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ORIGINAL ARTICLE

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Phase I trial of fixed dose-rate gemcitabine in combination with carboplatin in chemonaive advanced non-small-cell lung cancer: a Cancer Therapeutics Research Group study

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Abstract *Purpose*: To determine the maximally tolerated dose (MTD) of gemcitabine administered at a fixed dose-rate of 10 mg/m^2 per min in combination with fixed dose carboplatin, to evaluate the toxicity of this regimen and to determine the pharmacokinetics of plasma gemcitabine. *Methods*: Patients with advanced stage non-small-cell lung cancer (NSCLC) received carboplatin (AUC 5) on day 1 followed by gemcitabine at a fixed dose rate of 10 mg/m^2 per min in escalating durations of infusion on days 1 and 8 every 21 days. Pharmacokinetic sampling was obtained on day 1, cycle 1 of treatment. *Results*: A total of 15 patients received carboplatin and gemcitabine in cohorts of three to six patients at three dose levels. The doses of gemcitabine studied were 600, 750, and 900 mg/m^2. The MTD was reached at 900 mg/m^2. Dose-limiting toxicities were thrombocytopenia and liver failure, and with repeated dosing neutropenia was commonly observed. The recommended phase II dose of gemcitabine was 750 mg/m^2. Partial responses were observed at 600 and 750 mg/m^2 of gemcitabine. Plasma gemcitabine did not reach steady state except in one patient with the durations of infusion studied. Plasma concentrations, however, were above 10 μmol/l between 20 and 90 min in all patients. *Conclusions*: Gemcitabine administered as a 75-min infusion at a fixed dose rate of 10 mg/m^2/min on days 1 and 8 in combination with carboplatin on day 1 every 21 days is tolerable and active in NSCLC. Pharmacokinetic studies demonstrated that the target plasma gemcitabine concentration above 10 μmol/l was achieved. Further studies are warranted to compare this regimen against standard regimens of carboplatin and gemcitabine.

Keywords Gemcitabine · Fixed dose rate · Non-small-cell lung cancer · Phase I study

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Introduction

The combination of cisplatin and gemcitabine is considered one of the standard regimens in advanced-stage non-small-cell lung cancer (NSCLC) [13]. As carboplatin has a more favorable non-hematologic toxicity profile than cisplatin, combinations of carboplatin or cisplatin with gemcitabine have been compared in randomized phase II and III studies in NSCLC and both combinations have been shown to be equally tolerable and active [15, 18, 20].

Gemcitabine (2′,2′-difluorodeoxycytidine, dFdC), a nucleoside antimetabolite, is a prodrug that requires phosphorylation intracellularly to its active form gemcitabine triphosphate. The phosphorylated forms of gemcitabine are retained within cells for longer periods, with an intracellular half-life of greater than 10 h for gemcitabine triphosphate. Preclinical studies have shown that the rate-limiting step in the activation of gemcitabine is the phosphorylation of gemcitabine by deoxycytidine kinase [7, 11]. The optimal rate of intracellular gemcitabine phosphorylation is reached with a plasma gemcitabine concentration between 10 and 20 μmol/l. This concentration corresponds to the saturation of deoxycytidine kinase activity within the cell [7, 8]. The continuous saturation of deoxycytidine kinase

activity is achieved when gemcitabine is infused at a fixed dose rate of 10 mg/m^2 per min [1, 8, 9, 10]. The infusion of gemcitabine at 10 mg/m^2 per min has demonstrated increased tumor efficacy in a randomized phase II study of advanced pancreatic cancer [16]. A higher median intracellular gemcitabine triphosphate level was achieved in the fixed dose rate schedule.

Infusion of gemcitabine at a fixed dose rate generally results in higher toxicity than a 30-min infusion. Increased myelosuppression and hepatic dysfunction are the usual toxicities observed [14, 19]. Phase II studies of standard doses of gemcitabine administered at 10 mg/m^2 per min in combination with platinum in patients with advanced-stage NSCLC have been reported [5, 6]. Preliminary results reported in abstract form have suggested tolerability and a favorable response rate.

The pharmacologic advantage of administering gemcitabine at a fixed dose rate of 10 mg/m^2 min and the proven efficacy of combination with carboplatin in NSCLC and the anticipated higher toxicity with this regimen compared to the conventional 30-min gemcitabine schedule were the basis for our study. We conducted a phase I study of fixed dose-rate gemcitabine in combination with fixed AUC-dose carboplatin in patients with advanced-stage NSCLC to establish the maximally tolerated dose (MTD) of gemcitabine administered at 10 mg/m^2 per min, to evaluate the toxicity of this regimen and to determine the pharmacokinetics of plasma gemcitabine.

Patients and methods

Patient selection

Eligibility criteria for study entry included histologically or cytologically confirmed stage IIIB or stage IV NSCLC. Patients were required to have measurable or evaluable disease and to have received one or no prior chemotherapy for advanced disease. Previous neoadjuvant or adjuvant chemotherapy, or chemotherapy given concurrently with radiotherapy for non-metastatic disease was allowed if the last dose had been administered 6 months or more before study entry. Patients who had received prior platinum and/or gemcitabine were excluded. Patients with symptomatic central nervous system metastases requiring steroid were excluded. Prior radiotherapy was allowed as long as the indicator lesion(s) was not within the previous radiation field and the last dose of radiotherapy had been completed at least 3 weeks before study entry. Patients were required to have a Karnofsky performance status of ≥70%, WBC count ≥3500/μl, neutrophils ≥2000/μl, platelet count ≥100,000/μl, hemoglobin ≥9 g/dl, serum creatinine <133 μmol/l or creatinine clearance >30 ml/min (based on the Cockcroft formula), serum bilirubin not more than 1.5 times the upper limit of normal (ULN), serum transaminase levels not more than twice ULN (not more than five times ULN if liver metastases were present), life expectancy >3 months, and age ≥18 years. The study was approved by the institutional review board and all patients were required to provide written informed consent.

Treatment plan

Treatment consisted of carboplatin on day 1 followed by fixed dose-rate gemcitabine on days 1 and 8 every 21-day cycle. 5-Hydroxytryptamine-3 receptor antagonists were routinely used as antiemetics. Prophylactic growth factors were not used routinely. Carboplatin was given at a dose to target an area under the curve (AUC) of 5 mg/ml·min [4] over 1 h. Gemcitabine was infused at a constant rate of 10 mg/m^2 per min. The starting dose level of infusional gemcitabine was 60 min with subsequent levels planned at 30-min increments. At a constant rate of 10 mg/m^2 per minute, the starting dose level corresponded to 600 mg/m^2 per dose. The duration of infusion was identical for days 1 and 8 in any individual patient.

Doses were assigned at registration and no dose escalation was allowed in an individual patient. Treatment-related toxicity was evaluated after each cycle. The dose limiting toxicity (DLT) was defined based on toxicities experienced during the first cycle of chemotherapy only. Cohorts of at least three patients were treated at each dose level. Dose escalation proceeded if no patients developed DLT after the first cycle. If one of three patients experienced DLT, a further three patients were treated at that level. Dose escalation was stopped if one-third of patients at a given dose level developed DLT. The last patient at each dose level was evaluated for first cycle toxicity before a new patient was entered into the next dose level. DLT was defined as grade 4 neutropenia for 7 days or more, grade 4 thrombocytopenia, grade 3 neutropenia with fever or grade 3 thrombocytopenia with active bleeding, failure to recover from toxicity to receive a second cycle of chemotherapy despite a delay of more than 1 week from the scheduled day and non-hematologic toxicity of grade 3 or more (except for reversible elevation of transaminases, nausea, vomiting and alopecia). MTD was defined as the dose level immediately below the level that resulted in at least one-third of patients experiencing DLT.

If DLT was experienced, responding patients were allowed to continue treatment with dose reduction. Dose modifications were based on weekly blood counts and assessment of toxicity. On day 22 of each cycle, for neutropenia of grade 1 or more and/or platelets $<100{,}000$/μl, treatment was delayed for 1 week. On day 8 of each cycle, for neutropenia of grade 3 or more and thrombocytopenia of grade 2 or more, the gemcitabine dose was reduced by 25% and maintained for the next cycle, and for grade 4 neutropenia and/or grade 3/4 thrombocytopenia, gemcitabine was omitted and then decreased by 25% for the next cycle after marrow recovery and carboplatin was also reduced by 10% for the next cycle. The nadir count of the previous cycle also influenced dose adjustment for the next cycle. Gemcitabine was reduced by 25% and carboplatin by 10% for a grade 4 neutropenia with fever, or grade 4 neutropenia for more than 7 days or thrombocytopenia of grade 3 or more with bleeding or platelets $<25{,}000$/μl. Patients requiring a third dose reduction were taken off study. Patients who experienced a non-hematologic toxicity of grade 3 or more, except for nausea, vomiting, fatigue and reversible elevation of transaminases, were taken off study.

Patient evaluation

Before initiation of chemotherapy, all patients underwent a history and physical examination and determination of performance status. A complete blood count with differential, serum biochemistry, urinalysis, and ECG were obtained at baseline for each patient. Chest radiography, thoracic and abdominal computed tomography (CT) scans were performed as required for assessment of measurable or evaluable disease. CT scan of the brain and bone scan was performed if clinically indicated. Patients were assessed weekly throughout treatment by complete blood count, serum biochemistry and recording of toxicities. Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria, version 2.

Tumor response evaluation was performed after every two cycles according to the RECIST criteria [17]. Patients with at least stable disease or better continued with treatment to a maximum of six cycles. If DLT was experienced, responding patients continued treatment with a reduced dose. Patients with progressive disease were withdrawn from the study.

Pharmacokinetic study of plasma gemcitabine

Analytical grade gemcitabine and its metabolite 2′,2′-difluorodeoxyuridine (dFdU) were gifts from Eli Lilly and Company (Ina, Ind.). Plasma concentrations of gemcitabine and dFdU were measured in selected patients. Venous blood samples were drawn from the arm contralateral to the arm used for drug infusion of patients on day 1 of cycle 1 at the following times: before initiation of gemcitabine infusion (baseline), 10 min, 30 min, 10 min before the end of the infusion, and 30 min, 1 h and 2 h after the end of the infusion. At each point, 6 ml of blood was drawn into 15-ml heparinized tubes preloaded with 1 mg tetrahydrouridine. Blood samples were centrifuged for 15 min at approximately 1200 *g* at room temperature. The blood samples were kept at −20°C until analysis.

Determination of gemcitabine and dFdU in human plasma was performed by ion-pair reversed-phase high-performance liquid chromatography. Briefly, 0.2 ml human plasma was deproteinized with 10 µl perchloric acid (60%) followed by centrifugation at 10,000 *g* for 5 min at 4°C. Gemcitabine and dFdU were then separated on a ZORBAX ODS C18 reversed-phase column using a mobile phase of ammonium dihydrogen phosphate buffer solution (30 m*M*, pH 3.1) containing 10 m*M* sodium 1-heptanesulfonate/methanol (85:15 v/v) with a flow rate of 0.8 ml/min. The detection UV wavelength was set at 272 nm. Paracetamol was used as internal standard. The retention times of gemcitabine, dFdU and internal standard were approximately 6.1, 22.5 and 8.9 min, respectively. The lower limit of quantitation of gemcitabine was 0.08 µg/ml with linearity over the range 0.08–10.0 µg/ml and the lower limit of quantitation of dFdU was 0.1 µg/ml with linearity over the range 0.1–25.0 µg/ml. The correlation coefficients were greater than 0.9991 for all standard curves. The analyses of quality control samples of gemcitabine and dFdU demonstrated excellent precision with all coefficients of variation ($n = 15$) less than 6%. The method was accurate with overall mean calculated concentrations for quality control samples being less than 8% from theoretical data for both compounds.

Calculations and statistical analysis

Non-compartmental methods were used to estimate the AUC of plasma gemcitabine by the linear trapezoidal method using WINNONLIN software version 3.1 (Pharsight Corporation, Apex, N.C.). The terminal portion of the curve was determined by extrapolation of the log-linear concentration-time curve to infinity and regression of the last three time points of the curve using a weighting of 1/log-concentration^2. Derived parameters included half-life, clearance, and volume of distribution at steady state.

Results

Patient characteristics

A total of 15 patients were enrolled onto the study. Their median age was 57 years (range 35 to 81 years) and 11 were male. Of the 15 patients, 3 and 12 had stage IIIB and IV disease, respectively, and 13 had a Karnofsky performance status (KPS) of at least 90% and 2 a KPS of 70–80%. Adenocarcinoma was the predominant histologic subtype ($n = 10$). All patients were chemonaive. All patients were assessed for toxicity. A total of 51 cycles were administered. The median number of cycles per patient administered was three (range one to six). The relative dose intensities of gemcitabine at levels 1, 2 and 2A were 78%, 82% and 85%, respectively.

Table 1 Cycle 1 hematologic toxicities by dose level ($n = 15$)

Dose level	No. of patients	Neutropenia grade			Thrombocytopenia grade		
		1/2	3	4	1/2	3	4
1 (60 min)	3	1	0	0	1	0	0
2 (90 min)	6	1	0	1[a]	1	1[a]	0
2A (75 min)	6	3	2	0	1	0	0

[a]Same patient

Table 2 Cumulative grade 3/4 hematologic toxicities by dose level. Numbers in parentheses are the percentage of courses having the indicated toxicity

Dose level	No. of patients	Cycles	Neutropenia grade		Thrombocytopenia grade	
			3	4	3	4
1 (60 min)	3	8	1 (12)	3 (38)	3 (38)	0 (0)
2 (90 min)	6	20	3 (15)	1 (5)	2 (10)	0 (0)
2A (75 min)	6	23	10 (43)	0 (0)	0 (0)	0 (0)

Toxicity

At dose level 1, with infusion of gemcitabine over 60 min, no DLT were observed in three patients. The MTD was exceeded at dose level 2 (90 min). The DLT observed was grade 3 liver failure in one patient and grade 3 thrombocytopenia with hematemesis in the second patient. A study amendment was made to include an intermediate dose level (level 2A) of gemcitabine 750 mg/m^2 over 75 min. At this level, one out of six patients experienced DLT, which was grade 3 neutropenia with failure to recover in time to receive the second cycle of chemotherapy.

The frequency of cycle 1 grade 3/4 hematologic toxicity was low (Table 1). However, when all cycles of chemotherapy at a given level were analyzed, a different hematologic profile was observed. At level 1 (60 min), 50% of cycles were complicated by a nadir neutrophil count of grade 3 or 4. At levels 2 and 2A, 20% and 43% of cycles, respectively, were complicated by neutropenia grade 3 or 4. There were no episodes of febrile neutropenia. Cumulative thrombocytopenia, in contrast, was not as frequent (Table 2).

Non-hematologic side effects including fatigue, nausea, vomiting, constipation and fever were mild and not dose-dependent (Table 3). One patient developed grade 3 vomiting. Aspartate transaminase was mildly elevated in six patients but was not clinically significant and was reversible. Transient fever and rash were uncommon. One patient developed a non-hematologic DLT, manifested by grade 3 clinical liver failure (asterixis) at level 2. This patient had a previous history of heavy alcohol intake ceasing 5 months prior to study entry. At the time of chemotherapy, he had a grade 2 hypoalbuminemia, but liver function was otherwise normal. On day 15 of cycle 1 of chemotherapy, he

Table 3 Non-hematologic toxicity ($n = 15$)

Side effect	NCI CTC grade	
	1/2	3/4
Nausea	6	1
Vomiting	5	
Constipation	4	
Anorexia	1	
Mucositis	1	
Hyperbilirubinemia	2	
Elevated alanine transaminase	4	
Elevated aspartate transaminase	6	
Clinical liver failure		1[a]
Peripheral neuropathy	3	
Weight loss	3	
Rash	2	
Fatigue	10	
Fever	2	
Alopecia	4	

[a]DLT

developed confusion and asterixis. He had a grade 3 hypoalbuminemia, grade 1 transaminases and grade 2 hyperbilirubinemia. The patient recovered with supportive care but did not receive further therapy and was subsequently withdrawn from the study.

Response

Of the 15 patients, 10 were evaluable for response. A partial response was documented in two patients (20%) and stable disease was seen in five patients. One partial response was seen at level 1 and one at level 2A.

Pharmacokinetic data

The mean pharmacokinetic parameters for gemcitabine based on serial plasma concentration-time data from six patients at dose level 2A and one patient at level 2 are shown in Table 4. Plots of time against mean gemcitabine and dFdU concentrations at 75 min and 90 min infusions of gemcitabine are shown in Fig 1. Plasma concentrations of gemcitabine were above 10 μmol/l between 20 and 90 min in all patients.

Discussion

In this study, we determined that the MTD for fixed dose-rate gemcitabine at 10 mg/m^2 per min was 900 mg/m^2 when given in combination with carboplatin at a targeted AUC of 5 mg/ml·min. The dose-limiting toxicities encountered included thrombocytopenia, and liver dysfunction. The 750 mg/m^2 dose of gemcitabine was found to be tolerable based on the occurrence of DLT in one out of six patients, in whom there was failure to recover from neutropenia for retreatment in the first cycle. As observed in previous studies [14, 19], there was increased and cumulative hematopoietic toxicity with prolonged infusion. Hepatotoxicity has also been reported to be more frequent with longer infusions of gemcitabine [14] and was reflected by the frequency of elevated transaminases in our study patients, but this resulted in DLT in only one patient in this study.

In this study the MTD for fixed dose-rate gemcitabine at 10 mg/m^2 per min when given in combination with carboplatin was 900 mg/m^2. At a fixed dose rate of 10 mg/m^2 per min, higher doses of gemcitabine have been achieved in other studies. Administered alone, an MTD of 1500 mg/m^2 has been achieved [3] and this dose was the recommended phase II starting dose in another study [19]. Given in combination with irinotecan [2] or with mitoxantrone [12], the MTD of fixed dose-rate gemcitabine has been found to be 7200 mg/m^2. It has to be noted that the frequency of treatment in these studies was different from that in our study.

For a chemotherapy combination to be feasible, recommended dosing should allow maintenance of relative dose intensity with repeated dosing without dose delay due to cumulative toxicity. In our study, there was an increase in hematopoietic toxicity with repeated dosing, but the relative dose intensity was still an acceptable 85% and three out of six patients at the recommended phase II dose completed six cycles of treatment.

A phase II study of gemcitabine administered at 10 mg/m^2 per min combined with carboplatin has been conducted recently in patients with advanced-stage NSCLC [6]. In this study, reported in abstract form, gemcitabine 1200 mg/m^2 was administered over 120 min days 1 and 8 in combination with carboplatin AUC 5 day 1 every 3 weeks. Similar to our experience, the investigators also reported cumulative neutropenia. In contrast to our study in which no significant thrombocytopenia was seen at the recommended phase II dose, the investigators reported 16% grade 3/4 thrombocytopenia.

In a recent randomized phase II study in NSCLC using carboplatin and gemcitabine administered as a 30-min infusion, Thomas et al. [18] found 19% of cycles in the gemcitabine/carboplatin arm were associated with grade 3/4 thrombocytopenia and 28% with grade 3/4 neutropenia. Although the recommended phase II dose

Table 4 Pharmacokinetic parameters of plasma dFdC. Values are means ± SD (only one full data set available at 900 mg/m^2) (*AUC* area under the concentration-time curve, *CL* clearance, *Cmax* maximum concentration, $t_{1/2}$ half-life, *VDss* volume at steady state)

Dose (mg/m^2)	AUC (ng/ml·min)	CL (l/min)	Cmax (ng/ml)	$t_{1/2}$ (min)	VDss (l)
750 ($n = 6$)	315,400 ± 98,800	4.11 ± 1.20	4790 ± 1260	15.0 ± 3.5	76.0 ± 38.3
900 ($n = 1$)	730,900	2.24	9158.6	12.4	34.4

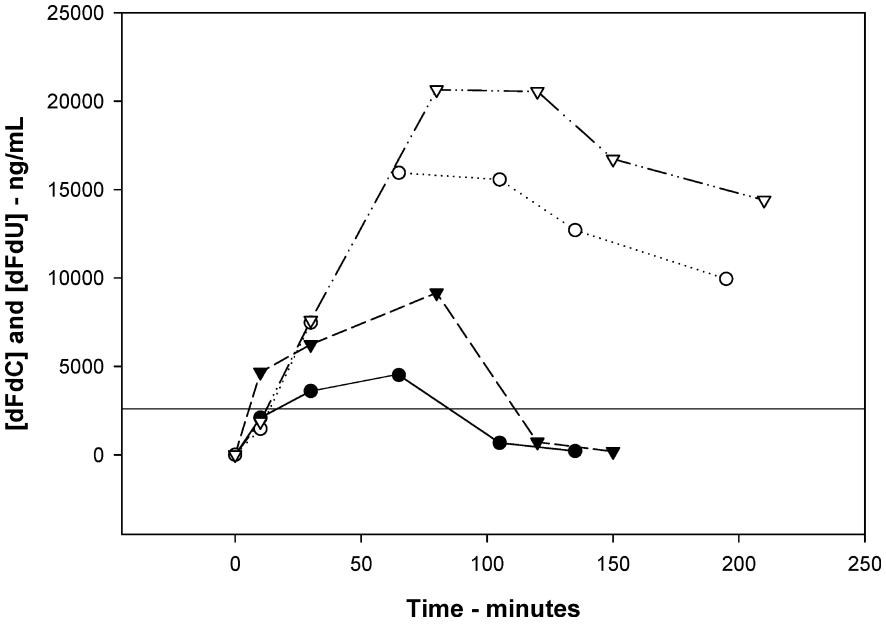

Fig. 1 Plots of time against mean gemcitabine and dFdU concentrations with 75-min and 90-min infusions of gemcitabine. The horizontal line represents the gemcitabine plasma concentration of 10 μmol/l (2630 ng/ml). The plots for the 75-min infusion represent the mean concentration values at each time point (● gemcitabine, 75-min infusion; ○ dFdU, 75-min infusion; ▼ gemcitabine, 90-min infusion; ▽ dFdU, 90-min infusion)

of gemcitabine in our study was 750 mg/m^2, it appeared that by infusing gemcitabine at 10 mg/m^2 per min, hematologic toxicities especially neutropenia, were similar to regimens using bolus administration of gemcitabine at higher doses.

The pharmacokinetics showed that plasma gemcitabine did not reach steady state with the durations of infusion studied, which is consistent with previous reports of steady state being reached after 6 h of infusion [12]. Despite this, plasma levels relevant for saturation of intracellular phosphorylated gemcitabine were achieved in most patients after 10 min of infusion. Clearance of gemcitabine was rapid, with a mean terminal half-life of 15 min. The patient with DLT from neutropenia at 75 min infusion did not have the highest AUC of plasma gemcitabine. This is expected of antimetabolites like gemcitabine, where intracellular active metabolites reflect better clinically observed pharmacodynamics. With constant rate infusion, it may be possible to increase the duration of exposure to pharmacologically relevant concentrations of active metabolites, resulting in better cytotoxicity.

In conclusion, gemcitabine administered as a 75-min infusion at a constant rate of 10 mg/m^2 per min in combination with carboplatin was tolerable and active in NSCLC. Pharmacokinetic studies demonstrated that the target plasma gemcitabine concentration above 10 μmol/l was achieved. A randomized phase II study to compare this regimen with the standard regimen of the two drugs using 30-min gemcitabine infusion is being conducted.

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