Liposomal Cisplatin Dose Escalation for Determining the Maximum Tolerated Dose and Dose-limiting Toxicity: A Phase I Study

G.P. STATHOPOULOS, S.K. RIGATOS and J. STATHOPOULOS

First Oncology Clinic, Errikos Dunant Hospital, Athens, Greece

Abstract. *Background: The aim of the present trial was to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of liposomal cisplatin (lipoplatin) using nephrotoxicity, gastrointestinal toxicity and myelotoxicity as the main adverse reactions. Patients and Methods: Lipoplatin, a liposomal formulation of cisplatin was first tested as monotherapy starting at a dose of 125 mg/m^2 and escalating up to 350 mg/m^2. Lipoplatin was then escalated in combination with paclitacel starting at a dose of 100 mg/m^2 escalating up to 250 mg/m^2 for the former and 100 mg/m^2 escalating up to 175 mg/m^2 for the latter. Results and Conclusion: The present trial determined the DLT for lipoplatin monotherapy at 350 mg/m^2 and the MTD at 300 mg/m^2; for lipoplatin-paclitaxel combination therapy, the DLT was 250 mg/m^2 for lipoplatin and 175 mg/m^2 for paclitaxel whereas the MTD was 200 mg/m^2 for lipoplatin and 175 mg/m^2 for paclitaxel.*

Over the last decades, cisplatin has been one of the most broadly used and most effective cytotoxic agents (1, 2). It has been applied for the treatment of epithelial malignancies such as lung, head-and-neck, ovarian, bladder and testicular cancers (3-7). Extensive clinical use has been impeded by adverse reactions, occasionally severe. Mild and severe renal and gastrointestinal toxicity, peripheral neuropathy, asthenia and cytotoxicity have been commonly observed (3, 4). The risk of nephrotoxicity caused by cisplatin frequently hinders the use of higher doses to maximise its antineoplastic effects (8, 9). Cisplatin is not particularly myelotoxic but nephrotoxicity is often unacceptable. Cisplatin analogues such as carboplatin and oxaliplatin have been marketed but as yet, none of these analogues has achieved superior effectiveness (10, 11).

Correspondence to: G.P. Stathopoulos, MD, Semitelou 2A, 115 28 Athens, Greece. Tel: +30 2107752600, Fax: +30 2107251736, e-mail: dr-gps@ath.forthnet.gr

Key Words: Liposomal cisplatin, dose escalation, lipoplatin.

Lipoplatin, a liposomal formulation of cisplatin, was developed in order to reduce the systemic toxicity of cisplatin while simultaneously improving the targeting of the drug to the primary tumour and to metastases by enhancing the circulation time in body fluids and tissues (12). Preclinical studies have shown lower nephrotoxicity of lipoplatin in rats and in mouse xenografts with breast and prostate human tumours, as compared to cisplatin (13). Cisplatin has been shown to cause renal insufficiency with clear evidence of tubular damage in animals. These animals, injected with the same dose of lipoplatin as cisplatin, were almost completely free of kidney injury (14). The pharmacokinetic study showed that lipoplatin's total body clearance was 0.18 l/(m^2 h) at a dose of 25 mg/m^2 and 0.49 l/(m^2 h) at a dose of 125 mg/m^2, which is considerably lower than the total body clearance for cisplatin (12). This difference may mean that in clinical practice lipoplatin can be increased to a much higher dosage than that of cisplatin without the adverse consequences of renal toxicity. In a previous phase I study, the lipoplatin dosage escalation reached 125 mg/m^2 without nephrotoxicity and without reaching the maximum tolerated dose (MTD) (12). This study is a new phase I trial testing doses higher than 125 mg/m^2, so as to define the MTD of lipoplatin monotherapy and in combination with a second cytotoxic agent.

The primary objectives of this study were to define the MTD and dose-limiting toxicity (DLT) of liposomal cisplatin using nephrotoxicity, gastrointestinal toxicity and myelotoxicity as the main adverse toxic reactions.

Patients and Methods

The study was a phase I cohort, dose escalation trial of liposomal cisplatin as monotherapy and also in combination with paclitaxel. The selection of paclitaxel for the combination was based on the fact that non-liposomal cisplatin in combination with paclitaxel is one of the common schedules used for the treatment of two of the most common malignancies, non-small cell lung cancer and ovarian cancer (15, 16). The main aim of the study was to determine the MTD as a recommended dose for phase II trials, and also, to define the DLT.

Table I. *Lipoplatin monotherapy.*

Dose level	Number of patients	Lipoplatin dose (mg/m^2 every 2 weeks)
I	4	125
II	4	150
III	4	175
IV	4	200
V	4	225
VI	4	250
VII	4	275
VIII	4+3	300
IX	4	350
Total	36+3=39	

Table II. *Lipoplatin-paclitaxel combination therapy.*

Dose Level	Number of patients	Lipoplatin mg/m^2 Every 2 weeks	Paclitaxel mg/m^2 Every 2 weeks
I	4	100	100
II	4	150	100
III	4	150	135
IV	4	200	135
V	4+3	200	175
VI	4	250	175
	Total: 24+3=27		

Study design

Dose escalation. Liposomal cisplatin (Lipoplatin) was previously tested at a dose of 120 mg/m^2 on days 1 and 2, administered once every week and once every two weeks (data not shown) without observing nephrotoxicity or other adverse reactions. Paclitaxel has also been administered weekly and every two weeks (17) with other agents (18). The present study was designed as a prospective non-randomised single centre dose escalation study. The drug administration was decided to be once every two weeks for both lipoplatin monotherapy and combined lipoplatin and paclitaxel. Lipoplatin monotherapy escalation started at the dosage of 125 mg/m^2 and reached 350 mg/m^2. The combination of both agents started at 100 mg/m^2 for lipoplatin and 100 mg/m^2 for paclitaxel and reached the doses of 250 mg/m^2 and 175 mg/m^2 for lipoplatin and paclitaxel, respectively (Tables I and II).

A minimum of four patients were planned to be tested at each dose level. Dose escalation was implemented if none of the four patients experienced DLT. If one patient experienced DLT, three more patients were recruited at that dose level. The dose increases were 25 mg/m^2 for the single lipoplatin escalation and 50 mg/m^2 in the combined escalation. The study aimed to start and integrate the single drug escalation and then to begin the combination. Paclitaxel escalation was based on dosages where experience with other agents exists (15). When three out of four patients experienced DLT, then the MTD (*i.e.* one dose level below DLT) had been reached and three additional patients were treated at the previous dose level. All toxicities at each level were defined on the basis of common toxicity criteria, namely any grade 3 or 4 haematological or non-hematological toxicity lasting up to 3 or more days (19).

Pretreatment eligibility. All patients were required to meet the following criteria: confirmed histological or cytological diagnosis of cancer, at least one bi-dimensionally measurable or evaluable disease, World Health Organisation (WHO) performance status 0-2, a life expectancy greater than 3 months, previous treatment by standard or first-line chemotherapy, and at the time of entry into the study, to have been refractory to any prior cytotoxic treatment. Patients were eligible if they had two or three previous treatment courses, provided they had been off treatment for at least 3 weeks.

Assessments. Eligible patients were required to have adequate haematological, renal and hepatic functions as defined by white blood cell count 3.5×10^9/l, haemoglobin level 9 g/dl, total bilirubin level 1.5 mg/dl, ALT and AST twice the upper normal limit in the absence of liver metastases or five times the upper normal limit in cases of documented liver metastasis, and creatinine level 1.5 mg/dl. Informed consent was required and obtained from all patients according to local regulatory requirements. Medical histology, physical examination, assessment of vital signs, electrocardiogram, chest and abdominal computed tomography (or ultrasound) were performed before treatment. During treatment (1 day before each course) blood count, blood urea and glucose, serum creatinine and uric acid tests and ECG were performed. A computed tomography assessment was performed in cases of clinical signs of disease progression.

Treatment. Lipoplatin was supplied by Regulon Inc. (Mountain View, CA, USA). Cisplatin was obtained from Heraeus (Hanau, Germany)/Flavine (Florida, USA) (mw 300). Lipoplatin was infused for 8 hours in 5% dextrose solution. Paclitaxel (Bristol-Mayers Squibb, NY, USA) was infused before lipoplatin in 200 ml normal saline for 2 hours, with dexamethasone premedication and both H_1 and H_2 receptor antagonists to prevent hypersensitivity reactions. Both treatments were given on day 1, on an outpatient basis.

Results

Patient characteristics are shown in Table III. Sixty-six patients (median age 64 years, range 42-78 years, 14 females, 52 males) entered the trial and all were evaluable for toxicity. All patients had a confirmed diagnosis of non-small cell lung cancer and had undergone previous first-line treatment. The time from the end of the prior treatment to their participation in this study ranged from 4 weeks to 5 months. No patients had undergone radiation therapy. The present treatment started at the end of 2007 and was completed in June 2009.

The patients received 2-3 cycles of the treatment at the planned dosage level. In total, 144 treatment courses were administered.

Toxicity. There were two groups of patients whose toxicity was examined at each dose level escalation. The first group of 39 patients was treated with lipoplatin monotherapy and the second group of 27 patients with the lipoplatin-paclitaxel

Table III. *Patient characteristics*.

	No.	%
Number of patients	66	100
Gender		
Male	52	78.79
Female	14	21.21
Age (years)		
Median	64	
Range	42-78	
Stage		
III	29	43.94
IV	37	56.06
Histology		
Non-small cell lung cancer	66	100
WHO performance status		
0	8	12.12
1	25	37.88
2	33	50.0
Prior chemotherapy		
Carboplatin-gemcitabine	66	100

Table IV. *Toxicity: Lipoplatin monotherapy.*

Dosage lipoplatin mg/m^2	Toxicity	Grade			
		1 n	2 n	3 n	4 n
150-250	Nausea-vomiting	–	–	–	–
	Fatigue	–	–	–	–
	Diarrhoea	–	–	–	–
	Nephrotoxicity	–	–	–	–
	Neutropenia	–	–	–	–
	Neurotoxicity	–	–	–	–
300	Nausea-vomiting	2/4	1/4	–	–
	Fatigue	2/4	1/4	–	–
	Neutropenia	1/4	–	–	–
	Nephrotoxicity	1/4	–	–	–
350	Nausea-vomiting	1/4	3/4	–	–
	Fatigue	1/4	3/4	–	–
	Neutropenia	2/4	1/4	1/4	–
	Nephrotoxicity	2/4	1/4	1/4	–

combination. Toxicities were based on WHO grades 1-4 per dose level as shown in Tables IV and V. In the first group, no haematological or non-haematological adverse reactions were observed up to and including the dose level of 250 mg/m^2. Patients at the dosage level of 300 mg/m^2 experienced grade 1-2 nausea and fatigue and grade 1 neutropenia and nephrotoxicity. At the 350 mg/m^2 dose level, grade 1-2 nausea and fatigue and grade 1-2-3 neutropenia and nephrotoxicity were observed. No treatment delay was needed in order to repeat the next treatment course.

Table V. *Toxicity: Lipoplatin-paclitaxel combination therapy.*

Dosage lipoplatin mg/m^2	Dosage paclitaxel mg/m^2	Toxicity	Grade			
			1 n	2 n	3 n	4 n
100-150	100-135	Nausea/vomiting	2/4	1/4	–	–
		Fatigue	2/4	1/4	–	–
		Diarrhoea	–	–	–	–
		Nephrotoxicity	–	–	–	–
		Neutropenia	1/4	–	–	–
		Neurotoxicity	2/4	–	–	–
		Alopecia	–	–	4/4	–
		Cardiotoxicity	–	–	–	–
200	175	Nausea/vomiting	2/4	1/4	–	–
		Fatigue	3/4	1/4	–	–
		Diarrhoea	1/4	–	–	–
		Nephrotoxicity	1/4	–	–	–
		Neutropenia	2/4	1/4	–	–
		Neurotoxicity	1/4	2/4	–	–
		Alopecia	–	–	–	–
		Cardiotoxicity	–	–	–	–
250	175	Nausea/vomiting	1/4	2/4	–	–
		Fatigue	1/4	2/4	1/4	–
		Diarrhoea	1/4	–	–	–
		Nephrotoxicity	2/4	1/4	1/4	–
		Neutropenia	1/4	2/4	1/4	–
		Neurotoxicity	–	2/4	2/4	–
		Alopecia	–	–	–	–
		Cardiotoxicity	–	–	–	–

In the second group where lipoplatin was combined with paclitaxel, the side-effects (up to grade 2, except for alopecia) started at the dose levels of lipoplatin of 100-200 mg/m^2 and increased at the level of 250 mg/m^2, while the dose of paclitaxel was 175 mg/m^2. At lower dosage levels, there were adverse reactions, but they were of a low grade. The main toxicities were neutropenia, fatigue, nausea-vomiting, neurotoxicity and also mild nephrotoxicity, which was temporary. Alopecia, due to paclitaxel administration was also observed. The side-effects are shown in Table V. On the basis of these data, for the lipoplatin/paclitaxel combination, DLT was defined at 250 mg/m^2 of lipoplatin and 175 mg/m^2 of paclitaxel. MTD was defined at 200 mg/m^2 of lipoplatin and 175 mg/m^2 of paclitaxel. With the use of such a combination of cytotoxic treatment, one could suggest that the paclitaxel dose should be more acceptable at 135 mg/m^2 if treatment were to be administered every 2 weeks. The low nephrotoxicity with liposomal cisplatin administration was always observed if the drug infusion lasted for at least 7 hours.

Discussion

The present trial aimed to establish the MTD and DLT of liposomal cisplatin when given as monotherapy and also when

combined with another agent, namely paclitaxel. When this new agent was administered in 5% 1000 cc dextrose for 8 hours, no serious nephrotoxicity was observed, even at a dose of 300 mg/m^2. There were some side-effects such as nausea or vomiting, fatigue or mild neutropenia at doses of 300 mg/m^2-350 mg/m^2. When combined with paclitaxel, toxicity increased and was observed at levels of 200-250 mg/m^2 with 175 mg/m^2 paclitaxel. Renal toxicity is a major factor to be considered when seeking a substitute for cisplatin, which is one of the most effective cytotoxic agents (20-22); the substitute for cisplatin is the analogue carboplatin (11) which is much less nephrotoxic but more myelotoxic. Lipoplatin is, at the present time, under investigation, but in current phase II trials, preliminary data have shown that it is a promising new agent. There are data that show that lipoplatin does not cause damage to the proximal kidney tubules as does cisplatin, for the following reasons: i) the reactivity of cisplatin in its lipoplatin formulation is strongly hindered because of the protection offered by the lipid capsule; the release of cisplatin from the liposome (*via* fusion with the cell membrane) is expected to render the drug active inside the cell where its cytotoxic effects are needed. It has been proposed that the entrance of lipoplatin particles into the kidney tubule cells is limited and, ii) lipoplatin is released through the kidney with a half-life of 60-117 hours compared to 6.5 hours for cisplatin (12). In practical terms, the uptake of total platinum in the kidneys after lipoplatin administration is 5 times lower than after cisplatin chemotherapy (12, 13). These pharmacokinetic differences may account for the low renal toxicity of lipoplatin which has been documented in animals using tubule cell necrosis and apoptosis, as well as impaired renal function assays (14). Lipoplatin is different from the SPI-77 liposomal formulation of cisplatin (23). SPI-77 has a half-life of 134 hours and urine excretion reaching only 4% of the total dose in 72 hours (23, 24).

In conclusion, the present trial has determined the MTD and DLT of liposomal cisplatin, a promising new agent, when given at dose level escalation, in pre-treated patients with non-small-cell lung cancer and it has also determined the MTD and DLT of liposomal cisplatin when combined with paclitaxel. The DLT for lipoplatin monotherapy was 350 mg/m^2 and the MTD 300 mg/m^2; for lipoplatin-paclitaxel combination therapy, the DLT was 250 mg/m^2 for lipoplatin and 175 mg/m^2 for paclitaxel whereas the MTD was 200 mg/m^2 for lipoplatin and 175 mg/m^2 for paclitaxel. It appears that lipoplatin is a new cisplatin analogue composed to reduce the toxicity of cisplatin, mainly of nephrotoxicity. It seems that the dose of lipoplatin can reach a level that is double or even higher than that of cisplatin without increasing the toxicity.

References

1 Rosenberg B: Noble metal complexes in cancer chemotherapy. Adv Exp Med Biol *91*: 129-150, 1977.

2 Livingston RB: Combination chemotherapy of bronchogenic carcinoma, I. Non-oat cell. Cancer Treat Rev *4*: 153-165, 1977.

3 Al-sarraf M: Chemotherapeutic management of head and neck cancer. Cancer Metastasis Rev *6*: 181-198, 1987.

4 Sternberg CN, Yagoda A, Scher HI, Watson RC, Geller N, Herr HW, Morse MJ, Sogani PC, Vaughan ED, Bander N, Weiselberg L, Rosado K, Smart T, Yun Lin S, Penenberg D, Fair WR and Whitmore WF, Jr: Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. Cancer *64*: 2448-2458, 1989.

5 Oliver T and Mead G: Testicular cancer. Curr Opin Oncol *5*: 559-567, 1993.

6 Taylor AE, Wiltshaw E, Gore ME, Fryatt I and Fischer C: Long-term follow-up of the first randomized study of cisplatin *versus* carboplatin for advanced epithelial ovarian cancer. J Clin Oncol *12*: 2066-2070, 1994.

7 Non-Small Cell Lung Cancer Collaborative Group: Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. BMJ *311*: 899-909, 1995.

8 Humes HD: Insights into ototoxicity. Analogies to nephrotoxicity Ann NY Acad Sci *884*: 15-18, 1999.

9 Arany I and Safirstein RL: Cisplatin nephrotoxicity. Semin Nephrol *23*: 460-464, 2003.

10 Caraceni A, Marfini C, Spatti G, Thomas A and Onofrj M: Recovering optic neuritis during systemic cisplatin and carboplatin chemotherapy. Acta Neurol Scand *96*: 260-261, 1997.

11 Boulikas T and Vougiouka M: Recent clinical trials using cisplatin, carboplatin and their combination chemotherapy drugs. (review) Oncol Rep *11*: 559-595, 2004.

12 Stathopoulos GP, Boulikas T, Vougiouka M, Deliconstantinos G, Rigatos S, Darli E, Viliotou V and Stathopoulos JG: Pharmaco-kinetics and adverse reactions of a new liposomal cisplatin (Lipoplatin): Phase I study. Oncology Rep *13*: 589-595, 2005.

13 Boulikas T: Low toxicity and anticancer activity of a novel liposomal cisplatin (Lipoplatin) in mouse xenografts. Oncol Rep *12*: 3-12, 2004.

14 Devarajan P, Tarabishi R, Mishra J, Ma Q, Kourvetaris A, Vougiouka M and Boulikas T: Low renal toxicity of lipoplatin compared to cisplatin in animals. Anticancer Res *24*: 2193-2200, 2004.

15 Scaglioti GV, De Marinis F, Rinaldi M, Crino L, Gridelli C, Ricci S, Matano E, Boni C, Marangolo M, Failla G, Altavilla G, Adamo V, Ceribelli A, Clerici M, Di Costanzo F, Frontini L and Tonato M, for the Italian Lung Cancer Project 2002: Phase III randomized trial comparing three platinum based doublets in advanced non-small cell lung cancer, J Clin Oncol *20*: 4285-4291.

16 Taylor AE, Wiltshow E, Gore ME, Fryatt I and Fischer C: Long-term follow-up of the first randomized study of cisplatin *versus* Carboplatin for advanced epithelial ovarian cancer, J Clin Oncol *12*: 2066-2070, 1994.

17 Stathopoulos GP, Rigatos SK, Christodoulou C, Malamos NA, Deliyiannis F, Stathopoulos JG and Skarlos DV: Weekly administration of topotecan and paclitaxel in pretreated advanced cancer patients: a phase I/II study. Cancer Chemother Pharmacol *54*: 259-264, 2004.

18 Stathopoulos GP, Veslemes M, Georgatou N, Antoniou D, Giamboudakis P, Katis K, Tsavdaridis D, Rigatos SK, Dimitroulis I, Bastani S, Loukides S, Vergos K, Marosis K, Grigoratou T, Kalatzi E, Charalambatou M, Paspalli A, Michalopoulou P, Stoka M and Gerogianni A: Front-line paclitaxel-vinorelbine *versus* paclitaxel-carboplatin in patients with advanced non-small cell lung cancer: a randomized phase III trial. Ann Oncol *15*: 1048-1055, 2004.

19 ICH Efficacy Guidelines EG (R1) Good clinical practice consolidated guideline, http://www.ich.org/cache/compo/475-272html.

20 Hanigan MH and Devarajan P: Cisplatin nephrotoxicity: molecular mechanisms. Cancer Ther *1*: 47-61, 2003.

21 Santoso JT, Lucci JA III, Coleman RL, Schafer I and Hannigan EV: Saline, mannitol, and furosemide hydration in acute cisplatin nephrotoxicity: a randomized trial. Cancer Chemother Pharmacol *52*: 13-18, 2003.

22 Gullo JJ, Litterst CL, Maguire PJ, Sikic BI, Hoth DF and Woolley PV: Pharmacokinetics and protein binding of *cis*-dichlorodiammine platinum (II) administered as a one hour or as a twenty hour infusion. Cancer Chemother Pharmacol *5*: 21-26, 1980.

23 Newman MS, Colbern CT, Working PK, Engbers C and Amantea MA: Comparative pharmacokinetics, of cisplatin encapsulated in long-circulating, pegylated liposomes (SPT-077) in tumor-bearing mice. Cancer Chemother Pharmacol *43*: 1-7, 1999.

24 Veal GJ, Griffin MJ, Price E, Parry A, Dick GS, Little MA, Yule SM, Morland B, Estlin EJ, Hale JP, Pearson AD, Welbank H and Boddy AV: A phase I study in paediatric patients to evaluate the safety and pharmacokinetics of SPI-77, a liposome-encapsulated formulation of cisplatin. Br J Cancer *84*: 1029-1035, 2001.

Received February 24, 2010
Revised March 21, 2010
Accepted March 23, 2010