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ORIGINAL ARTICLE

Phase II study of gemcitabine and carboplatin in patients with advanced non-small-cell lung cancer

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Abstract
Purpose To evaluate the efficacy and safety of gemcitabine in combination with carboplatin at standard rate or fixed dose rate infusion in patients with advanced non-small-cell lung cancer (NSCLC).
Patients and methods In this prospective study, patients with chemonaive advanced NSCLC were randomized to receive gemcitabine at a standard rate (gemcitabine 1,200 mg/m^2 over 30 min, the standard arm) or a fixed dose rate (gemcitabine 1,200 mg/m^2 over 120 min, the FDR arm) on days 1 and 8 every 3 week cycle. In both treatment arms, carboplatin at AUC of 5 was administered over 4 h following gemcitabine on day 1 of each cycle.
Results From November 2003 to June 2005, a total of 42 patients, in which 7 (17%) patients had stage III_B disease and 35 (83%) had stage IV disease, were enrolled into this study. All patients were included in efficacy and toxicity assessment. No patient had a complete response. Seven (33%) patients in the standard arm and 10 (48%) in the FDR arm had a partial response. The median time to progression and median overall survival time in the standard arm was 5.4 months (95% CI, 3.8–7 months) and 11.5 months (95% CI, 8.2–14.8 months), respectively, while in the FDR arm was 6.5 (95% CI, 4.4–8.6 months) months, 12.0 months (95% CI, 11.3–12.7 months), respectively. The most frequently reported grade 3 or 4 hematological toxicities were thrombocytopenia (38% patients in the standard arm and 43% in the FDR arm) and neutropenia (24% in the standard arm and 33% in the FDR arm). Although hematological toxicity occurred in a little higher percent of patients in the FDR arm than in the standard arm, there were no discernible differences by statistical analysis in both treatment arms ($P > 0.05$). And significant nonhematologic toxicities were infrequent and tolerable in both arms. No significant difference existed also ($P > 0.05$).
Conclusion In this phase II study, gemcitabine in combination with carboplatin either at standard rate or fixed dose rate infusion was clinically effective and well tolerated in patients with advanced NSCLC.

Keywords Non-small-cell lung cancer · Chemotherapy · Gemcitabine · Fixed dose rate · Carboplatin

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Introduction

Non-small-cell lung cancer (NSCLC) currently is the leading cause of death related to cancer in the world [1]. Platinum-based chemotherapy for NSCLC has improved survival compared to best supportive care alone [2]. Furthermore, the combination of gemcitabine (2′, 2′-difluorodeoxycytidine, dFdC) and carboplatin has been shown active and tolerable in advanced NSCLC in randomized phase III studies [3–5].

Gemcitabine, a new pyrimidine antimetabolite, is a novel deoxycytidine analogue with cytotoxic activity in

NSCLC [6–8], and is a prodrug requiring intracellular phosphorylation to its active form gemcitabine triphosphate (dFdCTP) [9, 10]. The rate-limiting step in the activation of gemcitabine is the phosphorylation of gemcitabine to its monophosphate form by deoxycytidine kinase, and the optimal rate of accumulation of gemcitabine triphosphate reaches with a plasma gemcitabine concentration between 10 and 20 μmol/L, which corresponds to the saturation of deoxycytidine kinase activity within the cell [11–13]. In phase I studies, this concentration range of plasma gemcitabine and continuous saturation of gemcitabine triphosphate levels were achieved when gemcitabine was infused at a fixed dose rate (FDR) of 10 mg/m^2 per min [14–17]. In addition, the infusion of gemcitabine at 10 mg/m^2 per min has demonstrated increased tumor efficacy in randomized phase II studies of advanced pancreatic cancer and achieved a higher median intracellular gemcitabine triphosphate level compared to the standard 30 min infusion arm [18, 19].

In light of the favorable activity of gemcitabine and carboplatin in advanced NSCLC and the benefits of the prolonged infusion schedule of gemcitabine, we conducted a randomized phase II study of gemcitabine and carboplatin in patients with advanced NSCLC, applying two different infusion schedules. One group of patients was assigned to be administered gemcitabine 1,200 mg/m^2 using a standard 30 min infusion (the standard arm, days 1 and 8 every 3 week cycle) with carboplatin (AUC = 5) on day 1 of each cycle and in the other group, gemcitabine 1,200 mg/m^2 was employed at a fixed dose rate of 10 mg/m^2 per min (the FDR arm, days 1 and 8 every three week cycle) with carboplatin (AUC = 5) on day 1. The response rate was used to evaluate the efficacy of gemcitabine and carboplatin combination treatment. Other parameters evaluating the efficacy were time to progression (TTP) and overall survival (OS).

Patients and methods

Patient selection

Patients with locally advanced or metastatic stage III_B or IV NSCLC, which was not amenable to surgery or radiotherapy with curative intent, were eligible for this study. The stage of NSCLC was determined by histological or cytological examination. Other eligibility criteria included: no previous chemotherapy or chemotherapy and radiotherapy $\geq$ 1 month before enrollment; the presence of at least one measurable lesion; Eastern Cooperative Oncology Group performance status (ECOG-PS) ≤ 2; life expectancy ≥ 3 months; age (range 18–75 years); adequate bone marrow function (WBC count $\geq 4.0 \times 10^9$/L, platelet count $\geq 100 \times 10^9$ per litre); adequate renal and liver function (serum creatinine ≤ 1.5 times normal value; serum transaminase ≤ 2 times normal value). All patients provided written informed consent before the enrollment.

The exclusion criteria included: pregnant or lactation women; serious infection or impairments on the organ function; central nervous system (CNS) metastasis or more than two metastases in other organs.

The study was approved by the Ethics Committee of The First Affiliated Hospital of Zhejiang University and was carried out in according with ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice.

Study design

This was a randomized phase II, single-centre, open-label and two-arm study. Stratified randomization was performed using the minimisation method based on baseline prognostic factors including the stage of NSCLC (IIIB or IV), ECOG-PS (0 or 1 or 2) and study sites. The treatment schedule consisted of gemcitabine (Gemzar, Eli Lilly and Company, Indianapolis, IN, USA) on days 1 and 8 every 3 week cycle, and carboplatin (Paraplatin, Bristol-Myers Squibb Company, USA) on day 1 of each cycle. Patients were randomly assigned to the following two treatment arms: (1) Intravenous (i.v.) administration of 1,200 mg/m^2 gemcitabine over 30 min, referred to as the standard arm or (2) 1,200 mg/m^2 gemcitabine at a fixed dose rate of 10 mg/m^2 per min, referred to as the FDR arm. An infusion pump was used to ensure exact infusion time. In both arms, carboplatin at AUC of 5 was administered as a 4 h i.v. infusion, following gemcitabine. Carboplatin dosage calculation was based on glomerular filtration rate according to the Calvert formula [20] and carboplatin dosage was adjusted prior to each cycle through re-determination of glomerular filtration rate.

All patients were scheduled to receive at least two cycles of treatment, and up to six cycles if there was no evidence of disease progression. Treatment was stopped early in case of patient refusal, severe toxicity or pregnancy. Patients, with documented progressive disease (PD) after two or four cycles or with stable disease (SD) after four cycles of chemotherapy were withdrawn from the study. Full supportive therapy, corticosteroids, anticonvulsants and antibiotics were given as needed. Antiemetic premedication included 5-HT_3 antigonists. No routine use of hematopoietic growth factors was planned. No prophylactic antibiotics were used. All patients were treated on an inpatient basis.

Dose adjustments during the treatment were based on hematological and nonhematological toxicities. On day 1, if neutrophil count was $< 1.5 \times 10^9$ per litre and/or platelet count $< 100 \times 10^9$ per litre, chemotherapy doses were either delayed (for up to 2 weeks) or reduced by 25% to

allow recovery from hematological toxicity. On day 8, for a neutrophil count $< 1.0 \times 10^9$ per litre and/or platelets $< 75 \times 10^9$ per litre, the gemcitabine dose was omitted, and the cycle continued without one dose of gemcitabine. Patients, who can not recover from hematological toxicity (neutrophil count $> 1.0 \times 10^9$ per litre and/or platelets $> 75 \times 10^9$ per litre) within 2 weeks were withdrawn from the study. Doses were reduced by 25% for any grade 3 non-hematological toxicity (excluding nausea, vomiting and alopecia). Treatment was discontinued in the event of grade 4 or frequent grade 3 nonhematological toxicity. For grade 2–4 neurological toxicity, carboplatin treatment was delayed until the patient recovered to grade 1, then the dose was reduced by 25%. If no recovery to grade 1 was achieved within 3 weeks, the patient was also excluded from the study.

Patient evaluation

Prior to chemotherapy, patients underwent a physical examination; ECOG-PS; chest X-ray; brain, thoracic and abdominal computer tomography scan (CT scan); bronchoscopy (if not performed at the time of diagnosis); bone scan; electrocardiogram; complete blood count and blood chemistry with liver function test and creatinine clearance. On days 1 and 8 during each cycle of treatment, a physical examination was performed, and ECOG-PS and blood count were assessed. All measurable and evaluable lesions were assessed by the same method used at baseline. Response to treatment was assessed for every two cycles with clinical and/or radiological tumor assessment, according to the RECIST criteria [21]. Confirmed responses required repeat CT scans at least 4 weeks later. Patients who finished six cycles of chemotherapy were assessed every 2 months. Assessment of TTP was determined by measuring the time interval from the beginning of treatment until the first documentation of progression regardless of the patient's treatment status. OS was determined by measuring the time interval from the beginning of the treatment to the date of death or last contact. Toxicities were evaluated every cycle using to the WHO criteria. No quality of life questionnaire was used in the present study.

Statistical analysis

The study was designed to select the better of the two regimens as reflected by the response rate, TTP, OS and toxicity. Each patient in the study was considered evaluable [intent-to-treat (ITT) analysis]. Response rates, including 95% confidence intervals (CIs), were calculated on an ITT basis. TTP and OS were calculated according to the Kaplan–Meier method with the appropriate censoring using SPSS 11.0 [22]. Statistical differences of toxicities between the two treatment arms were calculated using the Chi-square (χ^2) test.

Results

Patient characteristics

From November 2003 to June 2005, a total of 42 patients (21 patients in the standard arm and 21 in the FDR arm) were enrolled in this study in our centre (Table 1). The majority of patients were males (79%), with a median age of 64 years (range 40–74) in the standard arm and 61 years (range 42–74) in the FDR arm. ECOG-PS was 0 in 7%, 1 in 52% and 2 in 41% of patients. Seven patients (17%) had stage III_B disease and 35 (83%) had stage IV disease. Histological types of lung tumor were squamous carcinoma in 43% of the patients and adenocarcinoma in 36%, large cell tumor and other in 21%, respectively.

A total of 186 chemotherapy cycles were administered (91 cycles in the standard arm and 95 in the FDR arm), with a median number of four cycles per patient (range 3–6). Seven patients (33%) received three cycles, 6 (29%) four cycles, 2 (10%) five cycles and 6 (29%) six cycles, respectively, in the standard arm, and 7 patients (33%) three cycles, 3 (14%) four cycles, 4 (19%) five cycles and 7 (33%) six cycles, respectively, in the FDR arm. In the

Table 1 Patient's characteristics

	The standard arm ($n = 21$)		The FDR arm ($n = 21$)	
	No. of patients	%	No. of patients	%
Age (years)				
Median	64		61	
Range	40–74		42–74	
Sex				
Male	16	76	17	81
Female	5	24	4	19
ECOG-PS				
0	2	10	1	5
1	12	57	10	48
2	7	33	10	48
Stage				
III_B	4	19	3	14
IV	17	81	18	86
Histology				
Squamous cell	10	48	8	38
Adenocarcinoma	7	33	8	38
Large cell and other	4	19	5	24

FDR fixed dose rate, *ECOG-PS* Eastern Cooperative Oncology Group performance status

standard arm, 2.1% of gemcitabine doses were omitted and 17.5% were reduced, respectively, while in the FDR arm, 2.4 and 19.3% of gemcitabine doses were omitted or reduced, respectively. In both treatment arms, the most common reasons for dose omission and reduction were thrombocytopacnia and neutropaenia. Carboplatin was reduced in 13.1% of doses in the standard arm and 14.3% in the FDR arm.

Efficacy

All patients were included in the response assessment. No patient had a complete response (CR). Seven patients (33%; 95% CI 26–49%) in the standard arm and 10 (48%; 95% CI 24–52%) in the FDR arm had a partial response (PR). Of the remaining patients, 11 patients (52%) had SD as their best tumor response, 3 (14%) had PD despite treatment in the standard arm, while 7 patients (33%) had SD, 4 (19%) had PD in the FDR arm, respectively. The median TTP and median OS time was 5.4 months (95% CI 3.8–7 months) and 11.5 months (95% CI 8.2–14.8 months) for patients in the standard arm, respectively (Fig. 1), while in the FDR arm, 6.5 months (95% CI 4.4–8.6 months) and 12.0 months (95% CI, 11.3–12.7 months), respectively (Fig. 2). In addition, 1 year survival rate was 38.1% in the standard arm and 41.2% in the FDR arm.

Toxicity

Hematological toxicity was most significant adverse effect in this study (Table 2). In the standard arm, grade 3–4 thrombocytopenia was observed in 8 (38%) patients, grade 3–4 neutropenia in 5 (24%), grade 3–4 anemia in 4 (19%) and grade 3–4 leucocytopenia in 3 (14%) patients, respectively, while in the FDR arm, grade 3–4 thrombocytopenia was observed in 9 (43%) patients, neutropenia in 7 (33%), grade 3–4 anemia in 6 (29%) and grade 3–4 leucocytopenia in 5 (24%) patients, respectively. No bleeding episodes were recorded in both treatment arms. Although hematological toxicity occurred in a little higher percent of patients in the FDR arm than in the standard arm, there were no discernible differences by statistical analysis in both treatment arms ($P > 0.05$). Patients required platelet transfusion in 21 cycles [10 cycles (11%) in the standard arm and 11 cycles (12%) in the FDR arm] and hematopoietic growth factors support care in 42 cycles [19 cycles (21%) in the standard arm and 23 cycles (24%) in the FDR arm].

Significant nonhematological toxicities were infrequent and tolerable in both treatment arms (Table 3). There was no treatment related death. Grade 1–2 nausea/vomiting occurred in 19 patients (10 patients in the standard arm and 9 in the FDR arm), grade 1–2 skin rash occurred in 15 patients (7 patients in the standard arm and 8 in the FDR

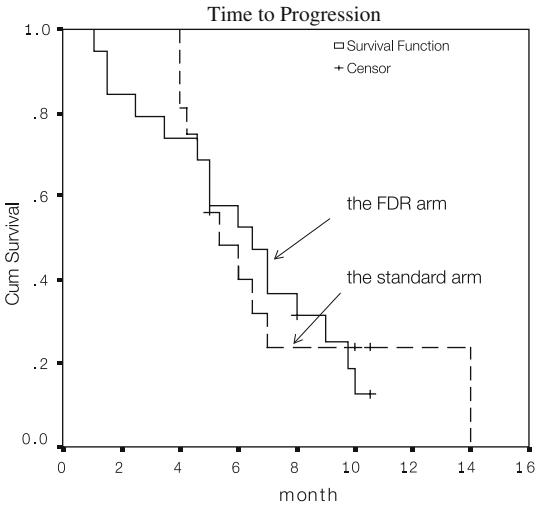

Fig. 1 Kaplan–Meier curve for time to progression for patients in the standard arm (gemcitabine 1,200 mg/m^2 over 30 min) and in the FDR arm (gemcitabine 1,200 mg/m^2 over 120 min)

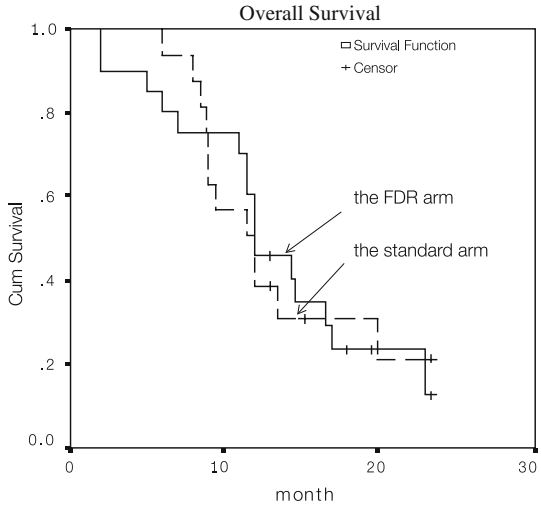

Fig. 2 Kaplan–Meier curve for overall survival for patients in the standard arm (gemcitabine 1,200 mg/m^2 over 30 min) and in the FDR arm (gemcitabine 1,200 mg/m^2 over 120 min)

Table 2 Hematological toxicities

Toxicity	Grade 3/4 (No. of patients)		*P*-value
	The standard arm	The FDR arm	
Leucocytopenia	3 (14%)	5 (24%)	0.70
Neutropenia	5 (24%)	7 (33%)	0.49
Thrombocytopenia	8 (38%)	9 (43%)	0.75
Anemia	4 (19%)	6 (29%)	0.47
Bleeding	0	0	

FDR fixed dose rate

Table 3 Nonhematological toxicities

Toxicity	The standard arm (No. of patients)				The FDR arm (No. of patients)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Nausea/vomiting	6	4	0	0	7	2	0	0
Skin rash	5	2	0	0	4	4	1	0
Diarrhea	0	0	0	0	0	0	0	0
Constipation	1	0	0	0	3	0	0	0
Increased AST	3	0	0	0	3	0	0	1
Increased creatinine	1	5	0	0	2	0	0	0
Alopecia	7	1	0	0	6	5	0	0
Neurological toxicity	1	0	0	0	1	0	0	0
Mucositis	2	0	0	0	1	0	0	0

FDR fixed dose rate; *AST* aspartate aminotransferase

No significant difference was seen between the two treatment groups ($P > 0.05$)

arm), grade 1–2 alopecia occurred in 19 patients (8 patients in the standard arm and 11 in the FDR arm). Grade 3 skin rash and grade 4 increased AST (aspartate aminotransferase) occurred in 2 patients in the FDR arm, respectively. Nonhematologic toxicities in both treatment arms were similar. No significant difference existed ($P > 0.05$).

Discussion

The combination of gemcitabine and cisplatin is a widely used regimen in Europe for the first-line treatment of advanced NSCLC. However, the significant side effects (such as hematological toxic, ototoxicity and nephrotoxicity, etc.) and difficult administration method of cisplatin has restricted its widespread use. The combination of gemcitabine and carboplatin as a front-line regimen for advanced NSCLC may be an appealing choice, which can be given to patients with an impaired renal function in the elderly. Furthermore, it is likely to present an acceptable toxicity profile [23, 24]. In our phase II study, gemcitabine in combination with carboplatin either at standard rate or fixed dose rate infusion was clinically effective and well tolerated in patients with advanced NSCLC.

A number of phase II or III studies have evaluated the combination of gemcitabine 1,000–1,250 mg/m^2 and carboplatin AUC 5 or 6 on a 21-day schedule in patients with advanced NSCLC [25–28]. These studies have shown response rate ranging from 26 to 55% and median survival times of 9.4–14.3 months, with rates of grade 3 or 4 thrombocytopenia of 9.4 to 62% and grade 3 or 4 neutropenia of 11–80%. In our study, the response rate was 33% for the standard arm and 48% for the FDR arm, and no patient had a CR. The median OS time was 11.5 months for patients in the standard arm and 12 months in the FDR arm. Toxicities were generally mild and treatment was well tolerated. A moderate rate of grade 3 and 4 hematologic toxicities occurred with both treatment schedules and the FDR infusion schedule seemed more toxic. However, there were no discernible differences by statistical analysis in both treatment arms. Other grade 1 and 2 nonhematologic toxicities such as nausea diarrhea, alopecia, fever and erythema were observed in two administration regimens and no statistically significant differences were noted between the two arms.

According to Soo et al. [29], 10 μmol/L or higher plasma concentrations was essential for gemcitabine to effective against solid tumor. A previous phase II study conducted in our centre has monitored the pharmacokinetics of gemcitabine administered at a fixed dose rate of 10 mg/m^2 per min (1,200 mg/m^2) in six NSCLC patients [30]. Compared to pharmacokinetic data from the literature [31, 32], no apparent difference was found with respect to $T_{1/2}$, AUC, and CL (Clearance rate). The mean parameters were shown as $T_{1/2}$ (10.67 ± 3.38) min, AUC (7.75 ± 1.53) μg.h/mL, and CL (3940.05 ± 672.08) mL per min. The maximum concentration (C_{max}) was (4.92 ± 1.79) μg/mL (16.42 ± 5.97 μmol/L), which differed significantly from the published data [(10.0–18.3) μg/mL (33.37–61.07 μmol/L), a dose of 1,000 mg/m^2 with 30 min infusion]. The discrepancy of maximum concentration may be due to the different infusion time and dosage. However, the prolonged infusion time in the study 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. It elevated the clinical therapeutic effect. Meanwhile, the hematologic toxicology was moderate.

The results of our study differed from those of study by Soo et al. [33]. In their results, the response rate was 34% in FDR arm and 42% in standard 30 min infusion arm. TTP, OS and toxicity were similar for both treatment arms. Mean plasma $Cmax_{gemcitabine}$, AUC in FDR arm was (20.8 ± 17.2) μmol/L and (35,079 ± 18,216) μmol·min/L, respectively, while in standard arm, (41.2 ± 13.9) μmol/L and (32,249 ± 11,267) μmol·min/L, respectively. dFdCTP

saturation was reached in standard arm but not in FDR arm. The data published by Tempero et al. [13], however, were also different from the present study. In this trial, the median survival of all patients in FDR arm was longer than those in standard arm with significant difference ($P < 0.05$). Furthermore, patients in the FDR infusion arm experienced consistently more hematologic toxicity.

A potential strategy to achieve more efficient activation of gemcitabine and to reduce the infusion period of the fixed dose regimen is to administer an initial rapid bolus of gemcitabine to saturate deoxycytidine kinase activity, followed by an infusion at 10 mg/m^2 per min [34]. Theoretically, through the above administration methods, a reduction in excessive gemcitabine levels would be obtained and a higher dFdCTP AUC could be achieved in a shorter duration of infusion. Assuming similar cellular transport characteristics in tumors, this approach may increase cytotoxicity.

The purpose of our study was to evaluate the efficacy and safety of gemcitabine in combination with carboplatin at standard rate or fixed dose rate infusion in patients with advanced NSCLC. This study does not definitively favor one regimen over the other. However, the clinical data support the continuation of evaluating the FDR infusion strategy for gemcitabine in combination with carboplatin in advanced NSCLC patients. Future development may involve in optimizing dose and infusion rate (FDR) of gemcitabine in combination with potentially synergistic drugs based on pharmacokinetic principles.

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