Liposomal cisplatin combined with gemcitabine in pretreated advanced pancreatic cancer patients: A phase I-II study

GEORGE P. STATHOPOULOS¹, TENI BOULIKAS², MARIA VOUGIOUKA², SOTIRIOS K. RIGATOS¹ and JOHN G. STATHOPOULOS¹

¹Errikos Dunant Hospital and Medical School of Athens, Greece; ²Regulon Inc., 715 North Shoreline Blvd, Mountain View, CA 94043, USA and Regulon, A.E., Grigoriou Afxentiou 7, Alimos, Athens 17455, Greece

Received November 10, 2005; Accepted January 9, 2006

Abstract. The present trial is a phase I-II study based on a new liposomal cisplatin (lipoplatin). Previous preclinical and clinical data (phase I pharmacokinetics) led to the investigation of a combined treatment modality involving lipoplatin and gemcitabine. The gemcitabine dose was kept standard at 1000 mg/m² and the lipoplatin dose was escalated from 25 mg/m² to 125 mg/m². The treatment was administered to advanced pretreated pancreatic cancer patients who were refractory to previous chemotherapy which included gemcitabine. Lipoplatin at 125 mg/m² was defined as dose limiting toxicity (DLT) and 100 mg/m² as the maximum tolerated dose (MTD) in combination with 1000 mg/m² of gemcitabine. Preliminary objective response rate data showed a partial response in 2/24 patients (8.3%), disease stability in 14 patients (58.3%) for a median duration of 3 months (range 2-7 months) and clinical benefit in 8 patients (33.3%). Liposomal cisplatin is a non-toxic alternative agent to bare cisplatin. In combination with gemcitabine, it has an MTD of 100 mg/m² and shows promising efficacy in refractory pancreatic cancer.

Introduction

Cisplatin, [cis-PtCI₂(NH₃)₂] is used world-wide for the treatment of testicular and ovarian cancer as well as for bladder, head, neck, lung, gastrointestinal and many other tumors (1-7). Although very effective against these tumors, cisplatin has been associated with severe side effects including nephrotoxicity (8) ototoxicity, neurotoxicity, nausea and vomiting (7-9). Carboplatin, a cisplatin analogue, is markedly less toxic to the kidneys and nervous system than cisplatin and causes less nausea and vomiting, while generally (and certainly for

Correspondence to: Dr G.P. Stathopoulos, Semitelou 2A, 115 28 Athens, Greece E-mail: dr-gps@ath.forthnet.gr

Key words: liposomal cisplatin, gemcitabine, pancreatic cancer

ovarian cancer and non-small cell lung cancer) retaining equivalent antitumor activity. However, hematological adverse effects are more frequent with carboplatin than with cisplatin (10.11).

Gemcitabine (Gemzar®, Eli Lilly, Indianapolis, IN), a nucleoside analogue, is administered in combination with cisplatin as first-line treatment of patients with inoperable, locally advanced (stage IIIA or IIIB) or metastatic (stage IV) non-small cell lung cancer and as front-line treatment for patients with locally advanced (non-resectable stage III) or metastatic (stage IIIB, IV) adenocarcinoma of the pancreas (12-14). The main adverse reaction is myelotoxicity. The advantage of using combinations of gemcitabine with platinum has been attributed to the inhibition of the DNA synthetic pathways involved in the repair of platinum-DNA adducts. Gemcitabine and cisplatin act synergistically, increasing platinum-DNA adduct formation and inducing concentration and combination-dependent changes in ribonucleotide and deoxyribonucleotide pools in ovarian cancer cell lines (15).

A previous study on lipoplatin (Regulon Inc., Mountain View, CA) showed 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 h in the blood, and promising therapeutic efficacy (16). In the present phase I-II study we attempted to explore the therapeutic efficacy and toxicity profile of the lipoplatin-gemcitabine combination, given every 14 days in advanced stage pretreated pancreatic cancer patients. Our primary objectives were to determine toxicity and the maximum tolerated dose (MTD) and our secondary aims, to determine the response rate and clinical benefit.

Patients and methods

Patients >18 years of age with histologically or cytologically confirmed adenocarcinoma of the pancreas and bidimensionally measurable disease, who had undergone chemotherapy pretreatment and had recurrent or non-responsive disease, were enrolled in the study. Other eligibility criteria included a World Health Organization (WHO) performance status (PS) of 0-2, life expectancy of at least 3 months, adequate bone marrow reserves (granulocyte count ≥1500/dl, platelet count ≥120000/dl) normal renal (serum creatine

concentration <1.2 mg/dl) and liver function tests (total serum bilirubin concentration, <3 mg/dl, provided that serum transaminases and serum proteins were normal), normal cardiac function with no history of clinically unstable angina pectoris or myocardial infarction, or congestive heart failure within the 6 months prior, and no central nervous system involvement. Prior surgery was allowed provided that it had taken place at least 3 weeks before. Patients with active infection, malnutrition or a second primary tumor (except for a non-melanoma skin epithelioma or *in situ* cervix carcinoma) were excluded from the study. All patients gave their written informed consent to participate in the study.

Treatment plan. The plan was to combine lipoplatin with gemcitabine. Lipoplatin, supplied by Regulon Inc., was administered as an 8 h i.v. infusion on days 1 and 15; 8 h was chosen in order to be able to control possible adverse effects on the basis of our experience in the phase I trial. Gemcitabine was given as a 60 min i.v. infusion in 500 ml normal saline on days 1 and 15 at a dose of 1000 mg/m² and cycles were repeated every 4 weeks (28 days). The infusions on days 1 and 15 were considered to be 1 cycle. Provided that patients had recovered sufficiently from the drug-related side effects, standard ondansetron antiemetic treatment was to be administered to all patients. Prophylactic administration of recombinant human granulocyte colony-stimulating factor (rhG-CSF) was not allowed. In cases of grade 3 neutropenia, these patients would receive subsequent infusions of pegfilgrastim 6 mg, on the 6th or 7th day and treatment would be postponed for one week. Treatment was administered for at least three cycles or until disease progression. The study was a phase I/II cohort, dose escalation trial of lipoplatin and gemcitabine. Its aims were to determine the dose limiting toxicity (DLT) of the combination and to define the MTD as a recommended dose for phase II and to collect preliminary data on the efficacy of the drug in pretreated patients with pancreatic cancer. Myelotoxicity with lipoplatin as a single agent was considered very mild in a previous phase I study (16). We started with a low dose of lipoplatin, combined with gemcitabine which is a myelotoxic agent, mainly to determine the extent of bone marrow adverse reaction. The starting dose of lipoplatin was 25 mg/m² and increased by 25 mg/m² per dose level (Table I). The protocol was approved by the Ethics and Scientific Committee of the hospital.

Dose adjustment criteria were based on hematological parameters. In cases of grade 3 or 4 febrile neutropenia, subsequent cycles were repeated with pegfilgrastim prophylactic administration, as described above. In cases of febrile neutropenia or grade 3 or 4 neutropenia, despite the administration of rhG-CSF, gemcitabine and lipoplatin doses were reduced by 25% in the following treatment infusion. In cases of grade 3 or 4 thrombocytopenia lasting for >5 days, the doses of both drugs were also reduced by 25%. Toxicities were graded according to WHO guidelines (17).

Pretreatment evaluation included complete medical history and physical examination, full blood cell count including differential leukocyte and platelet counts, a standard biochemical profile (and creatinine clearance when necessary), serum carcinoembryonic antigen (CEA), and CA 19-9 determinations, electrocardiogram, chest X-rays, ultrasound of the upper abdomen, and computed tomography (CT) scans of the chest, upper and lower abdomen. Additional imaging studies were performed upon clinical indication. Full blood counts with differential were performed weekly; in case of grade 3 or 4 neutropenia or grade 4 thrombocytopenia, full blood counts with differential were evaluated daily until the absolute granulocyte count was >1000/dl and the platelet count >75000/dl. A detailed medical and physical examination was completed before each course of treatment in order to document symptoms of the disease and treatment toxicities. Biochemical tests, ECG, serum CEA and CA 19-9 determinations, and chest X-rays were performed every 6 weeks and a neurologic evaluation was performed by clinical examination. Lesions were measured after each cycle if they were assessable by physical examination or by chest X-rays; lesions assessable by ultrasound or CT scans were evaluated after three chemotherapy cycles.

Definition of response. Complete response (CR) was defined as the disappearance of all measurable or evaluable disease, signs and symptoms and biochemical changes related to the tumor for at least 4 weeks, during which time no new lesions appeared. Partial response (PR) was defined as >50% reduction in the sum of the products of the perpendicular diameters of all measurable lesions compared with pre-treatment measurements, lasting for at least 4 weeks, during which time no new lesions appeared and no existing lesions enlarged. For hepatic lesions, a reduction of >30% in the sum of the measured distances from the costal margin at the midclavicular line and at the xiphoid process to the edge of the liver, was required. Stable disease (SD) was defined as <50% reduction and a <25% increase in the sum of the products of the two perpendicular diameters of all measured lesions and the appearance of no new lesions for 8 weeks. Progressive disease (PD) was defined as an increase in the product of the two perpendicular diameters of any measurable lesion by >25% over the size present at entry into the study, or, for patients who responded, the size at the time of maximum regression and the appearance of new areas of malignant disease. Bilirubin increase without recovery after endoscopic retrograde choledocho-pancreatography (ERCP) or stent set was considered as disease progression. A two-step deterioration in performance status, a >10% loss of pretreatment weight or increasing symptoms did not by themselves constitute progression of the disease; however, the appearance of these complaints was followed by a new evaluation of the extent of the disease. All responses had to be maintained for at least 4 weeks and be confirmed by an independent panel of radiologists.

Results

Patient demographics. From January 2003 until December 2004, 24 patients (11 male, 13 female; median age 66 years, range 47-80 years) were enrolled in the study. The patient characteristics are shown in Table II. WHO performance status was 0 in 4.2% of the patients, 1 in 45.8% and 2 in 50%. The great majority of the patients were stage IV (79.2%). All patients had undergone prior chemotherapy: eleven patients with gemcitabine as a single agent treatment and 13 with gemcitabine combined with irinotecan.

Dose No. of Lipoplatin Gemcitabine level patients (mg/m² per 2 weeks) (mg/m² per 2 weeks) First 4 25 1000 Second 4 50 1000 Third 4 75 1000 Fourth 4 + 4100 1000 Fifth 4 125 1000

Table I. Lipoplatin and gemcitabine dose escalation.

	Table III.	Hematologic	al toxicity	by dose	level
--	------------	-------------	-------------	---------	-------

	Lipoplatin mg/m ²	Gemci- tabine mg/m ²	Toxicity no. of pts	Maximum toxicity (grade)	Toxicity type
First	25	1000	-	-	-
Second	50	1000	-	-	-
Third	75	1000	-	-	-
Fourth	100	1000	2/4ª	2-3	Neutro- penia
Fifth	125	1000	2/4	3-4	Neutro- penia
^a Origina	14 patients.				

Table II. Patient characteristics at baseline.

		No.	%
No. of patients enrolled		24	100
Age (years) Median Range	66 47-80		
Gender Male Female		11 13	45.8 54.2
Performance status (WHO) 0 1 2		1 11 12	4.2 45.8
Disease stage III IV		5 19	20.8 79.2
Histology Well-differentiated Moderately differentiated Low differentiation		3 12 9	12.5 50.0 37.5
Previous treatment Gemcitabine 1 g/m ²	Days 1, 8, 15/ every 4 weeks	11	45.8
Gemcitabine 900 mg/m ² + Irinotecan 300 mg/m ²	Days 1, 8/ every 3 weeks + Day 8/ every 3 weeks	13	54.2

Dose intensity. The patients received 36 courses (108 infusions every two weeks) and the median number of courses was 2 (range 1-5). Of the 24 patients, 10 patients completed 3 courses. There was no dose reduction for either drug and the patients received 99.5% of the planned dose intensity (range 93-100%) of each drug up to the fourth dosage level.

Toxicity. No neurotoxicity or renal toxicity was observed. Temporary abdominal pain which lasted for 2-4 min, and

Table IV. Non-hematologic toxicity.

Dosage level	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Nausea	5 (20.8)	-	-	-
Vomiting	2 (8.3)	-	-	-
Alopecia	14 (58.3)	-	-	-
Fatigue	8 (33.3)	-	-	-
Diarrhea	2 (8.3)	-	-	-
Cardiotoxicity	-	-	-	-
Neurotoxicity	3 (12.5)	-	-	-
Nephrotoxicity	-	-	-	-
Thrombotic episodes	4 (16.7)	-	-	-

which righted itself, was observed in 10/24 patients at the beginning of the lipoplatin infusion. Grade 3 myelotoxicity was observed in 2 out of 4 patients at the fifth dosage level. No febrile neutropenia was seen. Toxicity is shown in Tables III and IV. The level five dosage (125 mg/m² of lipoplatin and 1000 mg/m² of gemcitabine) was considered as DLT and dosage level 4 as the MTD. Four additional patients were treated at the fourth dosage level.

Response to treatment. The determination of measurable response on computed tomography was performed by two independent radiologists and two experienced oncologists. No complete responses were detected. PR was achieved in 2 patients (8.3%) with durations of 6 and 5 months. Stable disease was seen in 14 patients (58.3%) with a median duration of 3 months (range 2-7 months). Clinical benefit mainly due to pain reduction was seen in 8 patients (33.3%). At the end of the study 7 patients (29.2%) were still alive. Median survival from the beginning of second-line treatment was 4 months (range 2-8+ months).

Discussion

This new liposomal cisplatin (lipoplatin) aims mainly at the avoidance of renal toxicity, which is often seen in cisplatin administration, while at the same time producing similar efficacy. The pharmacokinetics of lipoplatin are different from cisplatin, as has been shown in animal studies as well as in a clinical trial in patients (16). The lack of toxicity is a major advantage, which was shown when lipoplatin was administered as a single agent. In the present phase I-II trial, toxicity and efficacy were studied by administering lipoplatin in combination with gemcitabine, the toxicity of which is well defined, particularly when combined with other agents (5). The cisplatin-gemcitabine combination has been similarly used as treatment in non-small cell lung cancer, urothelial and pancreatic cancer (5,7,12). It seems that the data from the present trial indicate the advantage of very low toxicity. The every-two-week administration of the combination is very well tolerated up to the dose of 100 mg/m² of lipoplatin when gemcitabine is maintained at a standard dose of 1000 mg/m². At the dose of 125 mg/m² of lipoplatin, myelotoxicity reached grades 3 and 4 and therefore this dosage was considered as DLT. The 100 mg/m² of lipoplatin and 1 g/m² of gemcitabine were considered as the MTD. The combination achieved an objective response in 8.33% of the patients, disease stability in 58.3% and pain relief in 33.3%. Taking into account that all of the patients were refractory or in disease progression while on a prior treatment including gemcitabine, the response rate produced here should be attributed to the addition of lipoplatin.

Further testing of lipoplatin in combined chemotherapy schedules is needed in order to determine its role in treatment modalities for cancer patients.

Liposomal cisplatin combined with gemcitabine administered every two weeks in advanced pretreated pancreatic cancer patients, has an MTD of 100 mg/m^2 and 1000 mg/m^2 , respectively. It is a well tolerated treatment with promising signs of efficacy.

References

- 1. Rosenberg B: Platinum complexes for the treatment of cancer: why the search goes on. In: Cisplatin: Chemistry and Biochemistry of a Leading Anticancer Drug. Lippert B (ed). Zurich, Verlag Helvetica Chimica Acta, pp3-12, 1999.
- Sorenson C and Eastman A: Mechanism of cis-diamminedichloroplatinum (II)-induced cytotoxicity: role of G₂ arrest and DNA double-strand breaks. Cancer Res 48: 4484-4488, 1988.
- 3. Einhorn LH, Williams SD, Loehrer PJ, Birch R, Drasga R and Omura G: Evaluation of optimal duration of chemotherapy in favorable prognosis disseminated germ cell tumors: a Southeastern Cancer Study group protocol. J Clin Oncol 7: 387-391, 1989.
- 4. Aabo K, Adams M, Adnitt P, Alberts DS, Athanazziou A, Barley V, Bell DR, Bianchi U, Bolis G, Brady MF, Brodovsky HS, Bruckner H, Buyse M, Canetta R, Chylak V, Cohen CJ, Colombo N, Conte PF, Crowther D, Edmonson JH, Gennatas C, Gilbey E, Gore M, Guthrie D and Yeap BY: Chemotherapy in advanced ovarian cancer: four systematic meta-analysis of individual patient data from 37 randomized trials. Br J Cancer 78: 1749-1487, 1998.

- Kaufman D, Raghavan D, Carducci M, Carducci M, Levine EG, Murphy B, Aisner J, Kuzei T, Nicol S, Oh W and Stadier W: Phase II trial of gemcitabine plus cisplatin in patients with metastatic urothelial cancer. J Clin Oncol 18: 1921-1927, 2000.
- 6. Pignon JP, Bourhis J, Domenge C and Designe L: Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. Lancet 355: 949-955, 2000.
- 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. Br Med J 311: 899-909, 1995.
- Hayes D, Cvitkovic E, Golfey R, Golbey RB, Scheiner E, Helson L and Krakoff IH: High dose cis-platinum diaminedichloride: amelioration of renal toxicity by mannitol diuresis. Cancer 39: 1372-1378, 1977.
- Gandara DR, Nahhas NA, Adelson MD, Lichtman SM, Podczaski ES, Yanovich S, Homesley HD, Braly P, Ritch PS and Weisberg SR: Randomized placebo-controlled multicenter evaluation of diethyldithiocarbamate for chemoprotection against cisplatin-induced toxicities. J Clin Oncol 13: 490-496, 1995.
- 10. Sculier JP, Lafitte JJ, Lecomte J, Berghmans T, Thiriaux J, Florin MC, Efremidis A, Alexopoulos CG, Recloux P, Ninane V, Mommen P, Paesmans M and Klastersky J: European Lung Cancer Working Party: a three-arm phase III randomized trial comparing combinations of platinum derivatives ifosfamide and/or gemcitabine in stage IV non-small cell lung cancer. Ann Oncol 13: 874-882, 2002.
- Tognoni A, Pensa F, Vaira F, Vigani A, Caness P, Sinaccio G and Pronzato P: A dose finding study of carboplatin and gemcitabine in advanced non-small cell lung cancer. J Chemother 14: 296-300, 2002.
- 12. Burris HA III, Moore MJ, Anderson J, Green MR, Rothernberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD and van Hoff DD: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 15: 2403-2413, 1997.
- Heinemann V, Wilke H, Mergenthaler HG, Clemens M, Konig H, Illiger HJ, Arning M, Schalhorn A, Possinger K and Fink U: Gemcitabine and cisplatin in the treatment of advanced and metastatic pancreatic cancer. Ann Oncol 11: 1399-1403, 2000.
- 14. Stathopoulos GP, Rigatos SK, Dimopoulos MA, Giannakakis T, Foutzilas G, Kouroussis C, Janninis D, Aravantinos G, Androulakis N, Agelaki S, Stathopoulos JG and Georgoulias V: Treatment of pancreatic cancer with a combination of irinotecan (CPT-11) and gemcitabine: a multicenter phase II study of the Greek Cooperative Group for Pancreatic Cancer. Ann Oncol 14: 388-394, 2003.
- 15. Van Moorsel CJ, Smid K, Voorn DA, Bergman AM, Pinedo HM and Peters GJ: Effect of gemcitabine and cis-platinum combinations on ribonucleotide and deoxyribonucleotide pools in ovarian cancer cell lines. Int J Oncol 22: 201-207, 2003.
- Stathopoulos GP, Boulikas T, Vougiouka M, Deliconstantinos G, Rigatos S, Darli E, Viliotou V and Stathopoulos JG: Pharmacokinetics and adverse reactions of a new liposomal cisplatin (lipoplatin): phase I study. Oncol Rep 13: 589-595, 2005.
- Miller AB, Hoogstraten B, Staquet M and Winkler A: (WHO) Reporting results of cancer treatment. Cancer 47: 207-214, 1981.