcitabine 1,250 mg/m^2) because of marginally better dose intensity at this level compared to dose level 5.

Hematological toxicity was mild with no grade 4 neutropenia or febrile neutropenia. Thirty-three percent of patient experienced grade ≥3 thrombocytopenia with only one of these patients (known to have a chronic gastrointestinal condition) experiencing a non-fatal gastrointestinal haemorrhage. Two other episodes of

Table 5 Pharmacokinetic parameters of gemcitabine and oxaliplatin

Dose (mg/m^2)	No. of patients	C_{max} (μg/ml)	$AUC_{0-\infty}$ (μg/ml/min)	CL (l/h)	Vss (l)	$t_{1/2}$ (min)
Gemcitabine						
750	3	15 ± 5	516 ± 168	175 ± 54	41 ± 27	23 ± 27
1,000	3	15 ± 7	495 ± 216	254 ± 82	63 ± 38	12 ± 5
1,250	9	33 ± 7	1038 ± 131	128 ± 21	25 ± 5	11 ± 4
1,500	6	35 ± 18	1002 ± 189	173 ± 29	36 ± 18	11 ± 6
Mean ± SD				165 ± 56	36 ± 22	13 ± 11

Dose (mg/m^2)	No. of patients	Platinum C_{max} (μg/ml)	Platinum AUC_{0-168} (μg/ml/h)	CL (l/h)	Vss (l)	$t_{1/2}$ (h)
Oxaliplatin						
40	3	1.39 ± 0.49	48 ± 9	1.24 ± 0.26	133 ± 30	79 ± 3
50	3	1.41 ± 0.22	66 ± 20	1.12 ± 0.43	142 ± 32	97 ± 22
60	3	1.59 ± 0.13	59 ± 13	1.38 ± 0.39	157 ± 43	84 ± 2
70	6	2.19 ± 0.21	108 ± 11	0.73 ± 0.23	126 ± 45	154 ± 132
80	6	2.12 ± 0.49	104 ± 15	1.01 ± 0.25	140 ± 57	108 ± 65
Mean ± SD				1.03 ± 0.35	138 ± 42	112 ± 79

SD standard deviation

bleeding were noted but were not clearly related to drug therapy. There was no associated thrombocytopenia or coagulopathy, and neither drug has been shown to induce spontaneous bleeding in the absence of these predisposing factors.

Non-hematological toxicity was minimal. In particular, cumulative neurotoxicity was no worse than grade 1 and no dose-reductions were required for neurotoxicity. The dose of oxaliplatin administered in this study was modest—the median dose was 520 mg/m^2 (range 140–927 mg/m^2) and the median number of cycles was six. It is known that the incidence of neuropathy increases with increasing dose of oxaliplatin; it is frequent when cumulative doses over 1,020 mg/m^2 are administered, with 50% of such patients having grade 3 neurotoxicity [7]. Nevertheless, even allowing for this, it is surprising that we did not observe more substantial neurotoxicity in this study. Comparison with other studies where similar median doses of oxaliplatin were administered (390–650 mg/m^2) [22, 8, 20, 26], but where other schedules of administration were used, would suggest that 4–25% of patients would still be expected to have neurotoxicity impairing function. Only two other studies have delivered gemcitabine and oxaliplatin using a similar schedule to the one in this study [16, 31]. Both reported that the combination was well tolerated but that neurotoxicity causing functional impairment occurred in 8–9% of patients. Schuette et al. [31] treated mesothelioma patients with gemcitabine 1,000 mg/m^2 and oxaliplatin 80 mg/m^2 on days 1 and 8 every 21 days with 60% of patients received the full treatment protocol (6 cycles with a planned dose of 960 mg/m^2 of oxaliplatin). Franciosi et al. [16] treated NSLCL patients with gemcitabine 1,000 mg/m^2 and oxaliplatin 65 mg/m^2 on days 1 and 8 every 21 days with a median of four cycles delivered. In both studies, oxaliplatin was not dose re-

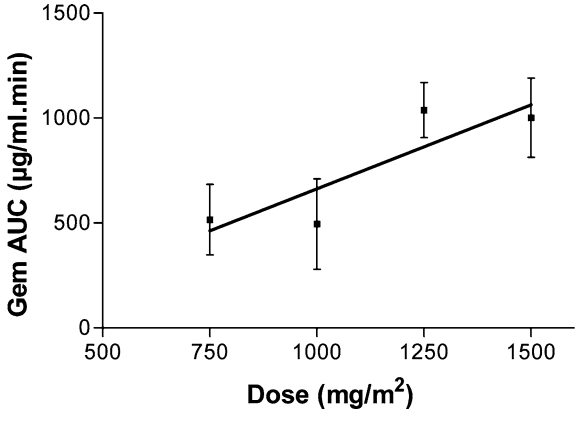

Fig. 1 The relationship between gemcitabine area under curve (AUC) and dose. Gemcitabine AUC increased linearly with dose, described by the equation AUC = 0.8(dose) − 138(r^2 = 0.75)

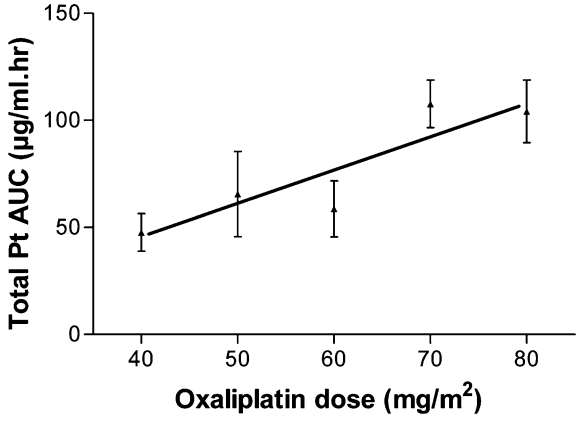

Fig. 2 The relationship between Pt area under curve (AUC) and dose of oxaliplatin. Pt AUC increased linearly with dose, described by the equation AUC = 1.6(dose) − 16 (r^2 = 0.80)

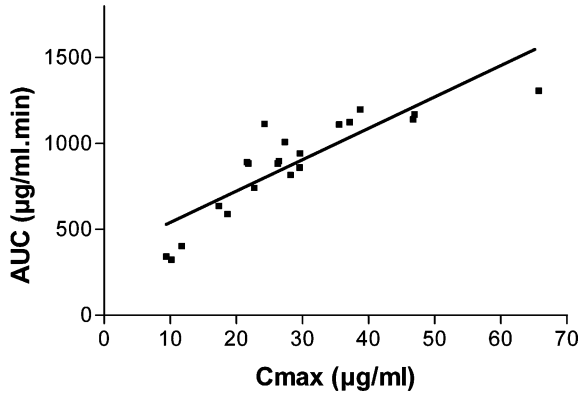

Fig. 3 Relationship between gemcitabine AUC and C_{max}. Gemcitabine AUC and C_{max} is described by the equation AUC = 18(C_{max})−20 ($r^2 = 0.75$)

duced until neurotoxicity was relatively advanced (WHO grade 3) and this may account for the increased incidence in neuropathy compared to our study.

The current study provides detailed pharmacokinetic data of this particular schedule of oxaliplatin and gemcitabine. Both drugs displayed a linear relationship between dose and AUC, with C_{max} reached at the end of the infusions. Concurrent administration of both drugs did not result in any pharmacokinetic interaction, which is in keeping with pharmacokinetic data from other studies. Faivre et al. [13] provided data about the pharmacokinetics of gemcitabine in a schedule where oxaliplatin and gemcitabine were given concurrently on a fortnightly schedule. Mavroudis et al. [25] recently provided pharmacokinetic data about another schedule of gemcitabine (days 1 and 8) and oxaliplatin (day 8).

Objective responses were seen in two patients (10%), both with mesothelioma, and it is noteworthy that all five of the other mesothelioma patients had disease stabilization. These data are in keeping with studies showing that cisplatin doublets [27, 34] and oxaliplatin doublets [15, 31, 14] have activity in mesothelioma. In particular, the study by Schuette et al. [31] is of interest as patients with mesothelioma were treated on a similar schedule of oxaliplatin and gemcitabine as in this study. A partial response rate of 40% and a stable disease rate of 24% was observed. Toxicity was minimal with the most common grade 3 and 4 toxicities being leucopenia (8%), emesis (8%) and neuropathy (8%). No pharmacokinetic data were available.

In conclusion, this schedule of oxaliplatin and gemcitabine (given on days 1 and 8 of a 21-day cycle) allowed both drugs to be delivered at full dose intensity with a high degree of tolerability, predictable pharmacokinetics and encouraging anti-tumour activity, especially in patients with mesothelioma.

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