A Pilot Study of Gemcitabine in Combination with Oxaliplatin and Vinorelbine in Patients with Metastatic Bladder Cancer

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Abstract. *Aim: To assess the safety and to obtain preliminary data on the efficacy of the three-drug combination chemotherapy with gemcitabine, oxaliplatin and vinorelbine in patients with metastatic bladder cancer. Patients and Methods: Patients with metastatic or locally unresectable advanced bladder cancer who had received either no or one previous systemic chemotherapy regimen were eligible. All patients received intravenous gemcitabine 700 mg/m^2 and vinorelbine 25 mg/m^2 on day 1, then intravenous oxaliplatin 85 mg/m^2 on day 2, every 14 days. Results: Fifteen patients were enrolled. Twelve patients were unfit for cisplatin. A median of five cycles per patient were delivered. The most common toxicities were neutropenia, nausea and vomiting, mucositis and diarrhoea. Two complete responses and one partial response were observed for an overall response rate of 23%. Median progression-free survival was 5.7 months and overall survival was 8.6 months. Conclusion: Although active and tolerable, the described three-drug combination chemotherapy showed no obvious incremental increase in efficacy compared with two-drug regimens. Further clinical trials are not recommended.*

Cisplatin-based chemotherapy is the mainstay of treatment for patients with advanced bladder cancer (ABC). The combination of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC regimen) or gemcitabine and cisplatin are currently considered as the most effective treatments. Nevertheless, in spite of overall response rates of around 50%, survival beyond five years is rare, with median survivals of about 14 months in randomised trials (1, 2). Moreover many patients are medically unfit to standard cisplatin-based chemotherapy, because of poor performance status or impaired renal function. Thus, new agents and chemotherapy combinations are needed for relapsed or unfit patients. Gemcitabine, oxaliplatin and vinorelbine, as single agents or as doublet chemotherapies, have showed promising antitumour activities with favourable toxicity profiles (3, 4). In a previous pilot study, it was reported that gemcitabine in combination with oxaliplatin (GO) was a safe therapy and had antitumour activity in pretreated and/or unfit patients with ABC (5). It was postulated that the addition of vinorelbine as a third drug to the GO doublet may enhance the antitumour activity, preserving the good tolerance. Therefore, in the present study a pilot trial of this triplet regimen (GON) was conducted to determine its toxicity and efficacy in patients with ABC.

Patients and Methods

Eligibility criteria required histologically proven advanced ABC, age ≥18 years, ECOG performance status of 0 to 3, measurable or assessable disease and adequate haematological (white blood cell count ≥3,000/μl, absolute neutrophil count (ANC) ≥1,500/μl, platelet count ≥100,000/μl) and hepatic (serum bilirubin level within normal limits, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2-fold the upper normal limit, unless liver metastases were present, in which case ≤5-fold the upper normal limit) functions. When serum creatinine concentration was ≥1.25 times the upper normal limit, the creatinine clearance had to be higher than 0.5 ml/s. Previous chemotherapy with gemcitabine was allowed as part of a neoadjuvant or adjuvant protocol but not for advanced ABC. Patients were included after informed consent.

Patients did not require hospitalisation for the treatment. On day one, gemcitabine (700 mg/m^2, 30-minute intravenous (*i.v.*) infusion) was delivered, followed by vinorelbine (25 mg/m^2, 20-minute *i.v.* infusion) and subsequently, on day two, oxaliplatin (85 mg/m^2, two-hour *i.v.* infusion). Chemotherapy was administered every two weeks without haematopoietic growth factor support. Baseline evaluation included a complete medical history, physical examination, complete blood count (CBC), blood chemistry including calcium, phosphorus, glucose, urea, creatinine, liver

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Table I. *Patient characteristics*.

Characteristic		%
Age (years)		
Median	69	
Range	42-84	
Histology		
Pure transitional-cell carcinoma	13	86
Urothelial and squamous	1	7
Pure adenocarcinoma	1	7
Previous treatments		
Cystectomy	7	47
Chemoradiotherapy	2	13
Radiotherapy	1	7
Chemotherapy	4	26
ECOG performance status		
0	1	7
1	9	60
2	4	26
3	1	7
Number of metastatic sites		
1	4	27
2	8	53
>2	3	20
Metastatic sites		
Bone	7	47
Lymph nodes	7	47
Lung	4	26
Pelvis	3	20
Peritoneum	2	13
Liver	1	7
Adrenal glands	1	7
Other	4	26
Prognostic groups (MSKCC classification)		
Good	3	20
Intermediate	11	73
Poor	1	7
Cisplatin eligibility		
Fit	3	20
Unfit	12	80
Performance status	8	
Renal function	4	
Biological parameters (median, range)		
Serum creatinine (μmol/l)	142 (60-670)	
LDH (UI/l)	345 (205-632)	
Haemoglobin (g/dl)	113 (79-134)	
Albumin (g/l)	36.6 (29.0-41.9)	

ECOG: Eastern Cooperative Oncology Group; MSKCC: Memorial Sloan Kettering Cancer Center; LDH: lactate dehydrogenase.

Table II. *Toxicity*.

Parameters	Cycle 1 (N=14)	Cycle 2 (N=14)	Cycle 3 (N=13)	Cycle 4 (N=10)
Neutropenia				
Grade 0	11	8	8	6
Grade 1	1	3	0	1
Grade 2	1	1	3	1
Grade 3	1	1	2	2
Grade 4	0	1	0	0
Neutropenic fever	0	1	0	0
Thrombopenia				
Grade 0	11	11	13	6
Grade 1	2	3	0	3
Grade 2	0	0	0	0
Grade 3	0	0	0	1
Grade 4	1	0	0	0
Anaemia				
Grade 0	6	3	1	3
Grade 1	4	6	7	2
Grade 2	4	5	5	5
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Nausea/Vomiting				
Grade 0	6	11	7	4
Grade 1	5	3	4	3
Grade 2	2	1	2	2
Grade 3	1	0	0	0
Grade 4	0	0	0	0
Mucositis				
Grade 0	14	15	12	8
Grade 1	0	0	2	0
Grade 2	0	0	0	1
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Diarrhoea				
Grade 0	11	12	9	6
Grade 1	2	3	2	2
Grade 2	1	0	2	1
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Neuropathy				
Grade 0	15	11	8	5
Grade 1	0	4	5	5
Grade 2	0	0	1	1
Grade 3	0	0	0	0
Grade 4	0	0	0	0

function test and electrolytes before registration. Radiological staging included computerised tomography scans of the chest, abdomen and pelvis, and a bone scan within four weeks before registration. Routine laboratory tests including electrolytes, creatinine, total protein, albumin, calcium, glucose, alkaline phosphatase, total and direct bilirubin, AST, ALT, and prothrombin time were evaluated on the first day of each course of chemotherapy. Additional CBCs was obtained weekly. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) scale (version 2) (6). In order to maintain the most efficient dose intensities, cycles were given provided that any NCI-CTC grade 2-4 non-haematological toxicity had ended and blood counts revealed ANC ≥0.500/μl and platelet count ≥100,000/μl. When patients did not fulfil these criteria on day 14, the cycles were delayed until recovery. A complete reassessment of all metastatic sites was planned every six cycles of treatment. Patients were assigned a response category based on RECIST criteria (7). Responding patients or

Table III. *Treatment delivery.*

	Cycle 1 (N=15)	Cycle 2 (N=14)	Cycle 3 (N=13)	Cycle 4 (N=10)
Number of cycles with dose reduction				
Gemcitabine	0	0	1 R	1 R
Oxaliplatin	0	0	0	1 C
Vinorelbine	0	1C	1 R, 1C	1R, 1C
Delayed cycles				
Number	0	2	5	3
Reason		Haematoma (1) Other (1)	Asthaenia (3) Neutropenia (1) Infection (1)	Asthaenia (1) Neutropenia (1) Other (1)

R: Dose reduction of 25%; C: dose cancelled.

Table IV. *Literature review of gemcitabine with oxaliplatin or vinorelbine in advanced bladder cancer.*

Chemotherapy	Number of patients	Cisplatin status	Objective response rate (%)	Progression-free survival (months)	Overall survival (months)	Reference
Gemcitabine 1000 mg/m^2 d1, d8 Vinorelbine 30 mg/m^2 d1, d8 Every 3 weeks	21	Unfit	48	5	15	4
Gemcitabine 1500 mg/m^2 d1 Oxaliplatin 85 mg/m^2 d1 Every 2 weeks	30	Fit	47	7	15	10
Gemcitabine 1200 mg/m^2 d1, d8 Oxaliplatin 100 mg/m^2 d8 Every 3 weeks	46	Unfit	48	5	6.5	11
Present study	15	Mostly unfit	23	6	9	

d: Day.

those with non-progressive lesions and improved symptoms would receive additional courses of chemotherapy at the discretion of the treating physician. After the completion of therapy, patients were monitored at two-month intervals until progression of disease. Follow-up evaluation was performed until the time of death.

The primary end point was to assess feasibility and toxicity. Secondary end points were response rate, overall survival (OS) and progression-free survival (PFS). OS was estimated by the Kaplan-Meier method, with time measured from the first day of treatment. OS was defined as the time from day one of treatment to death from any cause. PFS was defined as the time from day one of treatment to either disease progression or death from any cause.

Results

Patient characteristics. Fifteen patients (all male) were enrolled between March 2004 and April 2005 at the Montpellier Cancer Center (Table I). Thirteen patients had pure transitional-cell cancer. Most patients were respectively assigned into the intermediate prognostic group of the Memorial Sloan Kettering Cancer Center classification (8). Four patients had received previous chemotherapy as neoadjuvant or adjuvant treatment; GC in three patients and MVAC in one patient. The reason for offering treatment with the GON regimen as first-line

chemotherapy was poor performance status in four patients and impaired renal function (creatinine clearance <1 ml/s) in eight patients.

Toxicities and treatment administration. A total of 79 cycles of GON were delivered, with a median number of five cycles per patient (range, 1 to 10). One patient with liver metastasis died early of progressive disease after the first cycle of chemotherapy and was not assessed for toxicity. The remaining 14 patients discontinued treatment because of disease progression (eight patients) or treatment completion (six patients). On the whole, therapy was well tolerated. Haematological and non-haematological toxicities observed over the first four first cycles of the study are summarised in Table II. Among seven patients who had grade 3/4 neutropenia, only one experienced febrile neutropenia. Grade 4 thrombopenia also occurred in one patient and required platelet transfusion. No patient developed grade 3/4 anaemia. Non-haematological toxicities were also mild. Grade 3 nausea and vomiting was reported by one patient. The most common adverse events were grade 1/2 nausea/vomiting, mucositis, diarrhoea and peripheral neuropathy. Dose reductions were infrequent and the majority of patients tolerated the GON regimen at full dose intensity, as shown in Table III for the first four chemotherapy cycles. Overall a delay in chemotherapy administration or a dose reduction occurred in 19 cycles (24%) and 11 (14%) cycles, respectively. The major reasons were asthenia or haematological toxicities.

Tumour response and survival. Treatment efficacy was assessed in thirteen patients. Two complete responses and one partial response were observed for an overall response rate of 23% (95% confidence interval (CI): 8-38%). Disease was stable in two additional patients. A reduction in tumour markers was reported in four out of twelve patients with elevated markers at inclusion. All patients had died at the time of this analysis (median follow-up of four years). Median PFS was six months (95% CI: 2.7-16.3 months) and median OS was nine months (95% CI: 0.85-33.94 months).

Discussion

The present pilot study demonstrated the feasibility of the GON triplet in ABC. The same regimen has been recently assessed as first-line therapy in 39 patients with advanced non-small cell lung cancer (9). A similar toxicity profile was observed. No treatment-related death occurred. The most frequently reported treatment-related event was asthenia in 29 (74%) patients. Neuropathy occurred in 67% of patients but was usually mild with only 5 % of patients having grade 3-4 neuropathy. Febrile neutropenia occurred in two patients. A total of 34 cycles (13%) were delayed due to treatment-related adverse events. These results highlight the good tolerance profile of the GON triplet, in particular regarding haematological toxicity and potential life-threatening side-effects, which are an obvious concern given the fragile characteristics of ABC patients.

The efficacy of the GON triplet was rather disappointing since there was no obvious incremental increase compared to the results reported with two-drug regimens including gemcitabine and oxaliplatin or vinorelbine (Table IV). Objective response rates were twice as high in trials dealing with gemcitabine/vinorelbine or GO doublets. PFS was roughly similar in all studies, ranging from five to seven months. The difference in OS is likely to be related to prognostic factors since unfit patients for cisplatin usually portend a poor prognostic, with a median survival not exceeding twelve months in most series. Therefore, despite its good toxicity profile, the GON regimen is not recommended for future clinical trials. The French genitourinary tumour group (GETUG) is conducting a randomised phase II trial assessing the efficacy and toxicity of gemcitabine with or without oxaliplatin in unfit patients with ABC. Vinflunine, a novel microtubule inhibitor, recently received approval for second-line therapy in ABC (12). Its combination with gemcitabine or carboplatin may be of interest in unfit patients. Another promising approach will be the development of targeted therapies fitting with the understanding of ABC biology.

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