PERGAMON

European Journal of Cancer 37 (2001) 2212–2215

European Journal of Cancer

www.ejconline.com

A feasibility study of carboplatin with fixed dose of gemcitabine in 'unfit' patients with advanced bladder cancer

J. Bellmunt[a,*], R. de Wit[b], J. Albanell[a], J. Baselga[a]

[a]*University Hospital Vall d'Hebron, Barcelona, Spain*
[b]*Rotterdam Cancer Institute and University Hospital Rotterdam, The Netherlands*

Received 29 May 2001; received in revised form 21 June 2001; accepted 16 August 2001

Abstract

For the purpose of a subsequent phase II/III European Organization for Research and Treatment of Cancer (EORTC) trial, a gemcitabine/carboplatin feasibility study in 'unfit' patients with advanced urothelial cell cancer was conducted. Gemcitabine was given at 1000 mg/m^2 days 1 and 8 with carboplatin (area under the curve (AUC) 4.5 or 5) day 1 every 21 days. 16 patients were treated, median age 68 years (47–75) years, performance status (PS) 0/1/2 in 3/10/3 patients. Creatinine clearance was >1 ml/s in 3 patients, 0.5–1 ml/s in 9 and <0.5 ml/s in 4 patients. Half of the patients had visceral disease. Median number of cycles given was 4 (range 2–6), for a total of 69 cycles. The first 8 patients received 33 cycles using a carboplatin AUC of 5. World Health Organization (WHO) grade 3-4 toxicity was: haemoglobin 5 patients, platelets 6 patients, neutrophils 5 patients and febrile neutropenia 2 patients. In view of this haematological toxicity in subsequent patients, the carboplatin AUC was decreased to 4.5. At this dose level, 8 patients received 36 cycles. WHO grade 3-4 toxicity was: anaemia 1 patient, platelets 4 patients, neutrophils 4 patients with no febrile neutropenia. Thus, this dose level was regarded to be feasible. For the 16 evaluable patients, overall response rate was 44%, (1 complete response (CR), 6 partial response (PR)). In conclusion, the combination of gemcitabine with carboplatin at an AUC of 4.5 appears to be an active and well tolerated regimen with acceptable toxicity in this unfit patient population. Based on these data, a randomised trial in the framework of the EORTC-Genitourinary (GU) group of gemcitabine/carboplatin versus carboplatin/methotrexate/vinblastine (MCAVI) is ongoing.

Keywords: Bladder; Carboplatin; Gemcitabine; Unfit patient

1. Introduction

For more than a decade, methotrexate/vinblastine/doxorubicin/cisplatin (MVAC) has been the standard chemotherapy regimen in the treatment of urothelial cell cancer [1]. As cancer of the urinary tract occurs especially in elderly frail patients, many of whom have impaired renal function and/or cardiovascular disease, a considerable number of patients with metastatic disease do not qualify for cisplatin-based chemotherapy. In particular, the presence of impaired renal function, older age, poor performance status or underlying cardiac dysfunction in the so-called 'unfit' patient population has led to several modifications of the standard cisplatin-based programmes.

Because of its favourable toxicity profile, carboplatin has been substituted for cisplatin in unfit patients and especially in those patients with compromised renal function. The overall response rate in these carboplatin-substituted studies is approximately 50% (range 45–63%) and the median reported overall survival is approximately 9 months [2–6].

Gemcitabine, a novel nucleoside analogue, has recently been recognised as a new active agent in urothelial cell cancer. This drug was initially evaluated in an Italian phase I study conducted in 15 patients with metastatic bladder cancer [7]. The doses ranged from 875 to 1370 mg/m^2. The overall response rate was 27%. In a subsequent phase II trial in previously treated patients, a response rate of 28% was recorded [8]. Two recent trials that evaluated gemcitabine in previously untreated patients confirmed the high activity of this agent. Stadler and colleagues treated 40 patients with gemcitabine 1200 mg/m^2 weekly times 3, repeated every

* Corresponding author. Tel.: +34-93-274-6085; fax +34-93-274-6059.
E-mail address: bellmunt@hg.vhebron.es (J. Bellmunt).

0959-8049/01/$ - see front matter
PII: S0959-8049(01)00295-7

28 days, and reported an overall response rate of 28% [9]. Three complete responses (CRs) occurred in patients with liver metastasis. Moore and colleagues [10] reported an overall response rate of 24.3% (95% Confidence Interval (CI): 12–41%) in 37 assessable patients. In addition to its single agent activity in bladder cancer, gemcitabine is generally well tolerated. Furthermore, cisplatin/gemcitabine-based regimens are promising in advanced bladder cancer [11,12] and provide similar activity and less toxicity than MVAC [12].

Hence, the combination of carboplatin and gemcitabine appears an attractive notion in patients with impaired World Health Organization (WHO)-performance status and/or impaired renal function. A feasibility study of the combination of gemcitabine/carboplatin in this particular patient population was conducted for the purpose of a subsequent phase II/III randomised trial in the framework of the European Organization for Research and Treatment of Cancer-Genitourinary (EORTC-GU) Group.

2. Patients and methods

2.1. Patients

Eligibility criteria were: histologically-proven urothelial cell cancer of the urinary tract, distant metastases or pelvic disease not amenable to locoregional treatment and unfit for cisplatin-based combination chemotherapy for reasons of WHO performance status (PS) 2 and/or creatinine clearance below 1 ml/s. Patients had adequate bone marrow reserve, with an absolute neutrophil count (ANC) $>1500\times10^6$ cells/l and platelet count $>100\times10^9$ cells/l, and adequate hepatic and renal function (serum bilirubin level <25.65 μmol/l, alkaline phosphatase and serum glutamic oxaloacetic transaminase (AST) less than 2.5 times the upper limit of normal levels. Patients were allowed to have received previous chemotherapy for metastatic disease or in the adjuvant/neoadjuvant setting. Patients were ineligible if they had poor medical risk (WHO-PS 3 or 4). No measurable disease was required for study entry. All these patients were ineligible for standard cisplatin-based chemotherapy and gave consent to receive treatment with the carboplatin/gemcitabine combination.

2.2. Pretreatment and follow-up studies

Pretreatment assessment was performed within 3 weeks before initiation of therapy, and consisted of a complete history and physical examination, evaluation of the tumour burden either by physical examination or by appropriate imaging studies (chest-X-rays, abdomen and pelvis computed tomography scan, radionuclide bone scan and plain radiographs for bone lesions) and a complete blood count, serum chemistry and creatinine clearance. Patients' weight and WHO performance status were also recorded. Patients underwent weekly complete blood cell counts and serum chemistries were scheduled at the start of each treatment cycle. Tumour measurements were performed every two cycles of treatment or before if clinically indicated.

2.3. Treatment plan

Gemcitabine was given at a fixed dose of 1000 mg/m^2, days 1 and day 8 (in a 30-min infusion) in a 21-day schedule. Carboplatin was administered on day 1 (in a 30-min infusion) following gemcitabine at a dose of area under the curve (AUC) of 5 (dose level 1) [13]. This dose regimen had been shown feasible in non-selected patients with solid tumours. Since the targeted AUC of 5 was considered too toxic, a lower carboplatin dose was employed in a second cohort of patients, with a targeted carboplatin AUC of 4.5 (dose level 2). Dose modifications at day 8 and at rescheduled treatment day 1 are given in Table 1. In cases of neutropenic fever or grade 4 thrombocytopenia, treatment was resumed at 75% of both drugs upon recovery. If a patient required more than 3 weeks for haematological recovery, the patient was taken off study. Response was assessed accordingly to WHO criteria. Patients were evaluable for response if they had completed two cycles of chemotherapy, unless there was rapid early progression. All patients who had received at least one dose of chemotherapy were evaluable for toxicity, which was graded according to National Cancer Institute-Common Toxicity Criteria (NCI-CTC) criteria.

3. Results

3.1. Patient characteristics

Patient characteristics are shown in Table 2. From June 1997 to July 1998, a total of 16 patients were included in the study. The median age was 68 years

Table 1
Dose modifications

Neutrophils ($\times10^9$ cells/l)		Platelets ($\times10^9$ cells/l)	% dose of gemcitabine	% dose of carboplatin
Day 1				
$\geqslant1.5$	and	>100	100	100
<1.5	or	<100*	Withhold	Withhold
Day 8				
>1.5	and	>100	100	
1–1.5	or	>100	100	
0.5–0.9	or	50–99	50	
<0.5	or	<50	Withhold	

* If >75 recycle at 25% dose if no recovery after 1 week delay.

(range 47–75 years). The reasons for offering treatment with this carboplatin/gemcitabine combination were poor WHO-PS in 3 patients (PS 2) and creatinine clearance <1 ml/s in 13 patients. 3 patients had received prior neoadjuvant/adjunvant chemotherapy and 2 patients had received prior chemotherapy for metastatic disease.

3.2. Toxicity

The median number of cycles given was 4 (range 2–6), for a total of 69 cycles. All patients were evaluable for toxicity. The toxicity data are shown in Table 3. The first 8 patients received a total of 33 cycles at the scheduled dose level 1 of gemcitabine and carboplatin at AUC 5. Haematological toxicity was clinically significant, with grade 3/4 anaemia in 5 patients, thrombocytopenia in 6 and neutropenia in 5 of the 8 patients treated at this dose level. 2 patients were admitted for febrile neutropenia. Day 8 dose reduction was required in 2 patients and a 1 week delay (ANC $<1500\times10^6$ cells/l) in 3 patients. Granulocyte-colony stimulating factor (G-CSF) was administered to 2 patients. There were no episodes of grade 3-4 non-haematological toxicities.

In view of the dose-limiting myelotoxicity observed at dose level 1, comprising 4 patients with grade 4 thrombocytopenia, all of whom needed platelet and red blood cell transfusions, and 2 patients with febrile neutropenia, it was decided to decrease the dose of carboplatin to an AUC of 4.5 in the next cohort of patients (level 2).

8 additional patients were treated using dose level 2, where the dose of gemcitabine was the same dose as that administered in dose level 1 and the dose of carboplatin was reduced from an AUC of 5 to an AUC of 4.5. These patients received a total of 36 cycles. At this dose level, there was less severe thrombocytopenia, requiring platelet support in one patient in one cycle, and no grade 4 neutropenia or neutropenic fever (Table 3). Day 8 dose reduction was needed in 4 patients and a 1 week delay (ANC $<1500\times10^6$ cells/l) in 2 patients, with no G-CSF requirements. There was no grade $\geqslant3$ non-haematological toxicity.

3.3. Activity

Although the response evaluation was not an objective of this study, we analysed the antitumour activity observed with carboplatin/gemcitabine in these unfit patients. For the purpose of the response evaluation, the 16 patients were grouped together; 1 patient with a soft-tissue pelvic mass achieved a CR (6%), for a response duration of 17+ months, 6 patients achieved a partial response (PR) (38%), with response durations up to 18+ months, including 1 patient with a PR in liver metastases for more than 12 months. The overall response rate was 44%. 6 patients had stable disease and 3 patients had progressive disease at evaluation.

Table 2
Patient characteristics

Patients registered/evaluable	16/16
Male/female	12/4
Age (years): median (range)	68 (47–55)
Performance status 0/1/2	3/10/3
Creatinine clearance	
<1 ml/s	3
0.5–1 ml/s	9
>0.5 ml/s	4
Site(s) of disease	
Locally advanced only	1
Nodal/soft tissue only/pelvic mass	7
Liver	3
Bone	1
Lung	2
Suprarenal	1
Peritoneal	1

Table 3
Worst toxicities per patient (grades 3 and 4)

	Level 1 (AUC 5)		Level 2 (AUC 4.5)	
	8 patients		8 patients	
	Grade 3	Grade 4	Grade 3	Grade 4
Haemoglobin	2	3	0	1
Platelets	2	4	2	2 (d15)
Neutrophils	3	2 (d8 and d15)	4	0 (d8 and d15)
Febrile neutropenia		2		0
Infection		0		0
N & V		0		0
Mucositis		0		0
Neurotoxicity		0		0
Asthenia		0		0

AUC, area under the curve; N & V, nausea and vomiting; d, day.

4. Discussion

The EORTC-GU Group has recently defined separate investigational strategies in urothelial cell cancer for 'fit' versus 'unfit' patients. In patients unfit for cisplatin-based chemotherapy, a randomised study of gemcitabine/carboplatin versus carboplatin-MV was planned. To define a recommended dose of gemcitabine/carboplatin for this randomised trial, we conducted the present feasibility study in patients 'unfit' for cisplatin chemotherapy.

Carboplatin-based regimens are widely used as an alternative to cisplatin-based regimens in unfit patients. The pooled single agent activity of carboplatin in metastatic urothelial cell cancer is 12% (range 6–21%), and appears slightly inferior to single agent cisplatin [2].

When carboplatin is combined with methotrexate and vinblastine (Carbo-MV and MCAVI), response rates increase up to 30–40%. Two small randomised trials have suggested that cisplatin-based regimens are superior to carboplatin-based regimens [14,15]. However, it needs to be considered that carboplatin is currently being combined with new and highly active drugs that could overcome its reported inferior activity.

In this study, the regimen of carboplatin/gemcitabine resulted in 7 (44%) objective responses out of 16 unfit patients treated, which we consider as promising given that the majority of patients had PS > 1 and half had visceral disease, the two most well recognised adverse prognostic factors for chemotherapy benefit (Ref. [16] and Bellmunt and colleagues, data not shown) and, additionally, 5 patients had received prior chemotherapy.

When we combined gemcitabine with carboplatin for an AUC of 5 (dose level 1), dose-limiting myelotoxicity was observed and we decided to decrease the dose of carboplatin to an AUC of 4.5 in the next cohort of patients (level 2). At this dose level, carboplatin/gemcitabine was well tolerated and patients had a reduced myelotoxicity, indicating that it is a feasible regimen in cisplatin unfit patients. This schedule is recommended for further investigation in the multicentre phase II/III setting.

In view of the studies where cisplatin/gemcitabine is increasingly used for fit patients with bladder cancer, it was a logical step to combine carboplatin/gemcitabine for 'unfit' patients (current study and Ref. [17]). Because of the high response rates in phase II trials of cisplatin/gemcitabine [18–20], a randomised phase III trial comparing MVAC with cisplatin/gemcitabine has also been conducted. This study showed that the cisplatin/gemcitabine regimen has a similar efficacy to MVAC and is less toxic [12]. Because in fit patients with good WHO-PS (0 or 1) and preserved renal function the primary goal is to improve the efficacy of chemotherapy—aiming for long-term disease-free survival—a phase III study of the triplet of gemcitabine/cisplatin/paclitaxel [11] versus gemcitabine/cisplatin [12] has been launched as a collaborative study of the EORTC-GU group, the Spanish Bladder Cancer Study Group (SOGUG), South West Oncology Group (SWOG), National Cancer Institute Canada (NCIC) and the French Cooperative Group (GETUG).

The planned phase II/III study in cisplatin 'unfit' patients has already started as a randomised phase II study, designed to simultaneously test the efficacy and toxicity of the two regimens, and will extend into a phase III trial if the prerequisites of a minimum response rate of 30% and a severe acute toxicity rate of less than 20% are met. If the study is extended into phase III, the main objective will be to detect an increase of 50% in the median survival in the gemcitabine/carboplatin arm (from 9 to 13.5 months), which will require a total of 225 patients to be accrued.

References

1. Roth B. Chemotherapy for advanced bladder cancer. *Semin Oncol* 1996, **23**, 633–644.
2. de Wit R, Tesselaar M, Kok TC, *et al*. Randomized phase II trial of carboplatin and iproplatin in advanced urothelial cancer. *Eur J Cancer* 1991, **27**, 1383–1385.
3. Klocker J, Pont J, Schumer J, Pruger J, Kienzer H. Carboplatin, methotrexate and vinblastine (Carbo-MV) for advanced urothelial cancer. *Am J Clin Oncol* 1991, **14**, 328–330.
4. Bellmunt J, Albanell J, Gallego O, *et al*. Carboplatin, methotrexate, and vinblastine in patients with bladder cancer who were ineligible for cisplatin-based chemotherapy. *Cancer* 1992, **70**, 1974–1979.
5. Waxman J, Barton C. Carboplatin-based chemotherapy for bladder cancer. *Cancer Treat Rev* 1993, **18**, 21–25.
6. Small EJ, Fippin LJ, Ernest ML, Carroll PR. A carboplatin-based regimen for the treatment of patients with advanced transitional cell carcinoma of the urothelium. *Cancer* 1996, **78**, 1775–1780.
7. Pollera CF, Ceribelli A, Crecco M, Calabresi F. Weekly gemcitabine in advanced bladder cancer. A preliminary report from a phase I study. *Annals Oncol* 1994, **5**, 182–184.
8. Lorusso V, Pollera CF, Antimi M, *et al*. A phase II study of gemcitabine in patients with transitional cell carcinoma of the urinary tract previously treated with platinum. Italian Co-operative Group on Bladder Cancer. *Eur J Cancer* 1998, **34**, 1208–1212.
9. Stadler WM, Kuzel T, Roth B, Raghavan D, Dorr FA. Phase II study of single-agent gemcitabine in previously untreated patients with metastatic urothelial cancer. *J Clin Oncol* 1997, **15**, 3394–3398.
10. Moore MJ, Tannock IF, Ernst DS, Huan S, Murray N. Gemcitabine: a promising new agent in the treatment of advanced urothelial cancer. *J Clin Oncol* 1997, **15**, 3441–3445.
11. Bellmunt J, Guillem V, Paz-Ares L, *et al*. A phase I-II study of paclitaxel, cisplatin and gemcitabine in advanced transitional cell carcinoma of the urothelium. *J Clin Oncol* 2000, **18**, 3247–3255.
12. von der Maase H, Hansen SW, Roberts JT, *et al*. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. *J Clin Oncol* 2000, **17**, 3068–3077.
13. Calvert AH, Newell DR, Gumbrell LA, *et al*. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989, **7**, 1748–1756.
14. Petrioli R, Frediani B, Manganelli A, *et al*. Comparison between a cisplatin-containing regimen and a carboplatin-containing regimen for recurrent or metastatic bladder cancer patients. A randomized phase II study. *Cancer* 1996, **77**, 344–351.
15. Bellmunt J, Ribas A, Eres N, *et al*. Carboplatin-based versus cisplatin-based chemotherapy in the treatment of surgically incurable advanced bladder carcinoma. *Cancer* 1997, **80**, 1966–1972.
16. Bajorin DF, Dodd PM, Mazumdar M, *et al*. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. *J Clin Oncol* 1999, **17**, 3173–3181.
17. Carles J, Nogue M, Domenech M, *et al*. Carboplatin-gemcitabine treatment of patients with transitional cell carcinoma of the bladder and impaired renal function. *Oncology* 2000, **59**, 24–27.
18. Kaufman D, Stadler W, Carducci M, *et al*. Gemcitabine (GEM) plus cisplatin (CDDP) in metastatic transitional cell carcinoma (TCC): Final results of a phase II study. *Proc Am Soc Clin Oncol* 1998, **17**, 320a (abstr 1235).
19. Moore MJ, Winquist E, Murray N, *et al*. Gemcitabine plus cisplatin, an active regimen in advanced urothelial cancer: a phase II trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1999, **17**, 2876–2880.
20. von der Maase H, Andersen L, Crino L, Weinknecht S, Dogliotti L. Weekly gemcitabine and cisplatin combination therapy in patients with transitional cell carcinoma of the urothelium. *Ann Oncol* 1999, **10**, 1461–1465.