Phase I and Pharmacokinetic Study of IV Vinflunine in Combination with Gemcitabine for Treatment of Advanced Non-small Cell Lung Cancer in Chemonaive Patients

Caroline Tournoux-Facon, MD, Hélène Senellart, MD,† Etienne Lemarie, MD, PhD,‡ Jean Marc Tourani, MD, PhD,* Stéphanie Favrel, PharmD,§ Jean Christophe Pouget, MSc,§ Marie Claire Pinel, MD,§ and Jaafar Bennouna, MD, PhD†*

Introduction: Vinflunine (Javlor) has shown significant antitumour activity in advanced non-small cell lung cancer (NSCLC). We propose to define the recommended dose of vinflunine in combination with gemcitabine for treatment of advanced NSCLC in chemonaive patients.

Methods: A phase I and pharmacokinetic study was conducted to determine the maximum tolerated dose and to establish the recommended dose of vinflunine (VFL) administered on day 1 every 21 days combined with gemcitabine given on days 1 and 8 every 3 weeks.

Results: Nineteen patients were included in this study. Three patients experienced a dose limiting toxicity, with constipation in one patient, hypertension in one patient, and constipation and febrile neutropenia in one patient. The combination of VFL 320 mg/m^2 and gemcitabine 1250 mg/m^2 was defined as the maximum tolerated dose. The recommended dose was established at the dose of VFL 320 mg/m^2 combined with gemcitabine 1000 mg/m^2. Neither VFL nor gemcitabine seemed to be influencing the pharmacokinetics of each other. All patients were evaluable for tumor response. Seven presented a partial response and eight experienced a stable disease.

Conclusions: The combination of VFL 320 mg/m^2 administered on day 1 combined with gemcitabine 1000 mg/m^2 given on days 1 and 8 every 3 weeks is established as the RD and was shown to be active in these chemonaive NSCLC patients.

Key Words: Gemcitabine, Lung cancer, Pharmacokinetics, Phase I, Vinflunine.

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*Centre Hospitalier Universitaire-Pôle Régional de Cancérologie-CIC P802, Poitiers; †Centre René Gauducheau, Saint Herbain; ‡Centre Hospitalier Universitaire, Tours; and §Institut de Recherche Pierre Fabre, Boulogne-Billancourt, France.

Disclosure: Favrel, Pouget, and Pinel are employees of Institut de Recherche Pierre Fabre.

Address for correspondence: Marie Claire Pinel, MD, Institut de Recherche Pierre Fabre, 45 Place Abel Gance, 92654 Boulogne-Billancourt, France. E-mail: marie.claire.pinel@pierre-fabre.com

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Current regimens for treatment of patients with newly diagnosed inoperable stage (IIIB–IV) non-small cell lung cancer (NSCLC) consist of doublets of cisplatin in combination with either vinorelbine, gemcitabine, or pemetrexed or the combination of paclitaxel and carboplatin.[1,2] Nonplatinum combinations were developed, including paclitaxel, docetaxel, gemcitabine, and vinorelbine. They provide equivalent efficacy results whether or not the combination contains a platinum.[3–5] However, results have been uniformly disappointing, and improvements in survival are modest at best.[6]

Vinflunine (Javlor, Pierre Fabre Médicament, Boulogne-Billancourt, France) is a novel microtubule targeted agent obtained by semisynthesis using superacidic chemistry to selectively introduce two fluorine atoms at the 20′ position of catharanthine moiety of the vinca alkaloid scaffold. Javlor (320 mg/m^2) is indicated in monotherapy for the treatment of adult patients with advanced or metastatic transitional cell carcinoma of the urothelial tract after failure of a prior platinum-containing regimen.[7] Besides, the activity of the drug in treatment of NSCLC was also shown in phase II study, when given as single agent as second-line treatment.[8] Afterward, in a randomized phase III trial, Krzakowski et al. showed similar efficacy results for vinflunine and docetaxel: median progression-free survival was 2.3 months in each treatment arm, whereas median overall survival were 6.7 and 7.2 months for vinflunine and docetaxel, respectively.[9] In combination with cisplatin or carboplatin in first-line metastatic setting, the drug was also very promising.[10,11]

The combination of vinflunine and gemcitabine is conceptually attractive, as both drugs act in specific part of the cell division. Vinflunine and gemcitabine act on M and G2[12] and S[13] phases of the cell cycle, respectively. Thus, combining these drugs might enhance their cytotoxic potential.

The primary objective of the study was to establish the recommended dose (RD) of vinflunine administered on day 1 every 21 days combined with gemcitabine given on days 1 and 8 every 21 days. The secondary objectives were to assess the toxicities of the combination, to assess antitumour activity of the combination in advanced chemonaive NSCLC patients according to RECIST version 1.0,[14] and to investigate a potential pharmacokinetic drug-drug interaction between vin-

flunine and gemcitabine when both drugs are administered in combination.

PATIENTS AND METHODS

This open-label phase I study was conducted in three centers (France: 2; Italy: 1), in accordance with ethical principles set forth in the Declaration of Helsinki and in accordance with Good Clinical and Laboratory Practices. The protocol and its amendments were approved by the local Ethics Committee. All patients provided written informed consent.

Patient Selection

Patients with a histologically proven NSCLC, unresectable stage IIIB/stage IV disease, or patients with local or metastatic relapse after surgery and/or thoracic irradiation were included in this study. Patients may have had previous surgery for NSCLC but no prior chemotherapy; patients were eligible if they presented at least one measurable lesion outside an irradiated area (radiotherapy completed at least 4 weeks before registration), according to RECIST criteria.[14] Patients were at least 18 years old, with performance status of 0 or 1 and an expected life expectancy of at least 12 weeks. Normal electrocardiogram and adequate hematological, hepatic, and renal functions (i.e., neutrophils $\geq 2.0 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, hemoglobin ≥ 10 g/dl or 6.2 mmol/L, total bilirubin $\leq 1.5 \times$ Upper Normal Limit [UNL], transaminases $\leq 2.5 \times$ UNL, creatinine $\leq$ UNL, or calculated [Cockcroft Gault] creatinine clearance ≥ 50 ml/min) were required (within 7 days of first day of study drug treatment).

The exclusion criteria were as follows: patients who were pregnant, lactating, or at risk for pregnancy during the study; patients with brain and/or leptomeningeal metastases (a computed tomography scan or a magnetic resonance imaging was required before registration); symptomatic peripheral neuropathy grade ≥ 2 on National Cancer Institute Common Toxicity Criteria (NCI-CTC) scale; patients with active serious infection, diabetes mellitus, concurrent heart failure (New York Heart Association class II-III-IV), or progressive or unstable angina; patients who have had myocardial infarction within 6 months and/or poorly controlled hypertension, or pericardial effusion; uncontrolled hypercalcemia; unstable concomitant disease; active infection requiring IV antibiotics within 2 weeks before the beginning of treatment; superior vena cava syndrome; long-term oxygen therapy; preexisting uncontrollable symptomatic pleural effusion; and history of another malignancy within the past 5 years except basal cell carcinoma of the skin or carcinoma in situ of the cervix.

Treatment Plan

Vinflunine was administered on day 1 every 3 weeks combined with gemcitabine given on days 1 and 8 every 3 weeks. Three dose levels (DLs) were tested: DL1 with vinflunine 280 mg/m^2 and gemcitabine 1000 mg/m^2; DL2 with VFL 320 mg/m^2 and gemcitabine 1000 mg/m^2, and DL3 with VFL 320 mg/m^2 and gemcitabine 1250 mg/m^2.

Patients were to be treated until documented disease progression, unacceptable toxicity, or patient's refusal. Efficacy was to be assessed every two cycles of chemotherapy using RECIST criteria. Tolerance was to be assessed throughout the treatment period and before each administration according to the NCI Common Toxicity Criteria (Version 2.0). The prophylactic use of colony-stimulating factor was not allowed during the first cycle of study treatment; in further cycles, colony-stimulating factor could be given for therapeutic use according to institutional rules.

Dose Escalation

Groups of three patients were treated at each dose level without intrapatient dose escalation. In the absence of dose limiting toxicity (DLT) during the first cycle, the next highest dose level was explored. If one of three initial patients experienced a DLT, three additional patients were included at the same dose level. If three or more patients out of six experienced a DLT, the dose escalation was halted. Otherwise, continuation to the next dose level was allowed.

Dose Limiting Toxicity and Maximum Tolerated Dose

DLT was defined as any of the following adverse events occurring during the first cycle: hematological toxicity consisting of nadir absolute neutrophil count $<0.5 \times 10^9$/L for at least 7 days or $<0.1 \times 10^9$/L for at least 3 days; febrile neutropenia defined as absolute granulocyte count $<1.0 \times 10^9$/L and fever >38.5°C; platelets $<25 \times 10^9$/L or thrombocytopenia with bleeding or requiring platelet transfusion; any grade 3 or 4 major organ toxicity according to the NCI-CTC scale except alopecia and un-premedicated nausea/vomiting; and withdrawal of any patient after the first cycle due to delayed recovery from toxicity.

The MTD was defined as the dose level at which ≥ 2 of 3 or ≤ 3 of 6 patients developed a DLT during the first cycle. The RD was defined as the dose level one step below the MTD. To confirm the RD and to evaluate the antitumoral activity of the combination, six additional patients were to be treated at the RD level.

Dose Modifications

This was an open-label study, and patients were instructed to report during each visit any toxicity that occurred during each cycle and until the next administration. Treatment was to be modified in case of hematological and/or nonhematological toxicities. All dose adjustments were made according to the system showing the greatest degree of toxicities. If the study treatment could not be administered after a 2-week interval (day 35) because of any toxicity, it was to be definitively discontinued.

Pretreatment and Follow-Up Examinations

Preregistration assessments included a medical history, the date of histological diagnosis of NSCLC, any prior treatment for malignancy (surgery, radiotherapy), previous and concurrent illness, and all the concomitant medications that the patient received at study entry. All baseline screens had to be performed within a 3-week period before the first day of treatment. Computed tomography scan, magnetic resonance imaging, and physical examination were recom-

mended for tumor assessment. All positive imaging procedures at study entry had to be repeated every 6 weeks. Other investigations, not done or negative at study entry, had to be performed during the study only if clinically indicated. The clinical safety assessment was summarized before each cycle and included a complete physical examination, complete blood cell count, and biochemistry tests.

Pharmacokinetics

Blood sampling for pharmacokinetics (PK) was performed during cycle 1.

Blood sampling for the PK of vinflunine (VFL) and its only active metabolite 4-*O*-deacetylvinflunine (DVFL) was performed according to a limited sampling schedule after the administrations of VFL and gemcitabine on day 1. VFL and DVFL were assayed in whole blood by HPLC/UV (lower limit of quantification [LLOQ] = 2 ng/ml). Bayesian PK parameters of VFL (AUC_{inf} and Cl_{tot}) were estimated using a previously developed population PK model.[15] Concentrations of DVFL were compared with single agent data by a graphical approach. Plasma samples for the PK of gemcitabine (2′,2′-difluorodeoxycytidine [dFdC]) and its metabolite (2′,2′-difluorodeoxyuridine [dFdU]) were drawn according to a detailed sampling schedule after dFdC and VFL were coadministered on day 1 and after dFdC was administered alone on day 8. dFdC and dFdU were assayed in plasma by HPLC/UV (LLOQ = 1 μmol/L). Pharmacokinetic parameters of dFdC and dFdU (C_{max}, AUC_{last}) were derived using noncompartmental calculation methods. A potential impact of dFdC on the PK of VFL was assessed by building the 90% confidence interval (CI) for the test/reference ratio of geometric means of Cl_{tot} of VFL where reference was made up of PK parameters of 79 patients to whom VFL was administered as a single agent. A potential impact of VFL on the PK of dFdC and dFdU was assessed by building the 90% CI for the test (day 1)/reference (day 8) ratio of dose-adjusted AUC_{last} of dFdC and dFdU. A lack of PK interaction was concluded if the 90% CI fell entirely in the acceptance range of 0.8 to 1.25.[16]

RESULTS

Patients

All the 19 chemotherapy-naive patients with NSCLC included were treated. The median follow-up time was 38.2 months. The demographic data are presented in Table 1.

Two-thirds of patients were males (68%), with a median age of 60 years and all presenting with a good baseline performance status. All patients but four had locally advanced NSCLC at initial diagnosis, and most of them (79%) had metastatic disease at initial diagnosis, which was done just before study entry. Histology was adenocarcinoma in 11 patients (58%), squamous cell carcinoma in 6 patients (32%), and large cell carcinoma in 2 patients (10%). Median time interval from primary diagnosis or relapse disease to study entry was 6 weeks (range, 0–18).

Thirteen patients (68%) did not receive any prior cancer therapy. Six patients underwent prior surgery and/or previously received thoracic irradiation. All patients but three had lung involvement at study entry.

TABLE 1. Demographic Data

Demographic Data	Patients (N = 19)
Age, yr, median (range)	60.6 (44.5–78.8)
Sex	
Male	13 (68.4%)
Female	6 (31.6%)
WHO performance status	
0	11 (57.9%)
1	8 (42.1%)
NSCLC stage at diagnosis	
IB[a]–IIIB	4 (21%)
IV	15 (78.9%)
Histology	
Squamous cell	6 (31.6%)
Adenocarcinoma	11 (57.9%)
Large cell	2 (10.5%)
Disease extension at baseline	
1 organ involved	1 (5.1%)
2 organs involved	10 (52.6%)
≥2 organs involved	8 (42.1%)

Values are given as N (%).

[a] One patient presented with stage Ib at diagnosis (March 2002). At the time of study entry (September 2003), he was presenting with a second metastatic relapse in lung and bones (the first relapse had been irradiated).

WHO, World Health Organization; NSCLC, non-small cell lung cancer.

Drug Delivery

In the first dose level (DL1), no patient experienced a DLT. Of note, four patients were included at this dose level instead of three patients as required by the protocol because of an inclusion timing problem (the fourth patient had signed the informed consent 1 day before the inclusion of the third patient).

No DLT was declared by the investigators for the first three patients included at the second dose level (DL2).

The maximum tolerated dose was established at DL3, with three patients out of the total of six experiencing DLTs during cycle 1: one case of grade 3 constipation, one transient grade 4 hypertension, and, for the last patient, successively grade 3 constipation and febrile neutropenia.

To confirm the DL2 (vinflunine 320 mg/m^2 on day 1 combined with gemcitabine 1000 mg/m^2 on days 1 and 8) as the RD, six additional patients were included. In two of these additional patients, grade 3 constipation and grade 3 pulmonary infection occurred after cycle 1, respectively.

In this study, 19 patients received a total of 80 cycles of the combination of vinflunine and gemcitabine. Fourteen cycles were delivered to the four patients treated at the first dose level (median number of cycles: 3). At the second dose level, a total of 39 cycles were delivered to nine patients (median number of cycles: 4). At the highest dose level, six patients were given a total of 27 cycles (median number of cycles: 6). All patients received at least one cycle, and 16 of 19 (84.2%) received two cycles or more.

The median relative dose intensities of vinflunine per dose level and per patient were as follows: 98.0% (84.4–100.8), 98.1% (77.3–100.1), and 93.9% (80.0–99.8) in DL1, 2 and 3, respectively. For gemcitabine, the median relative dose intensities were 77.8% (73.7–85.5) in DL1, 87.9% (58.5–100.2) in DL2, and 96.8% (80.2–100.2) in DL3.

Six patients (31.6%) received at least one cycle with a delay of more than 3 days. Vinflunine dose reductions were applied in two patients at DL2 (one grade 3 pulmonary infection and one grade 3 asthenia/grade 2 diarrhea) and in one patient at DL3 (grade 3 constipation).

None of the 19 patients had gemcitabine dose reduced on day 1. Dose reductions on day 8 were applied in one patient in the DL1 (grade 1 thrombocytopenia) in three patients at DL2 (one grade 2 neutropenia and grade 1 thrombocytopenia, one grade 3 neutropenia, and one grade 2 thrombocytopenia). Gemcitabine dose cancellation on day 8 were applied in two patients at DL1 (one nonstudy drug-related adverse events and one due to infusion site phlebitis) and in three patients at DL2 (one grade 3 thrombocytopenia, one grade 3 asthenia, and one grade 4 diarrhea and disease progression).

Eight patients discontinued the treatment due to disease progression, two patients stopped treatment due to adverse events unrelated to study treatment, and one due to patient decision. Eight patients discontinued study treatment after a partial response or no change in tumor assessment because of no further benefit expected after four, six, or seven cycles of chemotherapy.

Toxicity

All the 19 patients were evaluable for toxicity. Adverse events graded according to the NCI-CTC scale are summarized in Table 2.

Hematological Toxicity

Anemia was recorded in three patients out of the total of four at DL1 (no episode of grade 3/4). At DL2 and DL3, all the 15 patients experienced anemia with two grade 3 at DL2 and one grade 3 at DL3. Neutropenia was observed in three patients (75%), nine patients (100%), and six patients (100%) treated at DL1, 2, and 3 respectively. At the RD level, grade 3 and 4 neutropenia were seen in 89% of patients for a total of 69% of cycles. Thrombocytopenia was recorded in 50%, 55%, and 50% of patients, respectively, at DL1, 2 and 3, but only four patients had grade 3 thrombocytopenia (two at DL2 and two at DL3), and no grade 4 was reported. Only one patient developed one episode of grade 3 febrile neutropenia at DL3.

Nonhematological Toxicity

One patient experienced a transient hypertension episode. Asthenia was reported in the majority of patients (89%

TABLE 2. Worst Grade of Related Adverse Events by Patient and by Dose Level

	Dose Level 1 (VFL 280 mg/m², Gem 1000 mg/m²), $N = 4$			Dose Level 2 (VFL 320 mg/m², Gem 1000 mg/m²), $N = 9$			Dose Level 3 (VFL 320 mg/m², Gem 1250 mg/m²), $N = 6$		
Preferred Term	**G ≥ 1**	**G 3**	**G 4**	**G ≥ 1**	**G 3**	**G 4**	**G ≥ 1**	**G 3**	**G 4**
Anemia	3 (75)	—	—	9 (100)	2 (22.2)	—	6 (100)	1 (16.7)	—
Leucopenia	3 (75)	2 (50)	1 (25)	9 (100)	4 (44.4)	3 (33.3)	6 (100)	1 (16.7)	2 (33.3)
Neutropenia	3 (75)	—	3 (75)	9 (100)	1 (11.1)	7 (77.8)	6 (100)	1 (16.7)	5 (83.3)
Thrombocytopenia	2 (50)	—	—	5 (55.6)	2 (22.2)	—	3 (50)	2 (33.3)	—
Febrile neutropenia	—	—	—	—	—	—	1 (16.7)	1 (16.7)	—
Abdominal pain	2 (50)	—	—	4 (44.4)	—	—	4 (66.7)	1 (16.7)	—
Constipation	2 (50)	—	—	2 (22.2)	1 (11.1)	—	5 (83.3)	2 (33.3)	—
Diarrhea	—	—	—	1 (11.1)	—	1 (11.1)	—	—	—
Nausea	3 (75)	—	—	8 (88.9)	—	—	4 (66.7)	—	—
Stomatitis	2 (50)	—	—	1 (11.1)	—	—	1 (16.7)	—	—
Vomiting	2 (50)	—	—	6 (66.7)	—	—	3 (50)	—	—
Fatigue	2 (50)	—	—	8 (88.9)	2 (22.2)	—	4 (66.7)	—	—
Pyrexia	—	—	—	5 (55.6)	—	—	3 (50)	1 (16.7)	—
Lung infection	—	—	—	1 (11.1)	1 (11.1)	—	1 (16.7)	1 (16.7)	—
Anorexia	—	—	—	2 (22.2)	—	—	4 (66.7)	—	—
Myalgia	—	—	—	3 (33.3)	—	—	1 (16.7)	—	—
Pain in jaw	1 (25)	—	—	4 (44.4)	—	—	2 (33.3)	—	—
Headache	—	—	—	2 (22.2)	—	—	2 (33.3)	—	—
Peripheral motor neuropathy	—	—	—	—	—	—	1 (16.7)	1 (16.7)	—
Peripheral sensory neuropathy	2 (50)	—	—	—	—	—	—	—	—
Syncope	—	—	—	1 (11.1)	1 (11.1)	—	—	—	—
Alopecia	1 (25)	—	—	4 (44.4)	—	—	1 (16.7)	—	—
Hypertension	—	—	—	—	—	—	1 (16.7)	—	1 (16.7)

Values are given as *N* (%).
VFL, vinflunine; Gem, gemcitabine.

TABLE 3. Pharmacokinetic Parameters of Vinflunine, dFdC, and dFdU After Day 1 Administration

Dose Levels VFL/dFdC (mg/m^2)	*n*	AUC_{inf} of VFL (h · ng/ml)	AUC_{last} of dFdC (h · ng/ml)	AUC_{last} of dFdU (h · ng/ml)
280/1000	2	11517 (9736–13297)	32.4 (24.2–40.5)	898 (382–1414)
320/1000	9	13336 (11492–18042)	28.9 (11.0–46.0)	1361 (502–2147)
320/1250	6	14440 (12716–17111)	47.3 (29.5–57.2)	1318 (744–2323)

Values are given as median (range).
VFL, vinflunine; AUC, area under the curve; dFdC, 2′,2′-difluorodeoxycytidine; dFdU, 2′,2′-difluorodeoxyuridine.

TABLE 4. Results of the Statistical Analysis on Cl_{tot} of VFL

No. of Observations	Geometric Mean of Cl_{tot} (L/h)	Test/Reference Ratio of Geometric Means of Cl_{tot}	90% CI of the Ratio of Geometric Means of Cl_{tot}
Test[a]: $n = 17$	40.3	0.98	0.88–1.09
Reference[b]: $n = 79$	41.1		

[a] Present study.
[b] Phase I studies where VFL was administered as a single agent.
VFL, vinflunine.

at the RD with two grade 3 toxicities). Nine patients complained of constipation in a total of 16 cycles. Most of the patients[5] who complained of constipation received the combination at DL3 with two grade 3 occurrences. One of these two patients reported a grade 3 concomitant abdominal pain. At the RD, two of nine patients had constipation, and only one of them experienced a grade 3.

Six study treatment-related serious or significant adverse events were reported in three patients. No significant unexpected adverse event was recorded during the study. During the study, none of the patients died in the 30 days from the last administration of any of the two drugs.

Pharmacokinetics

The PK dataset was made up of 17 evaluable patients for VFL and DVFL. For dFdC and dFdU, 16 patients were evaluable on day 1. Ten of them were evaluable on day 8 for dFdC and 9 for dFdU.

Values of VFL AUC_{inf} for the dose level of VFL of 320 mg/m^2 were similar regardless of the dose level of dFdC (Table 3). The 90% CI of the ratio of geometric means of Cl_{tot} of VFL was included in the 0.8 to 1.25 interval (Table 4). Residual variability (CV) on Cl_{tot} derived from the analysis of variance was 24%.

Values of DVFL concentrations from this study when VFL was given at 320 mg/m^2 fell entirely within the 95% CI built on phase I concentrations for a dose of VFL of 320 mg/m^2. This suggested a lack of effect of dFdC on the PK disposition of VFL and DVFL when both VFL and dFdC were coadministered on day 1.

Plasma concentrations of dFdC and dFdU on days 1 and 8 were comparable. AUC_{last} values on day 1 are presented for both compounds in Table 3. Depending on the dose level, interindividual variability on AUC_{last} of dFdC and dFdU ranged from 23 to 41% and from 37 to 40%, respectively. Given this substantial variability and despite the small number of observations, dose-normalized values of AUC_{last} of dFdC and dFdU on days 1 and on 8 overlapped one another, regardless of the dose level. For both compounds, the upper confidence bound was above the acceptance limit of 1.25, therefore equivalence between days 1 and 8 could not be concluded (Table 5).

However, the calculated lower confidence bound and ratio value 1 were included in the acceptance range of 0.8 to 1.25, and the geometric mean of AUC_{last}/Dose on day 1 was moderately (19% for dFdC and 9% for dFdU) higher than that on day 8. Given that observations from only 10 patients were used for the day 8 comparison, that no clear tendency was observed, and that intraindividual variability (CV derived from the analysis of variance of 32%) was marked, a more powerful analysis involving a larger number of patients would have been necessary to draw out conclusion.

Efficacy

During the study, a total of 7 patients out of 19 treated and evaluable for response presented a partial response according to RECIST. Most of responses (4 of 7) were achieved at the RD. The median duration of response was 6.6 months (95% CI: 4.2–6.6). Disease control (stable disease and partial response) was achieved in 15 patients (8 patients with stable disease). Among the seven patients who achieved partial response, six presented with stage IV at diagnosis (four adenocarcinoma and two squamous cell carcinoma) and one patient had been previously treated for an initial stage IIA squamous cell carcinoma. At the study cut-off date, all

TABLE 5. Results of the Statistical Analysis on AUC_{last}/Dose of dFdC and dFdU

	No. of Observations	Geometric Mean of AUC_{last}/Dose	Test/Reference Ratio of Geometric Means of AUC_{last}/Dose	90% CI of the Ratio of Geometric Means of AUC_{last}/Dose
dFdC	Test (day 1): $n = 16$	0.0292	1.19	0.94–1.50
	Reference (day 8): $n = 10$	0.0244		
dFdU	Test (day 1): $n = 16$	1.09	1.09	0.88–1.36
	Reference (day 8): $n = 9$	0.888		

AUC, area under the curve; dFdC, 2′,2′-difluorodeoxycytidine; dFdU, 2′,2′-difluorodeoxyuridine.

patients already progressed. The median progression free survival was 4.2 months (95% CI: 2.8–7.8). At the time of analysis, 15 patients failed and 4 were censored for survival analysis. The median overall survival was 13.6 months (95% CI: 8.2–23.4). All 15 patients died due to disease progression.

DISCUSSION

Despite the emergence of new combinations of therapies including targeted therapies, the treatment of advanced or metastatic NSCLC remains a palliative approach. Vinflunine, as a new compound of the vinca alcaloid class, already showed a good safety profile and a promising antitumor activity alone or in combination with cisplatin or carboplatin.[8–11] The rationale for the present phase I study was that the combination of vinflunine and gemcitabine might enhance their cytotoxic potential as both drugs act in specific part of the cell division.

A total of 19 chemonaive patients with a histologically proven NSCLC, unresectable stage IIIB/stage IV disease, or patients with local or metastatic relapse after surgery and/or thoracic irradiation were treated with the combination of vinflunine and gemcitabine. According to the protocol, the RD was established as follows: vinflunine 320 mg/m^2 day 1 combined with gemcitabine 1000 mg/m^2 days 1 and 8 once every 3 weeks. This dose was explored in nine patients. Vinflunine and gemcitabine combination according to this schedule has a good tolerance profile. All adverse events were manageable, no death occurred during the study, and no patient was withdrawn from the study due to toxicity. The main hematological toxicity was neutropenia with 15 patients experiencing a grade 4. No grade 4 thrombocytopenia was observed. Nonhematological toxicities were constipation (six patients $\leq$ grade 2 and three patients grade 3 toxicities) associated with abdominal pain (nine patients $\leq$ grade 2 and one patient with grade 3 toxicities); secondary prophylaxis with laxatives avoided the reoccurrence of constipation.

The PK analysis concluded that no effect of gemcitabine on the PK of vinflunine should be expected when both drugs are given in combination. Concerning the effect of vinflunine on the PK of gemcitabine, the large intraindividual variability observed on the PK of dFdC and dFdU and the small number of studied patients ($n = 10$) prevented any conclusive results based on a bioequivalence test. Nevertheless, the limited difference between days 1 and 8 and the overlapped pattern of individual values highly suggested the absence of a significant effect of VFL on the PK of gemcitabine. These findings are in agreement with the metabolism pattern of each drug. The metabolism pathway of vinflunine involves Cytochrome P450 3A4 enzymes and multiples esterases,[17] whereas gemcitabine is inactivated by deamination in reactions catalyzed by cytidine deaminase.[18] As a consequence, there is no common metabolism pathway shared between the two drugs. Renal excretion is a component of elimination route for both drugs. Nevertheless, none of the implied drugs is known to induce renal toxicity leading to impaired renal function.

Seven of the 19 evaluable patients presented a partial response (RECIST version 1.0), and a disease control rate was achieved in 80%. According to histology and among only these 19 patients, efficacy of vinflunine combined with gemcitabine seems similar with four and three objective responses in adenocarcinoma and squamous cell carcinoma, respectively. This result should, however, be confirmed on larger sample size. In addition, the increasing interest in combination of targeted therapies such as cetuximab or bevacizumab to conventional chemotherapeutic doublets points out the need for further clinical developments.[19–21] These new approaches could result in an improvement of clinical outcomes of these noncurable patients and moreover new agents can allow customizing treatments in a patient by patient basis. In conclusion, vinflunine and gemcitabine combination (320 mg/m^2 of VFL on day 1 combined with 1000 mg/m^2 of gemcitabine on days 1 and 8) in chemonaive advanced NSCLC patients provides an efficient regimen with a good tolerance profile according to this schedule. Based on these positive results the vinflunine-gemcitabine combination can be further investigated in larger trials alone or in combination with targeted therapies.

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