RESEARCH ARTICLE

LIPOSOMAL CISPLATIN IN CANCER PATIENTS WITH RENAL FAILURE

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Received 03 April 2012; Revised 30 April 2012; Accepted 09 May 2012, Available online 15 May 2012

ABSTRACT

One of the serious adverse reactions with the administration of chemotherapeutical agents is renal failure. In general, when the level of creatinine/glomerular filtration data is high, chemotherapy involving almost all cytotoxic agents is avoided or the dosage is reduced. Liposomal cisplatin (lipoplatin) is a new agent which has been tested in Phase I, II and III trials and no renal toxicity has been reported. In the present trial, this agent was tested as monotherapy and in combination with gemcitabine or paclitaxel or 5-fluorouracil-leucovorin, mainly in lung and bladder cancer patients with renal insufficiency. Forty-two patients, (14 with non-small-cell lung cancer, 2 with squamous cell carcinoma non-small-cell lung cancer, 16 with bladder cancer and 10 gastrointestinal tract cancer), were included. There were 40 men and 2 women, median age 65 y (range 49-84). Lipoplatin and gemcitabine were administered to patients with bladder cancer, the first day, repeated every 2 weeks; paclitaxel, plus lipoplatin as above, were administered to lung cancer patients; patients with gastrointestinal tract cancer received 5-fluorouracil and leucovorin, plus lipoplatin as above. The median number of courses was 6 (range 2-12). Serum creatinine was 1.6 mg/dl to 4.0 mg/dl (median 2.4 mg/dl). No serum creatinine increase was observed in any of the patients. Grade 1-2 myelotoxicity and anemia were observed in 28.57% and 50% of the patients, respectively. Liposomal cisplatin is a new agent, which according to the literature and the present study, is an eligible cytotoxic agent for patients with renal insufficiency.

Key words: Liposomal Cisplatin, renal failure, chemotherapeutic agent.

INTRODUCTION

Cytotoxic chemotherapy remains the main treatment for malignant tumors. Renal failure is one of the serious adverse reactions caused when chemotherapeutical agents are administered, since the majority of anticancer drugs are excreted through the kidneys. When the creatinine/glomerular filtration data (GFR) is higher than normal, chemotherapy involving almost all cytotoxic agents is avoided, or the dosage is reduced. The main agent accompanied by renal failure is cisplatin (CDDP); it has been in use for over 30 years and has been shown to be quite an effective agent in a great number of malignancies, such as lung, ovarian, head and neck, urethral and testicular cancers. [1-9] Cisplatin is one of the most important anticancer drugs with respect to effectiveness, but its toxicity is often an inhibitory factor. The main side effect is renal toxicity (renal failure). Other adverse reactions are nausea/vomiting, fatigue and neurotoxicity. [10-13]

Over the last decades, there has been an extensive effort to substitute other agents for CDDP. The cisplatin analogue, carboplatin, has been the drug mainly used, instead of cisplatin, for several malignant tumors. Taxanes (paclitaxel, docetaxel), gemcitabine and vinorelbine have also been tested in several malignancies such as non-small-cell lung cancer (NSCLC) and ovarian cancer. With the aforementioned agents, renal toxicity was avoided but other side effects such as myelotoxicity were observed. None of these drugs, however, were better than or equal to cisplatin in effectiveness.[14-20]

Liposomal cisplatin is new formulation of cisplatin which was produced some years ago. The main scope of this new agent was to reduce the nephrotoxicity caused by cisplatin, to avoid other adverse reactions and certainly to be effective. Up until now, there have been more than 16 studies (preclinical and clinical) published on liposomal cisplatin (lipoplatin). It has been tested in pancreatic cancer, in NSCLC, in breast and in head and neck cancers. In the majority of tumors tested, it has been as equally effective as cisplatin and much less toxic. [21-28] A recent study examined the effectiveness of lipoplatin versus cisplatin, each combined with paclitaxel, in adenocarcinoma of the lungs. It was found that the response rate was statistically significantly higher, in favour of lipoplatin Arm. [29]

The primary objective of the present study was to investigate the administration of lipoplatin in patients with renal insufficiency and secondly, to determine the response of patients with bladder cancer, the majority of whom received the present treatment as first-line therapy.

MATERIALS AND METHODS

Eligibility criteria

Patients >18 years of age with a histologically- or cytologically-confirmed diagnosis of malignant disease, who were pretreated or who were chemotherapy- and radiotherapy-naïve, were enrolled in the study. Other eligibly criteria included a World Health Organisation (WHO) performance status (PS) of 0-2, life expectancy of at least 3 months, adequate bone marrow reserve (granulocyte count $1500\mu l^{-1}$, platelet count $120000/\mu l^{-1}$), normal liver function and normal cardiac function with no history of clinically unstable angina pectoris or myocardial infarction or congestive heart failure within the 6 months prior. Patients with central nervous system involvement were eligible if they were asymptomatic. Patients with active infection, malnutrition or a second primary tumor were excluded from the study. Having had the experience from previous studies that liposomal

cisplatin causes no renal toxicity, patients with increased blood urea and with serum creatinine concentration >1.6-4mg/dl, were enrolled.

The study was approved by our institutional review board and all patients gave their written informed consent to participate.

Treatment plan

All patients were treated on an outpatient basis. Five patients were initially treated with lipoplatin monotherapy once every 2 weeks at a dose of 150-200 mg/m^2. Upon finding that no side effects were observed and there was no increase in serum creatinine, we started the treatment in combination with gemcitabine at a dose 1000 mg/m^2, for the patients with bladder cancer. The treatment was repeated every 2 weeks. Lipoplatin was infused for 8 hours and gemcitabine for 90 minutes; lung cancer patients received paclitaxel at a dose of 175 mg/m^2 for 3 hours, and lipoplatin as above; patients with gastrointestinal tract cancer received 700 mg/m^2 of 5-fluorouracil (5-FU) and 200 mg of leucovorin, for 2 hours and lipoplatin as above. Premedication involved dexamethasone (8 mg) and both H1 and H2 receptor antagonists to prevent hypersensitivity reactions. All agents were given on day 1. Dose adjustment criteria were based on hematological and renal parameters. In cases of grade 3 and 4 febrile neutropenia, we decided we would reduce all drug doses by 25% in the subsequent cycles and rhG-CSF was then to be administered. Toxicities were graded according to the WHO guidelines. [30]

Pretreatment evaluation included medical history and physical examination, full blood count including differential leukocyte and platelet counts, a standard biochemical profile, electrocardiogram, X-rays of the chest, 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 cases of grade 3 and 4 neutropenia or thrombocytopenia, full blood counts were to be evaluated daily.

A detailed medical and physical examination was completed before each course of treatment (once every 2 weeks), in order to document the symptoms of the disease and treatment toxicities. CT scans were performed every 3 cycles (once every 6 weeks).

Definition for response

For the assessment of response, we used imaging-based evaluation. A complete response (CR) was considered to be the disappearance of all measurable disease confirmed at 4 weeks at the earliest; a partial response (PR), a 30% decrease, also confirmed at 4 weeks at the earliest. In stable disease (SD), neither the PR nor the progressive disease (PD) criteria were met; PD was considered to be a 20% increase of tumor burden and no CR, PR or SD documented before increased disease. Response data were based on the response evaluation criteria in solid tumors (RECIST). [31] A two-step deterioration in performance status, a >10% loss in 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.

Statistical design

Simon's two stage minimax design was used for calculation of the sample size. The significance level was set to be 5% and the power 90%. Low response probability was set to be 20% and the level of useful activity 40%. In the first stage, 20 patients were enrolled in the study. If 5 or fewer responses had been observed, then the study would have been terminated. Otherwise, if more than 5 responses were observed, another 20 patients would be recruited for a maximum sample size of 40 patients.

RESULTS

From June 2006 till August 2011, 42 patients were enrolled in this one-clinic trial. All were evaluable for toxicity and response. The 16 patients with bladder cancer had renal insufficiency; 14 of these patients received lipoplatin and gemcitabine treatment as a first-line chemotherapy and 2 as second-line therapy. Sixteen other patients with NSCLC (14 with adenocarcinoma, 2 with squamous cell carcinoma) received lipoplatin plus paclitaxel as second- or third-line treatment. The 10 patients with gastrointestinal cancer received lipoplatin-5-FU-leucovorin as second-line or third-line treatment. There were 40 males and 2 females (median age 65y range 49-84y). Fourteen patients with bladder cancer had limited disease, whereas the remaining 28 enrolled patients had advanced (Table 1). At the end of the study, 11 patients were still alive.

Table 1: Patients' characteristics

	n	%
Patients enrolled	42	100
Patients evaluable	42	100
Gender		
Male	40	95.24
Female	2	4.76
Age (Years)		
Median	65	
Range	49-84	
Disease stage		
Limited	14	33.33
Advanced	28	66.67
Histology		
Adenocarcinoma/NSCLC	14	33.33
Squamous cell carcinoma/NSCLC	2	4.76
Bladder cancer	16	38.10
Gastrointestinal tract cancer	10	23.81
Performance status (WHO)		
0	17	40.48
1	20	47.62
2	5	11.90
NSCLC, non-small-cell lung cancer; WHO (World Health Organization)		

Two hundred and two chemotherapy cycles were administered (median 6 cycles, range 2-12). Twelve cycles were given to one patient during two different time periods. Treatment was delayed for one week in 4 patients; this delay was due to non-renal toxicity i.e. to the myelotoxicity produced by the second cytotoxic agent. There was no need to reduce the dose of lipoplatin but only that of the second cytotoxic agent, by 25%. At the time of analysis, 11 patients (26.19%) were still alive. The cause of death for the remaining patients was the disease (mainly NSCLC), and heart attack or brain metastasis.

Response to treatment and survival

Survival was evaluated on an intention-to-treat basis. There were 5 (11.9%) complete responses out of the 42 patients; all five responders had bladder cancer. The evaluation was done by bladder endoscopy and CT scan. Out of the total number of 16 bladder cancer patients the percentage of CR was 31.25%. A partial response was achieved by 15 patients, 8 of whom had bladder cancer and 7 who had tumors at other sites). Fourteen (33.33%) patients had stable disease, 3 of whom had bladder cancer. No response was observed in 8 (19.05%) patients (Table 2). The median duration of response was in total 7 months (range 3-11 months). Of the 16 patients with bladder cancer the median duration of response was 12 months (range 4-18 months). One patient with bladder cancer who had achieved a complete response, had a tumor recurrence after 12 months; he survived for 48 months and died of a heart attack.

Table 2: Response rate

Response	n	Site n (%)
Complete response	5	Bladder 5 (11.9)
Partial response	15	Bladder 8 (19.05) NSCLC 2 (4.76) GI tract 5 (11.9)
Stable disease	14	Bladder 3 (7.14) NSCLC 6 (14.29) GI tract 5 (11.9)
No response	8	NSCLC 8 (19.05)
NSCLC, non-small-cell lung cancer; GI, gastrointestinal		

Toxicity

All 42 patients were evaluable for toxicity. The treatment caused no renal toxicity; there was no increase in blood urea and serum creatinine and in some patients there was a reduction in these levels. In 10/16 patients with bladder cancer, the blood urea and serum creatinine levels decreased, towards normal levels; this reduction was observed in these patients who had had a urination obstruction, which after treatment returned to normal. Grade 1-2 nausea/vomiting was observed in 8 (19.05%) patients. Myelotoxicity was observed in 12 (28.57%) patients; this was attributed to the second agent given in combination with lipoplatin. Grade 1-2 anemia was observed in half of the patients. Grade 1-2 peripheral neuropathy was observed in 13 patients who received paclitaxel as the second agent. Mild fatigue was also observed in the majority of patients (Table 3).

Table 3: Toxicity

Adverse Reactions	Grade 1-2 n	%
Renal failure*	-	0.00
Nausea/Vomiting	8	19.05
Myelotoxicity	12	28.57
Anemia	21	50.00
Fatigue	25	59.52
Peripheral neuropathy	13	30.95
* None of the 42 patients had an increase in blood urea or serum creatinine		

DISCUSSION

Liposomal cisplatin (lipoplatin) is a new agent which could become a substitute for cisplatin. There are more than 16 trials concerning lipoplatin and it has shown equal effectiveness to cisplatin and a better response rate with a statistically significant difference (lipoplatin versus cisplatin) in adenocarcinoma of the lungs. [32] The most important parameter with regard to lipoplatin and part of its effectiveness is the lack of adverse reactions: in particular, there is no renal toxicity. This is due to the low excretion of the drug, through the kidneys (40% renal excretion in 3 days). [32] It is not only this lack of renal toxicity but the fact that one can infuse this agent for 8 hours in patients who already have renal toxicity. There are quite a number of patients with blood urea and serum creatinine at abnormally high levels where the administration of anticancer drugs is impossible with the proper (maximum tolerated dose); common treatment involves a combination of anticancer agents in order to achieve a better response. Lipoplatin may favorably be considered as the treatment solution for cancer patients with renal insufficiency. To date, the trials on lipoplatin have shown that it can be used as a substitute for cisplatin in adenocarcinoma of the lungs, in pancreatic and bladder cancer; in the future, it might be administred for other tumors, such as ovarian cancer, gynaecological malignancies, esophageal and gastric cancers.

In the present study, lipoplatin has shown effectiveness without toxicity problems in patients with renal failure. It has been tested in NSCLC, in gastrointestinal and in bladder cancer. Future trials may confirm the present data and be a cause for courage for certain groups of cancer patients.

ACKNOWLEDGEMENT: I wish to Acknowledge to my secretary Maria Kaparelou

No conflict of interest

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