SPANDIDOS PUBLICATIONS

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

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**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/m$^2$ and the lipoplatin dose was escalated from 25 mg/m$^2$ to 125 mg/m$^2$. The treatment was administered to advanced pretreated pancreatic cancer patients who were refractory to previous chemotherapy which included gemcitabine. Lipoplatin at 125 mg/m$^2$ was defined as dose limiting toxicity (DLT) and 100 mg/m$^2$ as the maximum tolerated dose (MTD) in combination with 1000 mg/m$^2$ 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/m$^2$ and shows promising efficacy in refractory pancreatic cancer.

## Introduction

Cisplatin, [cis-$PtCI_2(NH_3)_2$] 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 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

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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/m$^2$ 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/m$^2$ and increased by 25 mg/m$^2$ 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.

ipoplatin and gemcitabine dose escalation.

| Dose level | No. of patients | Lipoplatin (mg/m$^2$ per 2 weeks) | Gemcitabine (mg/m$^2$ per 2 weeks) |
|---|---|---|---|
| First | 4 | 25 | 1000 |
| Second | 4 | 50 | 1000 |
| Third | 4 | 75 | 1000 |
| Fourth | 4+4 | 100 | 1000 |
| Fifth | 4 | 125 | 1000 |

Table II. Patient characteristics at baseline.

| | | No. | % |
|---|---|---|---|
| No. of patients enrolled | | 24 | 100 |
| Age (years) | | | |
| Median | 66 | | |
| Range | 47-80 | | |
| Gender | | | |
| Male | | 11 | 45.8 |
| Female | | 13 | 54.2 |
| Performance status (WHO) | | | |
| 0 | | 1 | 4.2 |
| 1 | | 11 | 45.8 |
| 2 | | 12 | 50.0 |
| Disease stage | | | |
| III | | 5 | 20.8 |
| IV | | 19 | 79.2 |
| Histology | | | |
| Well-differentiated | | 3 | 12.5 |
| Moderately differentiated | | 12 | 50.0 |
| Low differentiation | | 9 | 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 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/m$^2$ of lipoplatin and 1000 mg/m$^2$ of gemcitabine) was considered as DLT and dosage level 4 as the MTD. Four additional patients were treated at the fourth dosage level.

Table III. Hematological toxicity by dose level.

| | Lipoplatin mg/m$^2$ | Gemcitabine mg/m$^2$ | Toxicity no. of pts | Maximum toxicity (grade) | Toxicity type |
|---|---|---|---|---|---|
| First | 25 | 1000 | - | - | - |
| Second | 50 | 1000 | - | - | - |
| Third | 75 | 1000 | - | - | - |
| Fourth | 100 | 1000 | 2/4[a] | 2-3 | Neutropenia |
| Fifth | 125 | 1000 | 2/4 | 3-4 | Neutropenia |

[a]Original 4 patients.

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) | - | - | - |

*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/m$^2$ of lipoplatin when gemcitabine is maintained at a standard dose of 1000 mg/m$^2$. At the dose of 125 mg/m$^2$ of lipoplatin, myelotoxicity reached grades 3 and 4 and therefore this dosage was considered as DLT. The 100 mg/m$^2$ of lipoplatin and 1 g/m$^2$ 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.

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