Cancer Chemother Pharmacol (2007) 60:211–218
DOI 10.1007/s00280-006-0363-x

ORIGINAL ARTICLE

The efficacy and relationship between peak concentration and toxicity profile of fixed-dose-rate gemcitabine plus carboplatin in patients with advanced non-small-cell lung cancer

Linrun Wang · Xiuhua Wu · Mingzhu Huang · Jie Cai · Nong Xu · Jian Liu

Received: 16 May 2006 / Accepted: 8 October 2006 / Published online: 24 November 2006

Abstract
Purpose To investigate the efficacy and relationship between plasma concentrations at the end of infusion ($C_{\text{end of infusion}}$) and toxicity profile of fixed-dose-rate gemcitabine plus carboplatin in chemotherapy-naive patients with advanced non-small-cell lung cancer (NSCLC).
Patients and methods Patients were given gemcitabine by 120 min infusion [at a fixed dose rate (FDR) of 10 mg/m^2/min] on days 1 and 8 of a 21-day cycle, immediately followed by carboplatin AUC 5 by 4 h infusion on day 1. $C_{\text{end of infusion}}$ of gemcitabine was determined by ion-pair reversed-phase high-performance liquid chromatography (HPLC).
Results By the close-out date, in our study population, the estimated median time to tumor progression (TTP) was 7 months (95% CI 4–10 months), median overall survival (OS) was 12 months (95% CI 11.2–12.8 months). The mean value of $C_{\text{end of infusion}}$ of 21 eligible patients was 16.48 ± 8.07 μmol/l (range 27.43–2.87 μmol/l). The main hematological toxicities were transient grade 3–4 thrombocytopenia. The mean percentages of reduction of WBC, NEC, PLTC and Hb of 21 eligible patients were 38.3 ± 38.1%, 31.3 ± 73.6%, 31.8 ± 53.5% and 12.0 ± 12.2%, respectively. The analysis of the $C_{\text{end of infusion}}$ of gemcitabine and the percentage of reduction in WBC showed a significant correlation ($r^2 = 0.4575$; $p < 0.05$). A significant correlation ($r^2 = 0.5671$; $p < 0.05$) was also observed between the percentage of reduction of PLTC and $C_{\text{end of infusion}}$ of gemcitabine infusion.
Conclusion The clinical data in this trial supports the further evaluation the regimen in advanced NSCLC patients, due to its predictable kinetic behavior and less severe toxicity profile than expected.

Keywords Non-small-cell lung cancer · Gemcitabine · Efficacy · Toxicity

L. R. Wang (✉) · X. H. Wu (✉) · M. Zh. Huang · J. Cai
Department of Pharmacy, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, People's Republic of China
e-mail: surehuaw@hotmail.com

N. Xu
Department of Medical Oncology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, People's Republic of China

J. Liu
Department of Clinical Pharmacology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, People's Republic of China

Introduction

Gemcitabine (2′,2′-difluorodeoxycytidine) is a deoxycytidine analog [1], with clinical activity against several solid tumors, such as ovarian cancer, non-small-cell lung cancer (NSCLC), bladder, pancreas and breast cancer [2–5]. After entering the cell, gemcitabine is initially phosphorylated by deoxycytidine kinase to gemcitabine monophosphate, and subsequent phosphorylation steps yield gemcitabine diphosphate and triphosphate [6]. Gemcitabine diphosphate inhibits ribonucleotide reductase [7], decreasing the cellular pool of deoxycytidine triphosphate that competes with gemcitabine triphosphate for incorporation into DNA. Incorporation of gemcitabine triphosphate into DNA inhibits replication with subsequent induction of

apoptosis [8–9]. As with other therapeutic nucleosides, phosphorylation of gemcitabine to the monophosphate by deoxycytidine kinase is the rate-limiting step in the accumulation of the active diphosphate and triphosphate metabolites [10]. 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. The continuous saturation of deoxycytidine kinase activity may be achieved during a fixed-dose-rate (FDR) infusion of 10 mg/m^2 gemcitabine/min for a longer period. This might not only saturate the enzyme in tumor tissue, which may yield a better efficacy, but also the enzyme in normal tissues and give optimal conditions to induce toxicity. This hypothesis, however, is still to be proved in the clinic.

Furthermore, although the combined administration of cisplatin and gemcitabine is considered to be a standard regimen for the treatment of advanced-stage NSCLC [11], carboplatin has significantly less nephrotoxicity and neurotoxicity than cisplatin. Phase II and III trials of combination of carboplatin or cisplatin with gemcitabine have been compared in NSCLC and have shown to be equally tolerable and active [12–14]. Previous study showed gemcitabine administered at a fixed rate dose of 10 mg/m^2/min infusion for 2 h in combination with carboplatin has satisfactory therapeutic effect and excellent profile of toxicity for the treatment of NSCLC [15]. Increased myelosuppression and hepatic dysfunction are the usual toxicities observed in the regimen of treatment at fixed dose rate of 10 mg/m^2/min infusion compared to the conventional 30 min infusion schedule [16]. But the effect of $C_{\text{end of infusion}}$ of individuals on the toxicity profile of fixed-dose-rate gemcitabine in chemotherapy-naive patients with advanced NSCLC is still unknown. This study aimed at investigating the efficacy and relationship between $C_{\text{end of infusion}}$ and toxicity profile of gemcitabine (1,200 mg/m^2, administered at 10 mg/m^2/min on day 1 and 8) combined with carboplatin (AUC 5; day 1) in patients with advanced NSCLC.

Patients and methods

Patient characteristics and treatment plan

The study was performed in accordance with the provisions of the recent version of the Helsinki Declaration and after approval by the local Ethics Committee. All the patients were advised of the investigational nature of this protocol and a written informed consent was obtained from each patient before enrollment.

Chemotherapy-naive patients with histologically or cytologically confirmed locally advanced or metastatic stage IIIB or IV NSCLC not amenable to surgery or radiotherapy with curative intent were eligible for this study. Additional eligibility criteria were: (a) 18–75 years of age; (b) ECOG performance status ≤ 2; (c) life expectancy of at least 12 weeks; (d) adequate bone marrow reserve (white blood cell [WBC] count $\geq 4.0 \times 10^9$ L^{-1}, absolute neutrophil count [ANC] $\geq 2.0 \times 10^9$ L^{-1} and platelet count [PLTC] $\geq 100 \times 10^9$ L^{-1}), hepatic function (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤ 2 times, and total bilirubin ≤ 1.25 times institutional upper limit of normal) and renal function (creatinine ≤ 1.5 times institutional upper limit of normal); (e) no medical conditions (uncontrolled hypertension, congestive heart failure, serious arrhythmia, unstable angina, recent myocardial infarction and interstitial lung disease with moderate-severe dyspnea) or psychiatric conditions that might expose patients at risk for participation in investigational treatment; (f) no prior chemotherapy or immunotherapy or concomitant radiotherapy was allowed. Prior radiotherapy was acceptable if completed 4 weeks before study entry.

Exclusion criteria included: (a) pregnant or lactating women; (b) serious infection or impairments of organ function; (c) central nervous system (CNS) metastasis or more than two sites of metastasis; (d) previous or concurrent malignancies; (e) absolute contraindication to the administration of steroids.

Twenty-three patients, enrolled in this study with advanced NSCLC, received gemcitabine (Gemzars®, Eli Lilly Company, Indianapolis, IN, USA) 1,200 mg/m^2 by 120 min i.v. infusion (at a rate of 10 mg/m^2/min) on days 1 and 8 of a 21-day cycle, immediately followed by carboplatin AUC 5 (Paraplatin®, Bristol-Myers Squibb Company, USA) by 4 h i.v. infusion on day 1. Carboplatin dosage calculation was based on glomerular filtration rate according to the Calvert formula. All patients were treated on an inpatient basis.

Sample collection

Blood (3 ml) was drawn immediately after the end of gemcitabine infusion. Samples were obtained by venipuncture contralateral to the infusion line and collected into EDTA-2Na-containing anticoagulated collection tubes. All blood samples were placed into a cup of slurry of ice water immediately, and plasma was separated by centrifugation at 4,000 rpm for 20 min at

4°C. Plasma samples were then stored at –20°C for a maximum of 2 weeks until drug assay.

Analysis of the peak plasma concentrations of patients

The plasma concentrations of gemcitabine at the end of infusion ($C_{\text{end of infusion}}$) were determined by ion-pair reversed-phase high-performance liquid chromatography (HPLC) methods using a Waters 2690 HPLC system with a Waters 996 diode array UV detector [17]. A Waters Symmetry C_{18} cartridge (4.6 mm × 250 mm, 5 μm) fitted with a security guard cartridge was used and maintained at a temperature of 25°C. The mobile phase consisted of 0.52% phosphate buffer (pH 2.66) and acetonitrile (containing 0.202% sodium heptanesulfonate) at a ratio of 85:15 (V:V) at a flow rate of 1.0 ml/min. Compounds were quantified by UV absorbance at a wave length of 273 nm.

Before determination, a calibration curve was prepared by analysis of 900 μl blank plasma samples spiked with 100 μl each of the gemcitabine working solutions (diluted with purified water) to obtain the concentration range of 0.1–100 (0.1, 0.5, 1.0, 5.0, 10.0, 25.0, 50.0, 100.0) μg/ml. Then 0.5 ml of these standard calibration samples was vortex-mixed vigorously with 30% trichloracetic acid for 20 s and centrifuged at 10800 rpm for 15 min. The supernatants of the mixtures were applied to Millex^{TM} and the filtrate (10 μl) was injected into the chromatography column. Plasma samples of patients were disposed as described above and then injected into the chromatography column. The chromatography data were collected and processed on Millennium^{32} software.

The calibration curve of gemcitabine in plasma was linear in the range of 0.1 to 100 μg/ml. The calibration curve's regression was $C = 20037A\text{-}21.873$, $r = 0.9999$. The minimum detectable concentration of gemcitabine (signal-to-noise ratio of 3) in plasma was determined to be approximately 0.05 μg/ml. The overall precision, expressed as %RSD (relative standard deviation) ($n = 6$), was less than 1.94% and 7.34% for intra-day and inter-day assay, respectively. The method recovery ($n = 6$) of 0.5, 10.0, and 100.0 μg/ml was within 97.39–103.11%. The $C_{\text{end of infusion}}$ of gemcitabine was calculated by peak area (A) values based on the calibration curves.

Evaluation

Pretreatment baseline evaluation included medical history, complete physical examination; ECOG-PS; chest X-ray; brain, thoracic and abdominal computer tomography scan (CT scan); bone scan; electrocardiogram; complete blood counts and blood chemistry measurements with liver function tests and creatinine clearance.

During treatment, patients were observed with a limited physical examination, weight measurement, assessment of ECOG-PS, blood count, disease-related symptoms and toxicity rating according to WHO scale before each treatment cycle. All measurable and evaluable lesions were assessed by the same method used at baseline. Response to therapy was assessed every two cycles with clinical and/or radiological tumor assessment. In responding patients, a confirmatory assessment was repeated after at least 4 weeks, according to the RECIST criteria [18].

Efficacy was measured by time-to-tumor progression (TTP) and overall survival (OS). TTP was defined as the time interval from initial therapy to the first objective documentation of tumor progression (for patients with measurable disease) or to the date of death, if death was ascribed to progression of disease. OS was defined as the time from initial therapy to the date of death; in the absence of confirmation of death, survival was censored at the last date of follow-up.

A two-stage design and the Simon (1989) hypothesis were used for the study. Every patient included in the study was considered evaluable (intent-to-treat analysis). Response rates, including 95% confidence intervals (CIs), were calculated on an intent-to-treat basis. Time-to-event end points were calculated using the Kaplan–Meier method, with the appropriate censoring [19].

Safety was evaluated in terms of adverse events and clinical laboratory abnormalities, graded according to WHO criteria. Adverse event assessments were performed on day 1 of each treatment cycle and at the end of treatment. Hematological tests were performed at baseline, on days 1 and 8 of each treatment cycle, and at the end of treatment. Due to myelosuppression being the main adverse effect of gemcitabine, percentage of decrease in white blood cell (WBC) counts, neutrophils counts (NE), platelet counts (PLTC), and hemoglobin (Hb) was calculated. Renal and hepatic function tests were performed on day 1 of each treatment cycle and at the end of treatment.

Analysis the relationship between $C_{\text{end of infusion}}$ and hematologic toxicity

The relationship between $C_{\text{end of infusion}}$ and hematologic toxicity of gemcitabine [20, 21] was evaluated. The percentage of decrease in hematologic count (neutrophils, leukocytes, platelets and Hb) was calculated as follows:

$$\%\ \text{Decrease in hematologic count} = 100 \times \frac{\text{pretreatment count - value of the final dose}}{\text{pretreatment count}}$$

and plotted as a function of plasma $C_{\text{end of infusion}}$ of gemcitabine [22]. Relationships were fitted using non-linear least-squares regression and a weighting factor of unity according to sigmoid model [23].

Statistical analysis

The data are presented as mean ± standard deviation (SD). Statistical analysis was performed by ANOVA. the level of significance was $p < 0.05$.

Results

Patient characteristics

Twenty-three patients were enrolled in the study between November 2003 and December 2005. Data were collected through March 2006. The majority of patients were male (82.6%), with a median age of 61 years (range 42–74 years). Patients' characteristics at baseline are presented in Table 1. The majority of patients (91.3%) had metastatic disease, with lung metastases documented in 13 patients (56.5%). All patients were chemotherapy-naive.

Table 1 Baseline patients' characteristics ($n = 23$)

Characteristics	No.	%
Age, years		
Median		61
Range		(42–74)
Sex		
Male/female	19/4	82.6/17.4
ECOG performance status		
0	1	4.3
1	12	52.2
2	10	43.5
Stage		
IIIB	3	13
IV	20	87
Histology		
Squamous	9	39.1
Adenocarcinoma	9	39.1
Large cell and others	5	21.7
Sites of metastases		
Lung	13	56.5
Liver	1	4.3
Bone	5	21.7
Nodes	6	26.1
Other	3	13

ECOG Eastern Cooperative Oncology Group

Efficacy

Of the 23 enrolled patients, 2 patients dropped out midway. Of the 21 eligible patients, the best response to treatment was assessed as a partial response (PRs) in 10 patients (47.6%), for an overall objective response rate of 47.6 %, and a stable disease in 7 patients (33.3%). The full response data are shown in Table 2.

Time to progression (TTP)

By the close-out date, 5 patients (31.25%) were alive without progression and 11 patients (68.25%) had progressed. The estimated median TTP was 7.0 months (95%; CI 4–10 months) (Fig. 1a).

Survival

By the close-out date, 10 patients (47.62%) were still alive and 11 patients (52.38%) had died. The estimated median OS was 12 months (95% CI 11.2–12.8 months) (Fig. 1b).

Toxicity

The main hematological toxicities (Table 3) were transient grade 3–4 thrombocytopenia observed in 9 (42.9%) patients, grade 3–4 neutropenia observed in 7 (33.3%) patients and grade 3–4 anemia in 6 (28.6%) patients. Non-hematological toxicity was generally mild (Table 4). Grade 4 increased AST occurred in 1 (4.8%) patient and grade 3 skin rash occurred in 1 (4.8%) patient. Grade 1–2 alopecia occurred in 12 (57.1%) patients. No serious adverse events were reported during the study.

Relationship between $C_{\text{end of infusion}}$ and hematological toxicity of gemcitabine

The mean value of $C_{\text{end of infusion}}$ of 21 eligible patients was 4.94 ± 2.42 μg/ml (equal to 16.48 ± 8.07 μmol/l; range, 27.43–2.87 μmol/l). The mean percentages of reduction of WBC, NE, PLTC and Hb of 21 eligible patients were 38.3 ± 38.1%, 31.3 ± 73.6%, 31.8 ± 53.5% and 12.0 ± 12.2%, respectively. The analysis of the $C_{\text{end of infusion}}$ /hematological toxicity profile of gemcitabine showed a significant correlation ($r^2 = 0.4575$; $p < 0.05$) between $C_{\text{end of infusion}}$ of gemcitabine and the percentage of reduction in WBC (Fig. 2a). The plot represented in Fig. 2b also showed the significant relationship ($r^2 = 0.5671$; $p < 0.05$) between the percentage of decrease in PLTC and the $C_{\text{end of infusion}}$ of gemcitabine, and the fitted E_{max} of

Table 2 Best overall response (n = 21)

	No.	%
Partial response (PR)	10	47.6
Objective response rate (RR)	10/21	47.6
Objective response rate (RR) ITT	10/23	43.5
Stable disease (SD)	7	33.3
Progressive disease (PD)	4	19.0
Not assessable (NA)	2/23	8.7

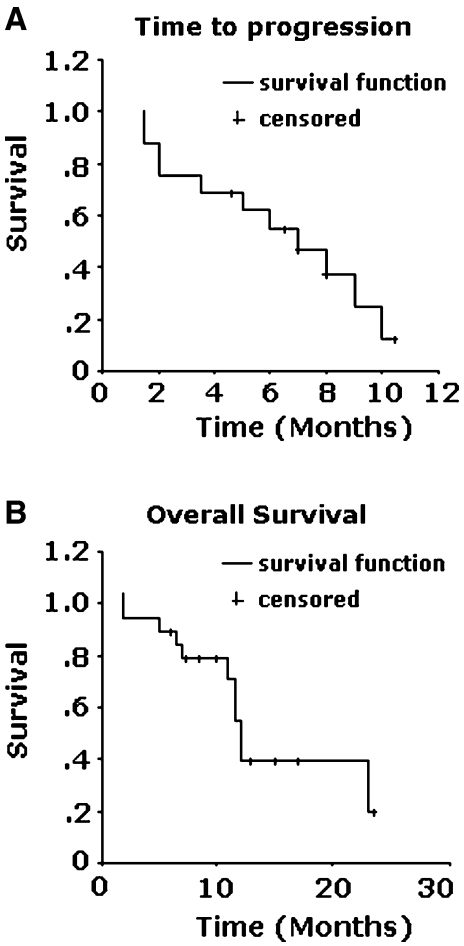

Fig. 1 The time to progression (*TTP*) and overall survival (*OS*) have been constructed by the Kaplan–Meier method. The mean *TTP* was 7.0 months (95% CI 4.0–10.0 months) (**a**) and the mean *OS* was 12.0 months (95% CI 11.2–12.8 months) (**b**)

sigmoid curve corresponded to a 51.7% reduction in PLTC, with respect to baseline, as described by the sigmoid pharmacodynamic model. In this patient population, 6 out of 16 patients had a percentage of decrease in WBC higher than 70%, but only 3 out of 16 patients had a percentage of decrease in PLTC higher than 70%. In addition, no patients had a percentage of decrease in Hb higher than 40% (data not shown).

Discussion

The combination of gemcitabine and carboplatin as a front-line regimen for advanced NSCLC may be an appealing choice. It is an effective combination with an acceptable profile of toxicity for the treatment of advanced NSCLC. Due to pharmacological features of gemcitabine, a longer infusion time would provide increased intracellular concentration of tumor tissues, thus enhancing the agent's efficacy. In a randomized phase II trial by Tempero et al. [24] in patients with pancreatic adenocarcinoma showed a better median survival (8 months) in FDR infusion (10 mg/m^2/min) than that in the standard 30 min infusion (5 months). The FDR infusion of gemcitabine allows maximal intracellular accumulation of the active triphosphate form of the drugs, and may result in optimal antitumor activity. Our present investigation showed a promising activity and manageable toxicity profile of FDR infusion combined with carboplatin in patients with stage IIIB/IV NSCLC, with an ORR of 47.6%, 10 PRs in the 21 eligible patients, median TTP and median OS was 7 and 12 months. The results are similar to those of the phase II study of gemcitabine combined with carboplatin in patients with advanced-stage NSCLC by Domine et al. [25], with a response rate of 47%, median TTP 28 weeks, and median survival 45 weeks.

In the present study, the toxicity profile was relatively low grade 3/4 hematologic toxicity rates. The rate of grade 3/4 neutropenia (33.3%) was also similar to the rates in the studies by Zatloukal et al. [14], Domine et al. [25] and Rudd et al. [26], 30.3, 36.5 and 34% respectively despite G-CSF being used systematically in some of these studies. Although the rate of grade 3/4 thrombocytopenia was up to 42.9% of

Table 3 Hematological toxicities (by patient)

Toxicity	WHO Grade (n = 21)				
	Grade 1(%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 3–4(%)
Leucocytopenia	3(14.3)	9(42.9)	5(23.8)	0	23.8
Neutropenia	2(9.5)	7(33.3)	3(14.3)	4(19.0)	33.3
Anemia	5(23.8)	2(9.5)	2(9.5)	4(19.0)	28.6
Thrombocytopenia	2(9.5)	4(19.0)	4(19.0)	5(23.5)	42.9

Table 4 Nonhematological toxicities (by patient)

Toxicity	WHO Grade (n = 21)				
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 3~4%
Nausea/Vomiting	7(33.3)	2(9.5)	0	0	0
Skin rash	4(19.0)	5(23.8)	1(4.8)	0	1(4.8)
Diarrhea	0	0	0	0	0
Constipation	3(14.3)	0	0	0	0
Increased AST	3(14.3)	0	0	1(4.8)	1(4.8)
Increased creatinine	2(9.5)	0	0	0	0
Alopecia	7(33.3)	5(23.8)	0	0	0
Neurological toxicitity	1(4.8)	0	0	0	0
Mucositis	1(4.8)	0	0	0	0
Febrile	2(9.5)	3(14.3)			

patients, no bleeding episodes were recorded. These hematologic toxicities were transient, and of limited significance; remarkably, we recorded very few episodes of febrile neutropenia in this study population. The manageable toxicities kept rare dose adjustment and resulted in high-dose intensity for two drugs.

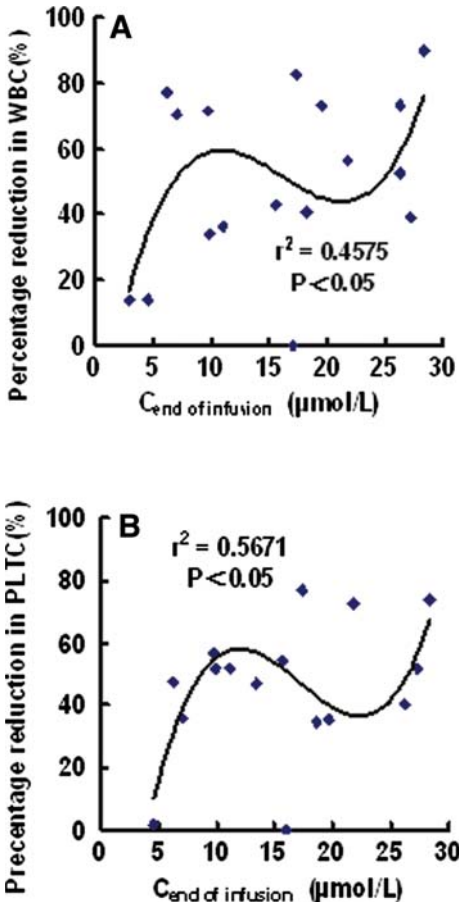

Fig. 2 Relationship between the plasma concentration at the end of infusion of fixed-dose-rate gemcitabine ($C_{\text{end of infusion}}$) and hematologic toxicity. Data were modeled according to the $E_{\max}$ sigmoid (variable slope) fitting. Points, individual data were from 16 patients. **a** Relationship between $C_{\text{end of infusion}}$ of gemcitabine and percentage of reduction in WBC. **b** Relationship between $C_{\text{end of infusion}}$ of gemcitabine and percentage of reduction in PLTC

According to our previous study, the maximum plasma concentration of gemcitabine 1200 mg/m^2 by 120 min i.v. infusion is approximately at the end of infusion [17]. In our present work, we determined the concentration at the end of infusion of gemcitabine instead of the maximum concentration of gemcitabine. A significant relationship between the decrease in PLTC and $C_{\text{end of infusion}}$ of gemcitabine in combination with carboplatin was observed. This analogy relationship was also reported by Kroep et al. [27]. In their study, the gemcitabine $C_{\max}$ was related to the percentage decrease in platelets in patients treated with gemcitabine-paclitaxel. This might demonstrate that haematological toxicity might have been related to gemcitabine as well, not merely to carboplatin. In addition, we described here a significant correlation ($p < 0.05$) between $C_{\text{end of infusion}}$ of FDR gemcitabine and the percentage of reduction in WBC. This correlation was also similar to the study of Yonemori et al. [28], which showed that an increased gemcitabine AUC was related to severe myeloid toxicity in one Japanese cancer patient treated with gemcitabine plus cisplatin. The above data suggested that the haematological toxicity may be associated with the infusion rate of gemcitabine. Furthermore, FDR infusion of gemcitabine was supported by the latest investigation of comparison of different infusion rates of gemcitabine by Soo et al. too [29]. Briefly, FDR infusion of gemcitabine in combination with carboplatin is associated with a predictable kinetic behavior and modest thrombocytopenia and leukocytopenia, and thus it may be an acceptable regimen for advanced NSCLC patients for future clinical studies.

Non-hematological toxicity was generally mild in this study. Severe non-hematologic toxicities were rare. Nausea/vomiting (42.8%), alopecia (57.1%), skin rash

(47.6%) and increased AST grade 1 (19.1%) was similar to both the Zatloukal [14] and Rudd trials [26]. In particular, only one patient with grade 1 neurotoxicity was in our study population (4.8%) as compared to rates as high as 19% reported in other studies.

In summary, the results of our study suggest that the combination of FDR infusion of gemcitabine and carboplatin is well tolerated and appears to be an acceptable, albeit not clearly superior, alternative to other gemcitabine/platinum regimens. In the absence of a clear winner among the different choices of regimens, factors such as safety profile and pharmacoeconomics may be critical in deciding which regimen represents the optimal chemotherapeutic backbone on which to add novel targeted agents in future study design. The administration of gemcitabine 1,200 mg/m^2 120 min i.v. infusion plus carboplatin was an acceptable regimen for advanced NSCLC patients for future clinical studies, due to its predictable kinetic behavior and less severe toxicity profile than expected.

Acknowledgments This work was supported by grants from the Medical Science Research Foundation of Zhejiang province, China (N0. 2004A028).

References

1. Hertel LW, Kroin JS, Misner JW et al (1988) Synthesis of 2-deoxy-2,2-difluoro-D-ribose and 2-deoxy-2,2-difluoro-D-ribofuranosyl nucleosides. J Org Chem 53:2406–2409
2. Yokoyama A, Nakai Y, Yoneda S et al (1997) Activity of gemcitabine in the treatment of patients with non-small-cell lung cancer: a multicenter phase study. Anti-cancer Drugs 8:574–581
3. Pollera CF, Ceribelli A, Crecco M et al (1994) Weekly gemcitabine in advanced bladder cancer: a preliminary report from a phase study. Ann Oncol 5:182–184
4. Burris HA, Moore MJ, Anderson J et al (1997) Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 15:2403–2413
5. Carmichael J, Possinger K, Phillip P et al (1995) Advanced breast cancer. A phase 2 trial with gemcitabine. J Clin Oncol 13:2731–2736
6. Heinemann V, Hertel LW, Grindey GB et al (1988) Comparison of the cellular pharmacokinetics and toxicity of 2′,2′-difluorodeoxycytidine and 1-β-D-arabinofuranosylcytosine. Cancer Res 48:4024–4031
7. Heinemann V, Xu Y-Z, Chubb S, et al (1990) Inhibition of ribonucleotide reduction in CCRF-CEM cells by 2′,2′-difluorodeoxycytidine. Mol Pharmacol 38:567–572
8. Huang P, Chubb S, Hertel LW et al (1991) Action of 2′,2′-difluorodeoxycytidine on DNA synthesis. Cancer Res 51:6110–6117
9. Huang P, Plunkett W (1995) Fludarabine and gemcitabine-induced apoptosis: incorporation of analogs into DNA is a critical event. Cancer Chemother Pharmacol 36:181–188
10. Grunewald R, Kantarjian H, Keating MJ et al (1990) Pharmacologically directed design of the dose rate and schedule of 2′,2′-difluorodeoxycytidine(gemcitabine) administration in leukemia. Cancer Res 50:6823–6826
11. Schiller JH, Harrington D, Belani CP et al (2002) Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346:92–98
12. Sederholm C (2002) Gemcitabine versus gemcitabine/carboplatin in advanced non-small cell lung cancer: preliminary findings in a phase III trial of the Swedish Lung Cancer study group. Semin Oncol 29:50–54
13. Thomas P, Robinet G, Gouva S et al (2006) Randomized multicenter phase II study of carboplatin/gemcitabine and cisplatin/vinorelbine in advanced non-small-cell lung cancer GFPC 1999–2001 study (Groupe francais de pneumo-cancerologie). Lung Cancer 51:105–114
14. Zatloukal P, Petruzelka L, Zemanova M et al (2003) Gemcitabine plus cisplatin vs. gemcitabine plus carboplatin in stage IIIb and IV non-small-cell lung cancer: a phase randomized trial. Lung Cancer 41:321–331
15. Manuel D, Laura GE, Ana L (2002) A phase II trial of a two hour infusion of gemcitabine with carboplatin for advanced non-small-cell lung cancer (NSCLC). Ann Oncol, 13(suppl.5):143
16. Schmid P, Akrivakis K, Flath B et al (1999) Phase II trial of gemcitabine as prolonged infusion in metastatic breast cancer. Anticancer Drugs 10:625–631
17. Wang LR, Huang MZ, Xu N, et al (2005) Pharmacokinetics of gemcitabine in Chinese patients with non-small-cell lung cancer. J Zhejiang Univ Sci B 6:446–450
18. Therasse P, Arbuck SG, Eisenhauer EA et al (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92:205–216
19. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457–481
20. Eisenhauer EA, Vermorken JB (1998) The taxoids. Comparative clinical pharmacology and therapeutic potential. Drugs 55:5–30
21. Noble S, Goa KL (1997) Gemcitabine. A review of its pharmacology and clinical potential in non-small-cell lung cancer and pancreatic cancer. Drugs 54:447–472
22. Fogli S, Danesi R, De Braud F et al (2001) Drug distribution and pharmacokinetic/pharmaco-dynamic relationship of paclitaxel and gemcitabine in patients with non-small-cell lung cancer. Ann Oncol 12:1553–1559
23. Rowland M, Tozer TN (1995) (Third edition) Clinical Pharmacokinetics: Concepts and Applications. Baltimore, Williams and Wilkins, Maryland
24. Tempero M, Plunkett W, Ruiz van H et al (2003) Randomized phase II comparison of dose-intense Gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Oncol 21:3402–3408
25. Domine M, Estevez L, Leon A et al (2002) Phase II trial of a two-hour infusion of gemcitabine with carboplatin for advanced non-small-cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 21:225b
26. Rudd RM, Gower NH, Eisen TG et al (2005) Gemcitabine plus carboplatin versus mitomycin, ifosfamide, and cisplatin in patients with stage IIIB or IV non-small-cell lung cancer: a phase III randomized study of the London Lung Cancer Group. J Clin Oncol 23:142–153
27. Kroep JR, Giaccone G, Voorn DA et al (1999) Gemcitabine and paclitaxel: pharmacokinetic and pharmacodynamic interactions in patients with non-small-cell lung cancer. J Clin Oncol 17:2190

28. Yonemori K, Ueno H, Okusaka T et al (2005) Severe drug toxicity associated with a single-nucleotide polymorphism of the cytidine deaminase gene in a Japanese cancer patient treated with gemcitabine plus cisplatin. Clin Cancer Res 11:2620–2624

29. Soo RA, Wang LZ, Tham LS et al (2006) A multicentre randomised phase II study of carboplatin in combination with gemcitabine at standard rate or fixed dose rate infusion in patients with advanced stage non-small-cell lung cancer. Ann Oncol 17:1128–1133