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Short report

Lobaplatin in advanced urothelial tract tumors

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Introduction

Bladder cancer is the fifth most common cancer in men and the seventh in women. Combination regimens containing cisplatin have produced response rates in 50%–70% of patients with complete responses in 20%–30% [1].

Lobaplatin (1,2-diamminomethylcyclobutane-platinum (II) lactate, D-19466) is a third generation platinum analogue. It is water soluble and stable and may not be cross-resistant with cisplatin [2, 3]. A favorable toxicity profile and similar efficacy to cisplatin stimulated a phase II study in patients with advanced urothelial tract tumors.

Patients and methods

Patients with histologically proven bidimensionally measurable metastatic or locally advanced TCC of the urinary tract were eligible. Patients with unresected carcinoma of the ureter or renal pelvis were excluded. Patients may have had only one prior chemotherapy regimen, WHO performance status ≤ 2 , age ≤ 75 years, creatinine clearance ≥ 40 ml/min, bilirubin ≤ 35 micromol/l, granulocytes > 2000 cells/mm³, platelets $> 125,000$ cells/mm³, and clinically normal auditory function.

Lobaplatin was supplied by ASTA Medica, Germany, and given at 50 mg/m² i.v. every three weeks. Drug was continued until development of progressive disease. Dose modification to 60 mg/m² (nadir $> 50,000$ and granulocytes $> 1,000$) or dose reduction to 40 mg/m² (treatment day platelets $< 100,000$ or granulocytes $< 1,500$) were permitted in subsequent cycles.

For a creatinine clearance ≥ 40 ml/min, 100% of the dose was given. For < 40 ml/min, lobaplatin was withheld. Patients were evaluable for response if they had received at least two treatment courses. However, those patients progressive after one course were considered as in progression. Response was evaluated after every two cycles of treatment. A partial response was defined as at least a 50% reduction of the bidimensionally measurable disease parameters, determined by two observations not less than four weeks apart.

The protocol was conducted according to the Helsinki declaration. Written or oral informed consent was attained according to the guidelines in each participating institution.

Results

Patient characteristics

There were 15 males and 4 females with a median age of 64 years (range 54–77 years), and a median WHO performance status 1 (0–2). The primary site was bladder in 16 patients, renal pelvis in two, renal pelvis + ureter in one. Twelve patients had prior chemotherapy including cisplatin or carboplatin in seven, and three had prior RT. Measurable disease sites were the primary tumor in seven patients, lymph nodes in 21, lung in seven, liver in four and bone in two.

Response

Twenty-two patients were entered in the trial, of whom three were ineligible. Two because they had received two previous lines of chemotherapy, and one because the performance status was 3 and no creatinine clearance was available prior to entry. Therefore, 19 patients were eligible. Two patients were inevaluable for response. One patient never received lobaplatin due to a myocardial infarction. Another patient had an early death caused by a CVA due to thrombosis.

The total number of cycles delivered to 18 patients was 50. The median number of cycles administered was 2 (range 0–6 cycles). Of 17 evaluable patients, two had a confirmed partial response, one in lymph nodes and the other in the skin for 27+ weeks and 20 weeks. Five patients were stable. One patient, with a creatinine clearance of 48 and no prior treatment had a PR in retroperitoneal lymph nodes and bladder. He was hospitalized with a platelet count of 5,000 cells/mm³ after two cycles of lobaplatin. He was subsequently treated with M-VAC, without a repeat CAT scan at one month, and was considered as stable. Thus, 2 of 17 (12%; 95% CI 0%–30%) patients had a PR and 5 of 17 (29%; 95% CI 8%–50%) had stable disease. Of note, patients who

Table 1. Hematological toxicity.

WHO grade	0 (%)	1 (%)	2 (%)	3 (%)	4 (%)
White blood cells	3 (16)	1 (6)	4 (22)	9 (50)	1 (6)
Granulocytes	3 (17)		4 (22)	6 (33)	5 (28)
Platelets	1 (6)	1 (6)		4 (22)	12 (67)
Hemoglobin	2 (11)	2 (11)	3 (16)	8 (46)	3 (16)

Table 2. Non hematologic side effects.

WHO grade	0 (%)	1 (%)	2 (%)	3 (%)	4 (%)
Nausea/vomiting	6 (33)	3 (17)	4 (22)	4 (22)	1 (6)
Diarrhea	16 (89)	1 (6)	1 (6)		
Liver	15 (83)	1 (6)	1 (6)		
Renal	16 (89)	2 (11)			
Pulmonary	17 (94)		1 (6)		
Drug fever	14 (78)	2 (11)	1 (6)		1 (6)
Infection	16 (89)		2 (11)		
Mucositis	15 (83)	1 (6)	2 (11)		
Neurotoxicity	13 (71)	1 (6)	3 (17)	1 (6)	
Ototoxicity	17 (94)	1 (6)			

responded had no prior cisplatin or carboplatin therapy. Ten patients progressed.

Toxicity

Hematologic toxicity, particularly thrombocytopenia, was significant, and described in Table 1. Grade 3 or 4 thrombocytopenia occurred in 89% of patients. Grade 3 or 4 neutropenia was observed in 61%. Platelet nadirs generally occurred on day 14, with recovery by day 21. In only three cycles, the platelet nadir was reported after day 17. In six cycles, recovery occurred at day 27. Four of these late recoveries were for the same patient.

Only two patients received six cycles, and previously observed toxicity might have contributed to the decision to stop therapy. Therefore, cumulative thrombocytopenia was not evidenced.

No statistical significance was found between creatinine at entry and platelets. No evidence of a relationship between previous carboplatin or cisplatin and platelets was found. Non-hematologic side effects were mild and described in Table 2.

Discussion

Lobaplatin was evaluated in three phase I studies, using one single dose, five doses on consecutive days and 72-hour continuous infusion [4-6]. Sixty-three patients were treated. Thrombocytopenia was observed at maximally tolerated doses, with the nadir at 14 and 18 days. Recovery was usually rapid, within seven days [3]. Emesis was moderate, even without antiemetic treatment. Nephrotoxicity, neurotoxicity and ototoxicity were not observed. No difference between the regimens was noted. In phase II studies, lobaplatin demonstrated activity in refractory

ovarian cancer [7], in testis cancer, and in esophageal tumors [8].

The present study was closed due to prohibitive thrombocytopenia, although 2 of the 17 (12%) evaluable patients obtained a PR. Of note, neither of these two patients had had prior carboplatin or cisplatin. The majority of patients entered into this study had therapy with a prior analogue. In a brief report of five patients with advanced TCC, treated with the combination of lobaplatin, methotrexate and vinblastine (LMV), the toxicity profile was acceptable [9].

The toxicity profile of lobaplatin resembles that of carboplatin, and consists of thrombocytopenia and leukopenia. In the present study, it was impossible to correlate creatinine clearance to thrombocytopenia. In retrospect, this trial should not have been conducted in this pre-treated patient population and should have excluded patients with low creatinine clearance upon entry. In conclusion, lobaplatin showed limited activity in this patient population.

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