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Comparison of pharmacokinetics, efficacy and toxicity profile of gemcitabine using two different administration regimens in Chinese patients with non-small-cell lung cancer*

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Abstract: Objective: To conduct a randomized comparative trial of pharmacokinetics, efficacy and toxicity profile treatment with 1 200 mg/m^2 gemcitabine using standard 30-min infusion or fixed dose rate (FDR) infusion [10 mg/(m^2·min)] on days 1 and 8 plus carboplatin AUC (area under curve) 5 on day 1 in Chinese non-small-cell cancer patients. Twelve patients were enrolled in this study. Methods: Plasma gemcitabine concentrations were measured by ion-pair reversed phase high performance liquid chromatography. Antitumoral activity and toxicity of gemcitabine was assessed according to World Health Organization criteria. Results: The obtained mean parameters, such as $T_{1/2}$ (elimination half time), AUC, and CL (clearance), were consistent with those reported in literature. Qualified response rate in our study was 33.3% for standard arm and 50% for FDR arm. Additional 50% and 33.3% patients contracted stable disease (SD) in standard arm and FDR arm, respectively. The predominant toxicity was hematologic, and patients in the standard infusion arm experienced consistently more hematologic toxicity. Conclusion: Pharmacokinetic and clinical data in this trial support the continued evaluation of the FDR infusion strategy with gemcitabine.

Key words: Gemcitabine, Non-small-cell lung cancer, Pharmacokinetics, Qualified response, Safety
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INTRODUCTION

Gemcitabine (2',2'-difluorodeoxycytidine, dFdC), a new pyrimidine antimetabolite, is a novel deoxycytiding analogue with cytotoxic activity in non-small-cell lung cancer (NSCLC) (Anderson *et al*., 1994; Abratt *et al*., 1994; Lund *et al*., 1994). Gemcitabine is a prodrug which, through deoxycytidine kinase and other nucleotide kinases, exerts its cytotoxic effects through its active intracellular metabolites, gemcitabine diphosphate and triphosphate (Guchelaar *et al*., 1996; Storniolo *et al*., 1997). Gemcitabine's unique mechanism of action and mild toxicity profile makes it an ideal candidate for combination therapy in the treatment of advanced NSCLC patients.

The combination of gemcitabine/cisplatin is a widely used regimen in Europe for first-line treatment of advanced NSCLC. However, the significant side effects (such as hemotologic toxicity, ototoxicity, and nephrotoxicity, etc.) and difficult administration method of cisplatin have restricted its use on patients (Zatloukal and Petruzelka, 2002).

Carboplatin may constitute a suitable alternative to cisplatin for combination with gemcitabine in NSCLC. A recent study demonstrated a synergistic interaction between carboplatin and gemcitabine similar to that observed between cisplatin and gemcitabine. Available data suggest that carboplatin and cisplatin have comparable effectiveness in advanced NSCLC. Advantages of the carboplatin/gemcitabine combination include relative ease of use in the outpatients setting and a better nonhematologic toxicity profile (Yanagihara and Beck, 2000).

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As with other therapeutic nucleosides, phosphorylation of gemcitabine to monophosphate by deoxycitidine kinase is the rate-limiting step in the accumulation of the active diphosphate and triphosphate metabolites (Grunewald *et al*., 1990). In addition, previous data revealed that gemcitabine plasma concentration ranging from 10~20 μmol/L (2.99~5.99 μg/ml) produced maximum intracellular triphosphate concentrations. A dose rate of 10 mg/(m^2·min) had been reported to provide gemcitabine plasma concentrations of 10 to 20 μmol/L (Shord *et al*., 2003). Prolonged infusion of gemcitabine had been shown to increase levels of the active triphosphate metabolite that theoretically could increase the survival rate and improved cytotoxicity (Tempero *et al*., 2003).

Numerous phase I studies of gemcitabine as a single agent led to the dose recommendation of 1000 mg/m^2, administered as a 30-min infusion (Guchelaar *et al*., 1996; Storniolo *et al*., 1997). Using this treatment schedule, the toxicity profile of gemcitabine is low, with myelosuppression being the major side effect (Green, 1996). Prolonged gemcitabine infusion [fixed dose rate of 10 mg/(m^2·min) for 120 min] was shown to have efficacy comparable to that of schemes using bolus administration of similar dose of gemcitabine (Manuel *et al*., 2002). However, this regimen has never been characterized in the Chinese advanced NSCLC patients until this study.

In light of these issues, a randomized study was designed exploring gemcitabine treatment of Chinese patients with NSCLC, using two different infusion schedules. One group of patients were assigned to be administered gemcitabine using a standard 30-min infusion (standard arm, days 1 and 8 every 21 d) with carboplatin [AUC (area under curve) 5] day 1 and in the other regimen gemcitabine was employed at a fixed dose rate of 10 mg/(m^2·min) (FDR arm, 1200 mg/m^2 two hours infusion days 1 and 8 every 21 d) with carboplatin (AUC 5) day 1.

PATIENTS AND METHODS

Patients

A group of 12 adult patients with historically or cytologically proven stage III_B or IV NSCLS, which was not amenable to surgery or radiotherapy with curative intent, were enrolled into this study. The inclusion criteria included: no previous chemotherapy or chemotherapy and radiation therapy ≥1 month before enrollment; Karnofsky performance status ≥70; estimated life expectancy ≥3 months; between 18 and 75 years of age; body weight between 50 and 60 kg; serum transaminase ≤2 times normal value; adequate bone marrow function [WBC (white blood cell) count $\geq 4.0\times10^9$ L^{-1}, platelet count $\geq 100\times10^9$ L^{-1}]; adequate renal function (serum creatinine ≤1.5 times normal value). The exclusion criteria included: pregnant or lactating women; serious infection or impairments of organ function; CNS (central nervous system) metastasis or more than two metastasis. Written informed consent to undergo pharmacokinetic studies was obtained from each patients.

Study design

The study was approved by the Ethical Committee of the First Affiliated Hospital, Zhejiang University and was carried out in accordance with the Declaration of Helsinki. The treatment schedule consisted of carboplatin (AUC 5) on day 1 and gemcitabine on days 1 and 8, repeated every 3 weeks. Patients were randomly assigned to the two treatment groups: in the first group of 6 patients, 1200 mg/m^2 by intravenous administration in 30 min, referred to as the standard arm; other 6 patients were administered gemcitabine at a fixed dose rate of 10 mg/(m^2·min) (1200 mg/m^2, two hours infusion), referred to as the FDR arm.

Drug and other chemicals

For clinical use, gemcitabine (trade name Gemzar®) was obtained from Eli Lilly Company. Carboplatin (trade name Paraplatin®) was provided by Bristol-Myers Squibb Company. Acetonitrile was HPLC grade and other chemicals were analytical grade.

Measurement of gemcitabine in plasma

A stock solution of gemcitabine was diluted with water to a series of concentrations of working solutions. Calibration curves were prepared by analysis of 1 ml plasma samples spiked with 100 μl each of the gemcitabine working solutions to obtain 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 up vigorously

with 30% trichloracetic acid for 20 s and centrifuged at 10800 r/min for 15 min. The supernatants of the mixtures were applied to Millex™ and the filtrate (10 μl) was injected on column.

Serum concentration of gemcitabine was carried out using a Waters 2690 high-performance liquid chromatography (HPLC) system with a Waters 996 diode array UV detector. Waters Symmetry C_{18} cartridges (4.6 mm×250 mm, 5 μm) fitted with a security guard cartridge were 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 l-heptanesulfonate) at ratio of 85:15 (v:v) and flow rate of 1.0 ml/min. Compounds were quantified by UV absorbance at a wave length of 273 nm. The chromatography data were collected and processed on Millennium^{32} software.

Pharmacokinetics

Plasma concentrations versus time data were analyzed using established noncompartmental methods with computer program 3P97 pharmaceutical kinetics software to determine a number of pharmacokinetic parameters and to simulate expected gemcitabine plasma concentrations. Venous blood samples were withdrawn into EDTA-2Na anticoagulated collection tubes at 30, 120, 130, 140, 150, 165, 180, 210 min after the start of the infusion. All blood samples were placed in an ice water bath until they were disposed as described above. Plasma samples were then stored in polypropylene tubes at −20 °C until analyzed. The maximum concentration (C_{max}) was observed values. $AUC_{0\to t}$ (area under the curve from zero to time t) was estimated by trapezoidal rule with extrapolation to infinity using the ratio C_n/K_e where C_n was the last measurable concentration. The elimination rate constant (K_e) was estimated from the terminal linear segment of the log serum concentration/time data. The elimination half life ($T_{1/2}$) was calculated from $\ln 2/K_e$. Clearance (CL) of the plasma drug was calculated by dividing the dose (D) of gemcitabine by $AUC_{0\to t}$: $CL=D/AUC_{0\to t}$ (ml/min). Mean residence time ($MRT_{0\to t}$) was calculated by:

$$AUMC_{0\to t}/AUC_{0\to t},$$

where $AUMC_{0\to t}$ is area under the first moment curve.

Response

Antitumoral activity was assessed according to the World Health Organization criteria every 6 weeks or more often in case of clinical suspicion of disease progression (Miller *et al*., 1981). Complete response (CR) was defined as the total disappearance of all measurable and assessable clinical evidence of cancer observed on two assessments separated by at least 4 weeks. Partial response (PR) was defined as at least a 50% reduction in the size of all measurable tumor areas as measured by the sum of the products of the greatest length and the maximal width of all measurable lesions. No lesions could have progressed, nor could new lesions have appeared. Tumor reduction must have been observed on two consecutive assessments separated by at least 4 weeks. An increase of more than 25% in the size of all measurable tumor areas as measured by the sum of the products of the greatest length and maximal width, or the appearance of any new lesions was qualified as progressive disease (PD). Stable disease (SD) was defined when a patient did not qualify for a response of PD.

Safety

Physical and clinical laboratory examinations involving hematology, serum chemistries, urinalysis and vital sign measurements were done for each subject before dosing, during the dosing period, and at the end of the study to assess the tolerability of gemcitabine. As myelosuppression is the main adverse effect of gemcitabine, percentage decrease in WBC (white blood cell), NE (neutrophil), PLT (platelet), and Hb (hemaglobin) was calculated using the following equation:

Percentage decrease=(pretreatment value−value of the final dose)/pretreatment value×100%,

which was evaluated in the safety analysis.

Data analysis

Results are expressed as the mean±*SD*. The study was designed to select the best of the two regimens as reflected by the response. However, for clinical treatment, other factors such as toxic effects will be taken into consideration for the ultimate selection of the better regimen.

RESULTS

Patient characteristics

Twelve (6 in the standard arm, 6 in the FDR arm) patients were enrolled in the study. The median age of patients was (65.50±8.65) years (range, 49 to 74 years), with 8 of the patents (66.7%) being men. The average weight and body area of patients were (61.46±8.11) kg and 1.67±0.13, respectively. Characteristics of these patients are listed in Table 1.

Table 1 Patient characteristics

	Standard arm (n=6)	FDR arm (n=6)
Age (years)		
Median	66.83±9.11	64.17±8.80
Range	49~72	50~74
Sex		
Male	4	4
Female	2	2
Weight (kg)	68±5.25	54.92±3.80
Body area	1.77±0.07	1.58±0.10
Biochemical parameters (mean±*SD*)		
WBC ($\times10^9$ L^{-1})	6.27±2.30	8.65±2.63
Ne (L^{-1})	4.00±1.28	6.07±2.11
Hb (g/L)	120.67±9.89	115.50±5.16
PLT ($\times10^9$ L^{-1})	214.30±95.05	271.83±184.59

Determination of gemcitabine in plasma

The calibration curve of gemcitabine in plasma was linear in the range of 0.1 to 100 μg/ml. The concentrations (C) were calculated by peak area (A) values. The calibration curve's regression equation was C=20037A−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% to 103.11%.

Pharmacokinetic studies

Gemcitabine concentrations in 6 patients who received the conventional 30-min infusion (standard arm) and 6 patients who received the FDR infusion in 120 min were analyzed. Pharmacokinetic parameters describing gemcitabine disposition in Chinese NSCLC patients are presented in Table 2. The results indicated that the data from the individual subjects (Fig.1) fitted two compartments.

Table 2 Pharmacokinetic parameters for gemcitabine calculated from Chinese NSCLC subjects as a 30-min infusion of 1200 mg/m^2 (standard arm) and an infusion at a rate of 10 mg/(m^2·min) (2 h infusion, FDR arm)

Pharmacokinetic parameters	$\bar{\chi}\pm SD$	
	Standard arm (n=6)	FDR arm (n=6)
K_e (min^{-1})	0.055±0.02	0.07±0.02
$T_{1/2}$ (min)	14.75±5.45	10.67±3.38
C_{max} (μg/ml)	26.79±10.06	4.92±1.79
$AUC_{0\to t}$ (μg·h/ml)	13.29±4.85	7.55±1.53
CL (ml/min)	2797.13±837.90	3940.05±672.08
$MRT_{0\to t}$ (min)	30.07±5.37	88.99±9.86

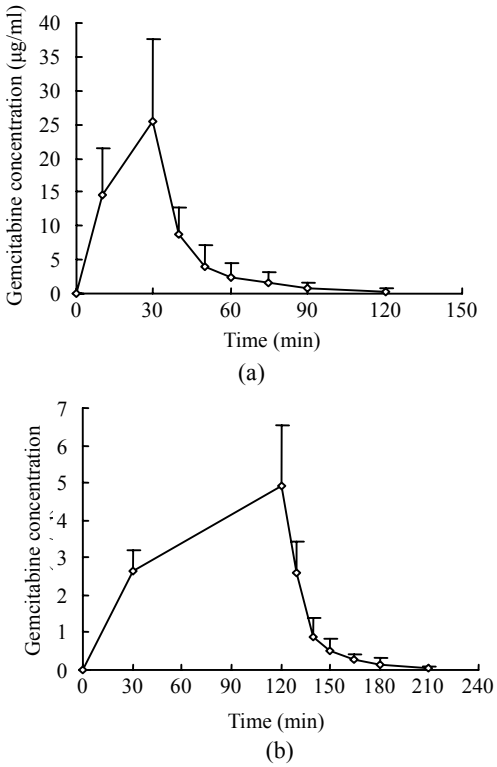

Fig.1 Plasma concentrations of gemcitabine-time curve from Chinese NSCLC subjects as (a) a 30-min infusion of 1200 mg/m^2 (standard arm) and (b) an infusion at a rate of 10 mg/(m^2·min) (2 h infusion, FDR arm)

Response

All patients were evaluated for response. The tumor response rates for standard arm and FDR arm were 33.3% with 2 patients attaining partial response (PR) and 50% with 3 patients attaining PR, respec-

tively. No complete response (CR) was observed. Of the remaining patients, 3 (50%) had stable disease (SD) as their best tumor response, 1 (16.7%) had progressive disease (PD) in standard arm and 2 (33.3%) had SD, 1 (16.7%) had PD in FDR arm.

Toxic effects

WHO grade of nonhematologic toxicities for each patient are summarized in Table 3. The toxicology was moderate in both treatment arms. There were no grades 3 or 4 toxicities observed in the study. A total of 10 episodes of WHO grade 1 or 2 toxicities were reported in the standard arm and 7 cases reported in the FDR arm.

Table 3 Nonhematologic toxicity summary

Treatment arm	Patient	WHO grade				
		Nausea	Diarrhea	Alopecie	Fever	Erythra
Standard	1	2	0	1	0	0
	2	2	0	0	0	0
	3	2	0	1	0	0
	4	1	0	1	0	0
	5	0	0	2	0	0
	6	1	0	1	0	0
FDR	1	0	0	1	0	0
	2	0	0	0	0	0
	3	0	0	0	2	2
	4	0	0	0	1	1
	5	0	0	1	0	2
	6	0	0	0	0	0

Hematological toxicity was the most significant adverse effect, and the hematologic toxicities are listed in Table 4. Nine episodes of WHO grades 3 or 4 toxicities were reported in the standard arm and 5 cases reported in the FDR arm.

Table 4 Hematologic toxicity summary

Treatment arm	Patient	WHO grade			
		WBC	NE	Hb	PLT
Standard	1	3	3	3	3
	2	2	1	0	0
	3	0	0	0	4
	4	2	3	0	3
	5	0	0	1	2
	6	3	3	0	0
FDR	1	3	2	4	3
	2	2	1	2	0
	3	0	0	1	0
	4	1	2	0	1
	5	2	1	0	4
	6	2	1	4	2

DISCUSSION

Our study showed that combination of gemcitabine and carboplatin is an effective regimen that is well-tolerated in Chinese patients with NSCLC.

To our knowledge, this is the only randomized study to be reported of gemcitabine using a standard 30-min infusion (standard arm) with carboplatin versus gemcitabine at a fixed dose rate of 10 mg/m^2 (FDR arm) with carboplatin in Chinese NSCLC patients.

Comparative pharmacokinetic studies of these two gemcitabine regimens were conducted on 12 subjects. Although there is considerable interpatient variability with both infusion rates, it was found that the pattern of the concentration-time profile of FDR arm was similar to the results of the standard arm. Compared to pharmacokinetic data from the literature (a dose of 1000 mg/m^2, 30-min infusion) (Abbruzzese *et al*., 1991; Kroep *et al*., 1999; Bhargava *et al*., 2001), no apparent difference was found with respect to $T_{1/2}$, AUC, and CL for two different infusion schedules. The maximum concentration (C_{max}) was (26.79±10.06) μg/ml and (4.92±1.79) μg/ml for standard and FDR infusion, respectively, which differed significantly from the published data that showed 10.0~18.3 μg/ml. The discrepancy may be due to the different infusion time, dosage and the different ethnicity of the patients.

A number of phase II or III studies evaluated the combination of gemcitabine 1000~1250 mg/m^2 and carboplatin AUC 5 or 6 on a 21-day schedule in patients with advanced NSCLC (Carrato *et al*., 1999; Zatloukal *et al*., 2001; Domine *et al*., 2000; Sederholm, 2002; Stani *et al*., 2001). These studies have shown response rate ranging from 26% to 55% and median survival times of 9.4~14.3 months, with rates of grades 3 or 4 thrombocytopenia ranging from 9.4% to 62% and grades 3 or 4 neutropenia ranging from 11% to 80%. In our study, the overall response rate was 33.3% for standard arm and 50% for FDR arm. Additional 50% and 33.3% of patients contracted stable disease (SD) in standard arm and FDR arm, respectively.

A moderate rate of grades 3 and 4 myelosuppression occurred with both treatment schedules. The standard infusion schedule seemed more toxic, with 33.3% of patients experiencing grade 3 leucopenia,

50% experiencing grade 3 neutropenia, 16.7% experiencing grade 3 hypochromia, and 50% experiencing grades 3 and 4 thrombocytopenia. However, patients receiving FDR infusion experienced 16.7% grade 3 leucopenia, 33.3% experiencing grade 4 hypochromia, and 33.3% experiencing grades 3 and 4 thrombocytopenia. Overall, other grades 1 and 2 nonhematologic toxicities such as nausea diarrhea, alopecie, fever, and erythra were seen in two administration regimens.

The prolonged infusion time in the FDR arm resulted in gemcitabine plasma concentrations being maintained substantially higher than the effective anti-tumor concentration of 10 μmol/L for longer time than the 30-min infusion (standard arm) and increase the clinical therapeutic effect. Meanwhile, the hematologic toxicology was moderate in the FDR infusion schedule.

The purpose of this trial was to assess the efficacy of two dose-intense schedules of gemcitabine using standard infusion time and infusion rate based on pharmacokinetic principles (FDR), to select a dose and infusion rate for further development in combination with potentially synergistic drugs. This study does not definitively favor one regimen over the other due to small sample size. However, both the clinical and pharmacologic data support the continued evaluation of the FDR infusion strategy for gemcitabine in combination with carboplatin.

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