Phase 1 Trial of Lipoplatin and Gemcitabine as a Second-line Chemotherapy in Patients With Nonsmall Cell Lung Carcinoma

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BACKGROUND. Lipoplatin is a new liposomal cisplatin that already has been tested in solid tumors, with encouraging results. The purpose of the current study was to determine the maximum tolerated dose (MTD) and the dose-limiting toxicity (DLT) of a 21-day regimen of lipoplatin plus a fixed dose of gemcitabine in patients with refractory or resistant nonsmall cell lung carcinoma (NSCLC) with an Eastern Cooperative Oncology Group (ECOG) performance status of $\leq$2.

METHODS. The lipoplatin dose was escalated at 100 mg/m^2 by increments of 10 mg/m^2 on Days 1 and 8, with gemcitabine at a dose of 1000 mg/m^2 administered on Days 1 and 8, repeated every 21 days. Hematopoietic growth factors were not allowed. Thirteen patients with advanced stage NSCLC who had been pretreated with platinum combination chemotherapy were enrolled in this phase 1 trial. At least 3 patients were entered at each dose level.

RESULTS. At the fourth dose level, the DLT was reached (grade 3 neutropenia [according to World Health Organization criteria] in 3 of 4 patients 75%]; the fourth patient demonstrated degradation of performance status). Therefore, the third dose level (lipoplatin at a dose of 120 mg/m^2) was defined as the MTD. At the same dose level, 2 of 4 patients had grade 3 thrombocytopenia. At the fourth dose level, 1 patient achieved a partial response and 1 patient had stable disease. Another patient achieved stable disease at the second dose level. Therefore, the overall disease control rate was 23% (3 of 13 patients). The median overall survival was 29 weeks (range, 4 weeks-59 weeks) and the median time to disease progression was 12 weeks (range, 3 weeks-36 weeks).

CONCLUSIONS. The pharmacokinetic profile of the 2 compounds used in the current study are not modified when they are administered according to the schedule evaluated in this trial. When one considers that the patients in the current study had refractory or resistant NSCLC, the authors concluded that the combination of lipoplatin administered at a dose of 120 mg/m^2 and gemcitabine administered at a dose of 1000 mg/m^2 on Days 1 and 8 every 3 weeks needs to be studied further in phase 2 trials. ***Cancer*** **2008;113:2752–60.** © *2008 American Cancer Society.*

KEYWORDS: phase 1, lipoplatin, gemcitabine, nonsmall cell lung cancer, chemotherapy.

Lung cancer remains the most common fatal malignancy. Despite more aggressive therapies, only a slight improvement in survival has been obtained during the last several decades.[1] Patients with nonsmall cell lung cancer (NSCLC) account for approximately 75% of cases, with the majority found to have locally advanced or metastatic disease at the time of diagnosis.[2]

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Although chemotherapy appears to have little impact on the survival of patients with advanced or metastatic NSCLC,[3] it has been proven to be beneficial in controlling cancer-related symptoms and improving quality of life.[4] Cisplatin-containing chemotherapy generally offers a superior survival benefit compared with noncisplatin-containing combinations of older[3] or newer[5] generation agents in advanced NSCLC. A major cause of tumor recurrence in patients with NSCLC who are receiving chemotherapy is the development of tumor cell resistance to platinum compounds.[6] In addition, the efficacy of platinum-based regimens is often limited by renal and hematologic toxicities, which leads to chemotherapy interruption.[7]

Lipoplatin (Regulon Inc, Mountain View, Calif) is a liposomal formulation of cisplatin that was developed to reduce the systemic toxicity of cisplatin while simultaneously improving the efficacy of the drug in tumor cells.[8] Lipoplatin is able to deliver the drug in a nanoparticle form that evades immune surveillance and extravasates preferentially through the leaky vasculature that is characteristic of tumor cells with intense neoangiogenesis. It consists of liposome particles of an average size of 110 nanometers with a lipid-to-cisplatin ratio of 10 mg:24 mg. The fusogenic anionic lipid dipalmitoyl phosphatidylglycerol (DPPG) on its surface is supposed to promote fusion between the lipid bilayer of the liposome and the cell membrane. In addition, the nanoparticle nature of the drug results in a higher uptake believed to arise from a more avid phagocytosis of lipoplatin particles by tumor cells compared with normal cells.[9] Studies of lipoplatin have demonstrated a low toxicity profile, an ability to concentrate in tumors and to escape immune cells and macrophages, a slow clearance rate from the kidneys, long circulation properties in body fluids, a half-life of 36 hours in the blood, and promising therapeutic efficacy.[10]

Gemcitabine (Gemzar; Eli Lilly, Indianapolis, Ind), a nucleoside analogue, is administered in combination with cisplatin as the first-line treatment of patients with inoperable, locally advanced, or metastatic NSCLC.[11] The main adverse reaction is myelotoxicity. The advantage of using combinations of gemcitabine with cisplatin has been reported to be the inhibition of the DNA synthetic pathways involved in the repair of platinum-DNA adducts.[12,13]

We performed a phase 1 trial[14] to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of the combination of lipoplatin and gemcitabine in patients with advanced NSCLC that was refractory or resistant to cisplatin.

TABLE 1
Patient Characteristics (n=13)

Median Age, (range), y	63 (53-84)	
Female/male	3/10 (76.9%)	
ECOG performance status		
0	1	(7.7%)
1	6	(46.1%)
2	6	(46.1%)
Histology		
Adenocarcinoma	7	(53.8%)
Squamous cell	4	(30.8%)
Low-differentiation NSCLC	2	(15.4%)
Stage at inclusion		
Stage IV	11	(84.6%)
Stage IIIB	2	(15.4%)
Median no. of metastatic sites (range)	1 (1-3)	
1	6	(46.1%)
2	4	(30.8%)
3	3	(23.1%)
Initial treatment with curative intent		
Surgery	2	(15.4%)
Adjuvant chemotherapy	2	(15.4%)
Adjuvant radiotherapy	1	(7.8%)
Palliative treatment before inclusion		
First-line platinum-based chemotherapy	13	(100%)
Second-line chemotherapy	2	(15.4%)
Radiotherapy	2	(15.4%)

ECOG indicates Eastern Cooperative Oncology Group; NSCLC, nonsmall cell lung cancer.

MATERIALS AND METHODS

Patient Inclusion

Between July 2004 and September 2006, 13 patients with histologically proven, recurrent or refractory, advanced NSCLC were included in the study (Table 1). Inclusion criteria were the presence of measurable or evaluable disease; =2 previous chemotherapy regimens with at least 1 containing a platinum compound; prior chemotherapy that ended at least 4 weeks previously; age $\geq$18 years; an Eastern Cooperative Oncology Group (ECOG) performance status of $\leq$2; adequate bone marrow reserve (neutrophil count $\geq$1500mm^{-3} and a platelet count $\geq$120,000mm^{-3}); adequate renal and hepatic function; absent or stable brain metastases; and an estimated life expectancy $\geq$12 weeks. The protocol was registered at the Hellenic National Drug Administration, and was approved by the Ethics Committee of both the University Hospital of Alexandroupolis and Crete Interclinic Hospital of Heraklion. All patients provided written informed consent before their inclusion in the study.

Treatment and Dose Escalation

Gemcitabine was administered first at a fixed dose of 1000 mg/m^2 on Days 1 and 8 through intravenous

infusion in 250 mL of normal saline over 30 minutes. Lipoplatin was administered on Days 1 and 8 through intravenous infusion in 500 mL of dextrose over 4 hours after the administration of gemcitabine. The starting dose of lipoplatin was 100 mg/m^2, with escalation in 10-mg/m^2 increments. The treatment was administered every 3 weeks up to a maximum of 6 cycles. Patients who had been treated with prior chemotherapy containing gemcitabine were excluded from the study.

Doses were escalated in successive groups of patients according to a modified Fibonacci scheme. At least 3 patients had to be treated at each dose level and 3 cycles had to be administered per patient; no intrapatient dose escalation was allowed. In the case of grade 3/4 toxicity occurring in a patient within a cohort, 1 additional patient would be recruited if the toxicity affected the chemotherapy schedule and/or the patient's performance status. If a grade 3 or 4 hematologic toxicity occurred in at least 2 of the 3 patients within the same cohort, the dose level was considered to be the DLT. The dose level immediately before the DLT was defined as the MTD. The treatments were administered on an inpatient basis. All patients received prophylactic antiemetic treatment with steroids and anti-5-HT3. Granulocyte-colony-stimulating factor and erythropoietin were not used.[15,16]

Gemcitabine was purchased as a lyophilized powder in 200-mg and 1000-mg vials and stored at room temperature. It was reconstituted with normal saline to yield 40 mg/mL. Lipoplatin was supplied by Regulon as solution of 50 mL in clear glass vials containing 150 mg of compound (concentration of 3 mg/mL), and stored at a temperature of 4°C in light-protected packages.

Treatment and Toxicity Evaluation

Disease evaluation was performed at baseline and every 3 cycles or as required to confirm clinical suspicion of disease progression. Chest x-ray and computed tomography scans of the chest, brain, and upper abdomen were used for tumor assessment. Bone scan was performed only after there was a clinical suspicion of bone metastases. Stage of disease was determined according to the Mountain classification.[2] Before each cycle, the patient's history, results of a physical examination, and ECOG performance status were noted. Routine laboratory tests were performed on Days 1, 8, and 15 of each cycle.

Assessment of toxicity and response was performed according to the World Health Organization (WHO) criteria.[17] DLT was defined as the occurrence of any grade 3 nonhematologic toxicity, except emesis, in $\geq$3 patients at any dose level. Myelosuppressive DLT was also defined in relation to $\geq$3 patients at any dose level: neutropenia with a neutrophil count of $\leq$500 mm^{-3} lasting >7 days or a neutrophil count $\leq$1000 mm^{-3} with fever (temperature of $\geq$38°C) lasting >3 days, thrombocytopenia $\leq$25,000mm^{-3}, or grade 3 neutropenia associated with infection that required hospitalization. The occurrence of a DLT led to either removal from the study of involved patients or dose reduction to a lower level, according to the judgment of the treating physician.

Pharmacokinetics

Blood samples into tubes treated with ethylenediaminetetraacetic acid (EDTA) were taken at baseline and before the administration of gemcitabine and then at 0, 2, 4, 8, 12, 24, 48, 72, 120, 168, and 192 hours after the initiation of the lipoplatin infusion. Tubes were centrifuged at 4°C at 3000 cycles/minute for 5 minutes and the plasma was separated and stored at −20°C until determination.

Total plasma was analyzed for platinum. Total platinum concentrations were determined in plasma using a graphite furnace atomic absorption spectrometry (GF-AAS) assay. Standard solutions were prepared by the dilution of platinum with water. A solution of Triton X-100 (1 mL/L) and nitric acid (0.02 g/L) was used as the matrix modifier.[10] The linear range of the assay in plasma was 0.02 to 0.26 μg Pt/mL, and the limit of detection did not exceed 12 ng Pt/mL. Further details of the furnace program were as follows: wavelength of 265.9 nanometers (nm); slit width (in nm) of 0.2 low; read time of 4 seconds; injected sample volume of 20 μL; and a furnace temperature escalation program of 6 steps (90°C, 100°C, 300°C, 450°C, 1400°C, and 2650°C). Estimates of pharmacokinetic parameters were obtained by noncompartmental analysis, based on statistical moment theory. These parameters were determined by a numeric integration procedure such as the trapezoidal rule, which was used to determine the plasma concentration time curve (area under the curve [AUC]).[18] The mean residence time (MRT) was calculated from the equation MRT = AUMC/AUC, in which AUMC is the area under the first moment curve and MRT represents the time for 63.2% of the administered dose to be eliminated. $1/K_{elim}$ (elimination rate constant) is the MRT, the statistical moment analogue to half-life $t_{1/2}$. The $t_{1/2}$ (elimination half-life), the total body clearance (Cl), and the volume of distribution at the steady state (V_{ss}) were calculated using standard equations such as for $t_{1/2}$ = 0.693 (1/Kel), and (infused dose × AUMC/AUC^2)-(infused

TABLE 2
Treatment Analysis and Dose Intensity of 13 Evaluable Patients

Dose Level	No. of Patients	No. of Courses	No. of Cycles Delayed for Toxicity	No. of Cycles With Omission	Dose Intensity of Lipoplatin	Dose Intensity of Gemcitabine
Level 1 (n=3) (100 mg/m^2)	3	16	0	4*	80%	80%
Level 2 (n=3) (110 mg/m^2)	3	18	1	0	100%	100%
Level 3 (n=3) (120 mg/m^2)	3	18	1	0	100%	100%
Level 4 (n=4) (130 mg/m^2)	4	22	3	8†	71%	73.3%

* All cycles were omitted due to disease progression.
† Three cycles were omitted due to disease progression and 5 were omitted due to toxicity. All cycles delayed for toxicity were delayed for just 1 week with no impact on dose intensity noted.

TABLE 3
Hematologic Toxicity According to Dose Level in 13 Evaluable Patients*

	Neutropenia			Thrombocytopenia			Anemia		
Dose Level	Grade 1/2	Grade 3	Grade 4	Grade 1/2	Grade 3	Grade 4	Grade 1/2	Grade 3	Grade 4
Level 1 (n=3) (100 mg/m^2)	0	1	0	0	0	0	0	1	0
Level 2 (n=3) (110 mg/m^2)	0	1	0	0	0	0	1	0	0
Level 3 (n=3) (120 mg/m^2)	1	0	0	0	0	0	1	1	0
Level 4 (n=4) (130 mg/m^2)	0	1	2	0	2	0	3	0	0

* Toxicity was graded according to World Health Organization criteria.

dose × T/[2×AUC]) for V_{ss}, in which T is the infusion time.[18]

Pharmacokinetic analysis of gemcitabine was performed for the 3 patients in the first cycle on Day 1 of the therapy at the MTD, according to the protocol, to determine whether any interaction between the 2 drugs occurred. Blood samples were drawn into tubes containing tetrahydrouridine before gemcitabine infusion and then at 30 minutes and 45 minutes and at 1, 2, 4, 8, and 24 hours thereafter. Samples were immediately centrifuged at 4°C at 3000 g for 5 minutes and plasma was separated and stored at −80°C until analysis. Gemcitabine concentrations were measured by a reverse-phase liquid chromatography method as described previously.[19] Gemcitabine standard solutions were used to calculate standard calibration curves over the analytical range of 20 to 0.1 μg/mL, with good linearity (correlation coefficient [r^2] ≥0.9996). The detection limit was determined to be 0.078 μg/mL plasma.

Statistical Analysis

The Student *t* test was used for analysis of the distribution of the observed frequencies. A *P* value ≤.05 was considered to be statistically significant in the mean values. Time to treatment failure and median survival time were calculated according to the Kaplan-Meier product-limit method with death from cancer as the outcome.[20] Statistical evaluation of the data was performed using StatView 4.5 software (Abacus Concepts Inc., Berkeley Calif).

RESULTS

Toxicity

Thirteen patients were evaluable for toxicity and tumor response (Table 1) (3 patients each for dose levels 1, 2, and 3 and 4 patients for dose level 4). One patient achieved dose level 4 and thus another patient was enrolled. Two patients died during the study because of disease progression, 1 at dose level 1 and another at dose level 4. A total of 74 courses (median of 6 courses; range, 3 courses-12 courses) were administered to the 13 evaluable patients (Table 2). The median numbers of cycles was 3. The administered dose intensity of each drug is shown in Table 2. At dose level 4 (130 mg/m^2), 3 chemotherapy courses were delayed for only 1 week because of toxicity (Table 2). At dose level 4, myelo-DLT was achieved in 3 patients. Therefore, the MTD was defined as dose level 3 (120 mg/m^2).

Tables 3 and 4 show the main hematologic and nonhematologic side effects by dose level in evaluable patients. At dose level 1 (100 mg/m^2), 1 patient demonstrated grade 3 anemia (6.2% of the dose level 1 courses) and neutropenia (6.2% of the dose level 1 courses). At dose level 2 (110 mg/m^2), 1 patient had

TABLE 4
Nonhematologic Toxicities According to Dose Level in 13 Evaluable Patients*

	Flu-like		Nausea/Vomiting		Skin Rash		Constipation		Fatigue		Anorexia	
Dose Level	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Level 1 (n=3) (100 mg/m^2)	0	1	2	0	0	0	1	0	1	0	0	0
Level 2 (n=3) (110 mg/m^2)	0	1	1	0	2	0	1	0	0	0	0	0
Level 3 (n=3) (120 mg/m^2)	1	1	2	0	1	0	0	0	0	0	0	0
Level 4 (n=4) (130 mg/m^2)	2	2	1	2	1	0	3	0	1	1	1	1

* Toxicity was graded according to World Health Organization criteria.

grade 3 neutropenia (5.5% of the dose level 2 courses). Neutropenia was noted at Day 15; a white blood cell count was performed on an ambulatory basis, and the patient recovered spontaneously. At dose level 3 (120 mg/m^2), 1 patient developed grade 3 anemia (5.5% of the dose level 3 courses), without any impact on the treatment schedule noted. Both patients (1 at dose level 1 and 1 at dose level 3) had already presented with grade 2 anemia with an ECOG performance status of 2 prior to inclusion in the study.

At dose level 4 (130 mg/m^2), the first patient who was enrolled experienced nonmyelo-DLT with significant vomiting and asthenia that affected his performance status, necessitating hospitalization. According to the protocol, another patient was recruited. A DLT was experienced at this level, because 3 of 4 patients required >1 week for bone marrow recovery (Table 3). Grade 3/4 neutropenia occurred in 13.6% and thrombocytopenia was reported in 22.7% of the 22 performed courses. Aplasia-related fever was not reported to occur in any patient. In addition, grade 4 thrombocytopenia did not occur in any patient.

The most frequent nonhematologic side effect reported at any dose level was a flu-like syndrome experienced by 8 patients (61.5%) that was grade 3/4 in 12.1% of the total courses. However, this flu-like syndrome always resolved spontaneously without affecting the patients' performance status and/or the treatment schedule. Grade 3/4 nausea and vomiting was reported in 13.6% of the courses administered at dose level 4. The patient with grade 4 vomiting at dose level 4 also experienced fatigue and anorexia, both of which were grade 4, which led to dehydration and necessitated hospitalization. One patient developed grade 4 neurotoxicity at dose level 4, but she had already had a grade 2 toxicity before inclusion in the study that was the result of previous cisplatin treatment. Mild renal toxicity (grade 1) was noted in 3 patients at dose level 3. Other rare side effects were epigastric pain in 1 patient at dose level 1, which resolved spontaneously, and cardiac arrhythmia necessitating the administration of amiodarone. Neither toxicity affected the treatment schedules. Elevated bilirubin levels associated with transaminase levels were noted in the 2 patients who died during the study. Those levels were more likely to be elevated because of disease progression of the patients' hepatic metastases than because of the chemotherapy itself. No deaths due to toxicity were reported.

Response

At dose level 4, 1 patient (7.7%) demonstrated a partial response, and a second achieved stable disease. Another patient demonstrated stable disease at dose level 2. Therefore, the overall response rate was 7.7% and the disease control rate (DCR) was 23% (3 of 13 patients).

One female patient was still alive at the time of last follow-up, although she did develop disease progression. The median overall survival was 29 weeks (range, 4 weeks-59 weeks). The Kaplan-Meier overall survival curve is shown in Figure 1. The median survival of responders was 48 weeks (range, 47 weeks-52 weeks), whereas that of nonresponders was 16 weeks (range, 4 weeks-59 weeks). This difference was statistically significant ($P = .01$).

Overall, the median time to disease progression was 12 weeks (range, 3 weeks-36 weeks). The median time to disease progression in responders was 24 weeks (range, 23 weeks-36 weeks), whereas that of nonresponders was 12 weeks (range, 3 weeks-24 weeks). This difference was statistically significant ($P = .01$).

Pharmacokinetics

Complete plasma concentration time curves for total platinum were obtained in 12 of the 13 evaluable patients and used for pharmacokinetic analyses. The mean plasma concentration time curves per dose

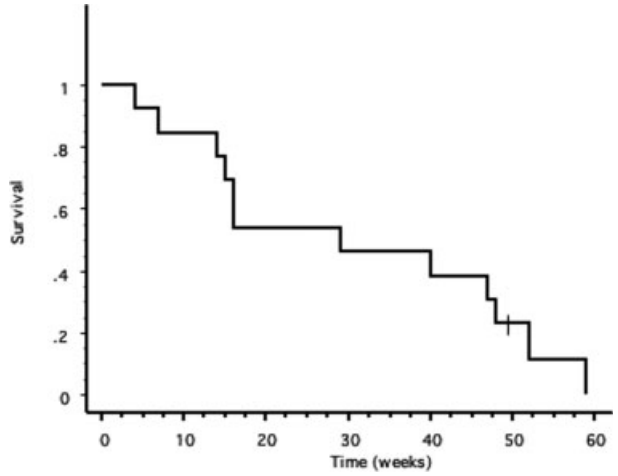

FIGURE 1. Kaplan-Meier overall survival curve of patients receiving the combination of lipoplatin and gemcitabine.

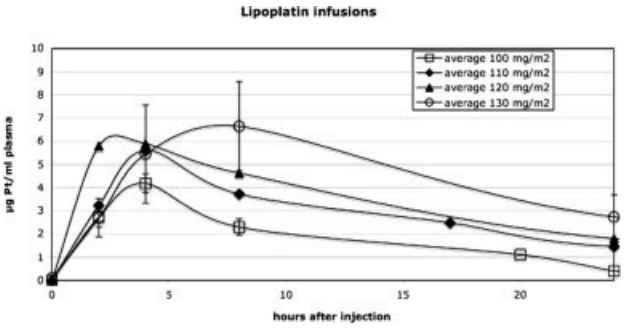

FIGURE 2. Depiction of mean plasma concentration time curves per dose level of lipoplatin (μg/mL) in patients for the first 24 hours.

TABLE 5
Pharmacokinetics of Plasma Lipoplatin at Different Dose Levels

Pharmacokinetic Parameters	Dose Level			
	100 mg/m^2	110 mg/m^2	120 mg/m^2	130 mg/m^2
AUC, μg•h/mL	84.0 ± 38.6	241.7 ± 48.1	236.5 ± 102.2	282.4 ± 73.7
C_{max}, μg/mL	4.2 ± 0.4	5.6 ± 2.1	6.6 ± 3.1	7.2 ± 2.0
MRT, h	15.5 ± 1.0	47.0 ± 19.3	57.2 ± 4.6	51.4 ± 4.4
K_{el}, 1/h	0.065 ± 0.005	0.025 ± 0.01	0.018 ± 0.001	0.020 ± 0.001
$t_{1/2}$, h	10.7 ± 0.7	32.5 ± 13.4	39.6 ± 3.2	35.6 ± 3.0
Cl, L/h*m^2	0.872 ± 0.319	0.301 ± 0.07	0.364 ± 0.15	0.320 ± 0.105
V_{ss}, L/m^2	11.7 ± 4.4	14.2 ± 7.0	19.5 ± 6.6	15.6 ± 4.3

AUC indicates area under the curve; C_{max}, maximum concentration; MRT, mean residence time; K_{el}, elimination rate constant; $t_{1/2}$, elimination half-life; Cl, total body clearance; V_{ss}, volume of distribution at the steady state.

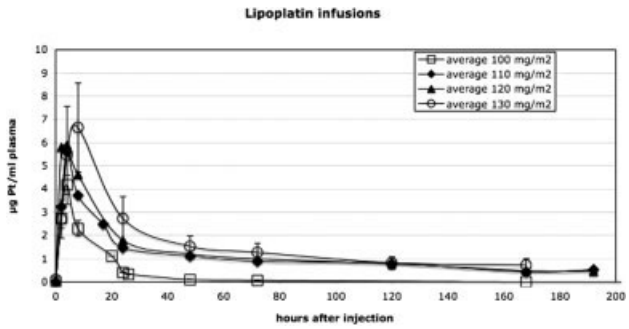

FIGURE 3. Depiction of mean plasma concentration time curves per dose level of lipoplatin (μg/mL) in patients for the first 7 days.

level for the first 24 hours are shown in Figure 2. During the 4-hour infusion period, the maximum platinum level in the plasma is attained at 4 hours at doses of 100 mg/m^2, 110 mg/m^2, and 120 mg/m^2 and declines thereafter. The infusion of lipoplatin at a dose of 130 mg/m^2 resulted in maximal levels of platinum in the plasma at 8 hours. Differences in the plasma levels of platinum at the different administered doses were registered; a maximum of 4.2 μg/mL was attained in the plasma 4 hours after an infusion of 100 mg/m^{2}of lipoplatin, a maximum of 5.6 μg/mL was attained in the plasma 4 hours after an infusion of 110 mg/m^2 of lipoplatin, a maximum of 6.6 μg/mL was attained in the plasma 4 hours after an infusion of 120 mg/m^2 of lipoplatin, and a maximum of 7.2 μg/mL was attained in the plasma 8 hours after an infusion of 130 mg/m^2 of lipoplatin (Table 5).

The plasma levels of platinum after lipoplatin infusion are reported to drop to normal levels after the fifth day for all doses except for dose level 1 (100 mg/m^2), whereas plasma levels drop after 24 hours (Fig. 3). The mean pharmacokinetic parameters for total platinum calculated for each dose level are shown in Table 5. At the MTD (120 mg/m^2), the AUC was 236.5μg•h/mL ± 102.2 μg•h/mL, whereas the maximum concentration (Cmax) of total platinum in the plasma reached was 6.6 μg/mL ± 3.1 μg/mL. The mean Cl was 0.364 L/(m^2•h) ± 0.15 L/(m^2•h). The $t_{1/2}$ was 39.6 hours ± 3.2 hours. The V_{ss} was 19.5 L/m^2 ± 6.6 L/m^2.

The pharmacokinetic parameters for gemcitabine obtained for 3 patients from the MTD dose level are shown in Table 6. The mean Cmax of gemcitabine was 25.2 μg/mL (range, 13.4 μg/mL - 41.2μg/mL), detected at the end of the infusion (30 minutes as Tmax) (Table 6). The mean plasma AUC was 12.2 μg•h/mL (range, 8.2μg•h/L-18.5μg•h/L) and the mean Cl was 95.3 L/h*m^2 (range 55.3 l/h.m^2-126.3 l/h.m^2) (Table 6). The calculated mean $t_{1/2}$ value was

TABLE 6
Pharmacokinetics of Plasma Gemcitabine at the MTD Dose Level

Pharmacokinetic Parameters	Mean ± SD
AUC, μg•h/mL	12.2 ± 4.5
C_{max}, μg/mL	25.2 ± 11.7
$t_{1/2}$, min	20.0 ± 3.4
Cl, L/h*m^2	95.3 ± 29.7
V_{ss}, L/m^2	47.5 ± 21.2

MTD indicates maximum tolerated dose; SD, standard deviation; AUC, area under the curve; C_{max}, maximum concentration; $t_{1/2}$, elimination half-life; Cl, total body clearance; V_{ss}, volume of distribution at the steady state.

20 minutes, and only 2% to 13% of Cmax was detectable at 1 hour after infusion.

DISCUSSION

To our knowledge the current study is the first trial of lipoplatin in combination with gemcitabine in patients with advanced NSCLC. The results of the current phase 1 study demonstrate the feasibility of this new 2-drug combination (lipoplatin and gemcitabine) for patients with advanced NSCLC. Furthermore, all patients in the current study had received previous treatment with platinum-based chemotherapy. The MTD of lipoplatin, administered as a 4-hour infusion in this combination, was determined to be 120 mg/m^2 on Day 1 and Day 8. In this combination, we administered gemcitabine at a fixed dose of 1000 mg/m^2 on Days 1 and 8 during a conventional 30-minute infusion before lipoplatin, and the pharmacokinetic profiles of lipoplatin and gemcitabine were not modified, as shown in previous reports in which patients received the same or proportional doses of gemcitabine in association with a diaminocyclohexane carrier platinum.[19,21] In addition, the results of the current study demonstrate that the combination of gemcitabine and lipoplatin is well-tolerated, even by patients with advanced NSCLC who were treated previously with platinum-based chemotherapy.

The low toxicity noted was not surprising in view of the nonoverlapping side effects of the 2 drugs. The good tolerance of the regimen is especially important in view of the characteristics of the patients in the current study, such as a median age of 63 years, an ECOG performance status of 2 in 6 patients (46.1%), and patients who were previously treated with platinum-based chemotherapy. Only in dose level 4 were significant grade 3 thrombocytopenia and neutropenia noted in 22.7% and 13.6%, respectively, of the courses. Moreover, there were no reported cases of febrile neutropenia, even at dose level 4. Only 1 of the 13 evaluable patients in the current study presented with significant vomiting and asthenia that necessitated hospital admission, also at dose level 4. It is interesting to note that in this phase 1 study of lipoplatin administered as a single agent on Days 1 and 15, the DLT was not reached because no significant toxicity was observed.[10] In a phase 1 study in patients with refractory pancreatic carcinoma, the MTD of lipoplatin was reported to be 100 mg/m^2 on Days 1 and 15, also in combination with a fixed dose of gemcitabine (1000 mg/m^2) administered on Days 1 and 15 in a 4-week regimen. In this study, the DLT was reached at a dose of 130 mg/m^2, and toxicity was also mild.[22] In general, it appears that the combination of lipoplatin and gemcitabine demonstrates lower hematologic and nonhematologic toxicities compared with the toxicity of classic combinations of platinum and gemcitabine[23] or compared with a regimen of diaminocyclohexane carrier platinum and gemcitabine.[19,21,24]

Allergic reactions, such as skin rash, fever, or flu-like syndrome, are normal toxicities in patients undergoing chemotherapy with liposoluble compounds. Overall, we observed these common toxicities in 8 patients (61.5%) at least once and with differing grades of allergic reaction. Nevertheless, these reactions were not clinically significant, and were mostly well tolerated, as was expected. The same percentage of patients (9 of 15 patients; 60%) presented those manifestations in a recent phase 1 study of the combination of oxaliplatin and gemcitabine in a patient population similar to that in the current study.[24]

Patients receiving treatment with platinum compounds classically develop peripheral sensory neurotoxicity. The incidence of neurotoxicity is attributable to the cumulative platinum dose. Only 1 patient in the current study presented with neurotoxicity at a DLT level. Nevertheless, this patient had already had grade 2 peripheral neurotoxicity at the time of inclusion into the study. This is even more important, considering that all patients were previously treated with some form of platinum combination chemotherapy. It has been reported that, with the use of diaminocyclohexane carrier platinum compounds, nearly all patients with cumulative dose levels of 540 mg/m^2 express some degree of peripheral neurosensory toxicity.[25] However, this neurotoxicity is reported to be reversible because 82% of patients have their neuropathy regress within 4 to 6 months, and 41% experience a complete recovery within 6 to 8 months. When lipoplatin was studied as a single agent in a phase 1 trial, no patient demonstrated any sensory neurotoxicity to a platinum dose of 250 mg/m^2 per cycle,[10] and when lipoplatin was administered in combination with gemcitabine, only 3

patients demonstrated grade 1 peripheral neurotoxicity.[22] Recent reports studying oxaliplatin also reported mild peripheral neurotoxicity. However, this finding was attributable to the relatively low cumulative dose of oxaliplatin administered.[19,21] In the current study, the mean cumulative dose of lipoplatin was 569 mg/m^2, which is not low enough to explain the low incidence of peripheral sensory neurotoxicity noted.

Another issue in the use of chemotherapy with cisplatin is the occurrence of renal toxicity, leading to further treatment limitations.[26] Nephrotoxicity after cisplatin treatment is common and may manifest after a single dose with acute renal failure or may present with a chronic syndrome of renal electrolyte wasting.[27] Despite various hydration protocols designed to minimize the nephrotoxicity, approximately one-third of patients who receive cisplatin develop evidence of acute renal failure.[28] Cisplatin accumulates in all nephron cells, but especially in the proximal kidney tubule cells within the S3 segment, which bear the brunt of the damage.[27] We did not observe any case of nephrotoxicity in the patients in the current study, although they had been previously treated with platinum compounds. This observation is common in patients undergoing chemotherapy with liposoluble platinum compounds. Indeed, lower levels of total platinum have been observed in the kidneys after liposoluble platinum infusion, compared with after cisplatin.[29] It appears that the lipid capsule offers protection in the kidney cells by rendering the drug active inside the tumor cell, in which its cytotoxic effect is needed.[29]

Patients with advanced stage NSCLC who have developed disease recurrence or progression while receiving platinum-based chemotherapy are less likely to respond to second-line regimens. The combination of lipoplatin and gemcitabine used in the current study had a DCR of 23%, with a median time to disease progression of 12 weeks (3 months) and an overall survival of 29 weeks (7.1 months). The median duration of response was 24 weeks (6 months). Although response and survival were not the primary endpoints in the current study, our findings are consistent with those of other studies reporting the activity of some platinum compounds in cisplatin-resistant tumors.[21,24-26,30] Furthermore, these findings suggest that, when combined with active agents not used in first-line therapy, lipoplatin may provide a useful alternative in patients with platinum-resistant NSCLC.

The results of the current study suggest that lipoplatin at a dose of 120 mg/m^2 combined with gemcitabine at a dose of 1000 mg/m^2 on Days 1 and 8 of a 21-day cycle is feasible, characterized by moderate toxicity and few cycle delays, in a population of NSCLC patients who received previous treatment with a platinum compound. To the best of our knowledge, the current study is the first dose escalation and pharmacokinetic study reported for the combination of lipoplatin and gemcitabine in this patient population. Based on the excellent tolerability observed, this regimen deserves further testing in phase 2 trials in patients with advanced NSCLC.

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