Combination of gemcitabine and oxaliplatin in urothelial cancer patients with severe renal or cardiac comorbidities

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Clinical trials in urothelial cancer exclude a large population of patients. An observational study evaluated the behavior of frail patients not eligible for cisplatin- or carboplatin-based regimens. Urothelial cancer patients requiring chemotherapy with either chronic renal failure (creatinine clearance <60 ml/min), and/or performance status (PS) ≥ 2 and/or cardiac dysfunction were prospectively observed. The treatment associated gemcitabine 1200 mg/m^2 and oxaliplatin 85 mg/m^2, bimonthly (GO). Over 2 years, 31 of 45 (69%) patients with urothelial cancer requiring chemotherapy were not eligible for cisplatin- or carboplatin-based chemotherapy. Sixteen (52%) had a PS ≥ 2, 23 (74%) had creatinine clearance <60 ml/min, and 20 (65%) had an underlying cardiopathy. A total of 178 cycles of GO were administered (median 6 per patient, range 2–12). No aggravation of renal or cardiac status was noted. Acute grade 3 and 4 neutropenia and thrombocytopenia were observed in 16 and 13% of patients, respectively, with one febrile neutropenia. The median progression-free and overall survival values were 4.2 and 9.5 months, respectively. The majority of urothelial cancer patients have severe renal or cardiac comorbidities, and we conclude that in this subset of patients the combination of gemcitabine and oxaliplatin is well tolerated, and its clinical activity warrants further evaluation. *Anti-Cancer Drugs* **16:1017–1021**

Anti-Cancer Drugs 2005, **16:**1017–1021

Keywords: cardiopathy, gemcitabine, oxaliplatin, renal failure, urothelial cancer, unfit

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Received 16 October 2004 **Revised form accepted** 23 June 2005

Introduction

Urothelial cancers of the bladder and urinary tract are the fifth most common causes of cancer deaths in Europe. Their incidence is increasing, estimated at 280 000 cases per year [1]. Patients with urothelial cancer are usually elderly patients (median age at diagnosis 69 years in men and 71 years in women [2]) with tobacco-related diseases (cardiovascular and respiratory comorbidities, considered as a risk for forced hydration), reduced renal function (due to age, previous surgery and cancer) and/or poor WHO performance status (PS). These patients have been under-represented in clinical trials [3,4] and we are lacking information on the tolerability of chemotherapy in the presence of a severe comorbidity. Hence, evidence-based treatment decisions are difficult to make for this subset of patients.

The introduction of systemic combination chemotherapy has improved the prognosis of metastatic or inoperable patients. Nevertheless, chemotherapy offers only a modest survival benefit [3,5] and metastatic disease is incurable, with only a small number of patients obtaining long-term disease control.

For more than a decade, combination chemotherapy for advanced urothelial cancer has been essentially based upon the most active single agents, cisplatin and methotrexate. The MVAC combination (methotrexate, vinblastine, doxorubicin and cisplatin) provided response rates of more than 50%, median survival times of 12–14 months and 3-year survival of 20–25% [6]. No chemotherapy regimen is clearly superior to MVAC in terms of survival. However, MVAC-induced toxicities can be severe, with mucositis, neutropenic fever and 3–5% toxic deaths in selected patients. The risk of neutropenic fever may be reduced by the prophylactic use of granulocyte colony-stimulating factor (G-CSF) [4] or by replacing the MVAC regimen by another less-toxic combination, most often a doublet [3,7–9]. Recently, a multicenter phase III study indicated that chemotherapy with gemcitabine plus cisplatin (GC) was associated with similar efficacy, but with less toxicity, than MVAC [3]. Nevertheless, these clinical trials included patients selected for good PS, age <75 years, no or mild reduction of renal function and no severe comorbidity. In particular, no data are available concerning the tolerability of these treatments in patients with cardiopathy. Indeed, PS is not only an

0959-4973

independent significant factor for survival, but is also predictive for chemotherapy toxicity [10–12]. The GC regimen has also substantial limitations, especially the nephrotoxicity of cisplatin, and the requirement for forced hydration in a population particularly sensitive to volemic changes and with already altered renal function. Renal failure is not only a problem for cisplatin, but also for carboplatin, since its elimination is dependent on glomerular filtration and the exact evaluation of creatinine clearance is difficult in the elderly. As recently pointed out, not only creatininemia, but also the popular creatinine clearance calculation based on the Cockroft–Gault formula are insufficient to precisely evaluate renal function in elderly cancer patients [13] and thus adjust carboplatin dosage.

Oxaliplatin is known to have a broad spectrum of clinical activity, which not only reflects the anti-tumoral activity of cisplatin [14–16], but is even wider with well-demonstrated clinical activity in colorectal cancer patients [17]. Interestingly, oxaliplatin is not nephrotoxic, has low hematotoxicity [14–17] and its toxicity is not dependent on creatinine clearance [18]. We therefore pragmatically decided to administrate oxaliplatin to urothelial cancer patients considered at high risk for either cisplatin renal toxicity or carboplatin hematologic toxicity. The combination of gemcitabine and oxaliplatin (GO) was found to be synergistic *in vitro* [19], and its clinical toxicity has already been reported as mild in phase I and II studies in other cancer patient populations using an every-other-week schedule [14,15,20].

We present the results of the treatment of 31 consecutive patients, having both indication for chemotherapy and at least one characteristic rendering them ineligible for cisplatin or carboplatin over a period of 30 months in a single institution. We show that the majority of our patients were not eligible for cisplatin or carboplatin on the basis of evidence-based data in clinical trials, and despite a high-risk profile for toxicity they could tolerate and benefit from the GO regimen.

Patients and methods

Patients with a diagnosis of urothelial cancer were discussed by the multidisciplinary staff of urologic oncology of Cochin hospital. Gemcitabine was given at a fixed dose of 1200 mg/m^2 as a 30-min infusion with oxaliplatin 85 mg/m^2 as a 2-h infusion the same day, every 14 days.

Anti-emetic prophylaxis consisted of 5-HT$_3$ receptor antagonist plus methylprednisolone on day 1.

Chemotherapy was administered if, on day 1 of treatment, the absolute neutrophil count (ANC) was $> 1500 \times 10^6$ cells/l and the platelet count was $> 100 \times 10^9$ cells/l; if counts were not adequate, then therapy was delayed until recovery.

The doses of both drugs were administered at 75% of the planned dose if any of the following toxicities occurred: neutropenic fever with hospitalization and/or i.v. antibiotics, grade 3 (associated with bleeding) or 4 thrombocytopenia and any grade 3 non-hematologic toxicity (except nausea/emesis).

Tumor evaluation was performed every 4 cycles of treatment, or before if clinically indicated, according to WHO criteria. Toxicity was assessed according to the WHO criteria [21] and oxaliplatin-specific scale [22]. Clinical benefit was defined as a 50% decrease in analgesic drugs requirements or improvement of PS.

Results

Patient characteristics

During the period from January 2002 to May 2004, 493 consecutive patients were diagnosed with an invasive or superficial urothelial carcinoma. Chemotherapy for metastatic disease was indicated for 44 patients. Amongst them, two were included in a phase II clinical trial and another 11 were treated with either cisplatin or carboplatin combined with gemcitabine. Patients were unfit for the phase II study because of either reduction of renal function (creatinine clearance < 60 ml/min) or any severe comorbidity.

Sixty-nine percent of them (31 of 44) were considered too fragile to receive either cisplatin or carboplatin, and were pragmatically treated with the combination of oxaliplatin and gemcitabine.

The characteristics of the 31 patients are shown in Table 1. The median age was 71 years (range 45–84 years). The reasons for offering treatment with GO were: poor WHO PS in 16 patients (52%), creatinine clearance < 60 ml/min in 23 patients (74%) and both reasons in 10 patients (32%). Twenty patients had a severe cardiac comorbidity (requiring two or more cardiotropic drugs). Patient comorbidities are listed in Table 2.

Regarding prognostic factors for time to progressive disease (TTP) [23,24], six patients had high alkaline phosphatases and eight had visceral metastases. Two patients had received prior chemotherapy for metastatic disease and three patients had received radiation for painful bone metastasis. Since altered nutritional and inflammatory status correlates with increased risk of severe hematologic toxicity [12], it is of interest to point out that 20 patients had C-reactive protein (CRP) levels > 5 mg/l and 18 patients had pre-albumin levels of < 0.25 mg/l.

Table 1 Patient characteristics

	N
Patients	31
Gender (M/F)	26/5
Age (years) [median (range)]	71 (45–84)
PS 0/1/2/3	2/13/13/3
BMI (kg/m^2) >25	12
High alkaline phosphatases (above upper limit of normal)	6
Sites of disease	
locally advanced only	4
lymph nodes	16
pelvis	7
bone	8
lung	3
liver	4
suprarenal	1
No. of metastatic sites	
1	12
2	10
≥3	5
Patients with measurable disease	10

PS, WHO performance status.

Table 2 Patient comorbidities

	No. patients (*N*=31)
Creatinine clearance (ml/min)	
>60	6
30–60	14
<30	11
Cardiac comorbidities	
hypertension	12
arrhythmia with auricular fibrillation	5
angina pectoris	5
myocardial infarction	4
Concomitant cardiotropic treatments	
β blockers	9
calcium blockers	6
angiotensine-converting enzyme inhibitors	8
angiotensin II receptors antagonists	1
amiodarone	3
digoxin	1
Other concomitant treatments	
acetylsalicylic acid	10
oral anticoagulants	3
statins	7
Diabetes mellitus	5
Baseline hemoglobin <10 g/dl	2

Toxicity

The median number of cycles given per patient was 6 (range 2–12), for a total of 178 cycles. The toxicity results are presented in Table 3. One patient was hospitalized for febrile neutropenia. A 1-week delay was required in six patients for neutropenia (ANC $< 1500 \times 10^6$ cells/l). No episode of grade 3–4 non-hematologic toxicity was noticed, except one grade 3 cumulative peripheral neuropathy. No toxic death occurred. In all patients, underlying renal or cardiac function impairment remained stable and no acute decompensation requiring medical intervention was noticed.

Activity

We analyzed the anti-tumor activity observed with the GO combination in this frail patient population. The median follow-up was 11 months (range 2–28). At the time of analysis, 13 patients were still alive.

Table 3 Acute hematologic toxicities per patient and medical resource assessment (31 patients; 178 cycles)

	Grade 3 toxicity	Grade 4 toxicity	Hospitalization	Transfusion
Hematologic				
anemia	2	1	–	–
thrombocytopenia	2	1	1	3 platelet units, 8 red blood cell units
neutropenia	5	–	–	–
neutropenic fever	1	1	–	
Non-hematologic				
peripheral neuropathy	1	–	–	–

Table 4 Characteristics of responding patients

Age (years)	Creatinine clearance (ml/min)	PS	Sites of metastatic disease	No. cycles	Survival (months)
75	54	2	nodes, liver	12	28+
83	42	1	nodes, lung	10	10
55	90	1	nodes	4	8
75	55	1	nodes	10	15
63	88	2	nodes, bone	8	10
64	47	1	nodes	6	3+

PS, WHO performance status.

Ten patients had measurable disease. The median TTP was 4.2 months (range 2–12). The median overall survival was 9.5 months (range 1.5–28). Among 10 patients with measurable disease, the median duration of response was 4 months (range 2–16).

No patient achieved a complete response. Six patients achieved a partial response, with response durations up to 16 months, including one patient with liver metastases responding for 12 months. The characteristics of the patients who experienced a tumor response are detailed in Table 4.

Six patients (19.4%) experienced progressive disease at first evaluation. Amongst 15 patients with pain, 12 (80%) had clinical benefit. Seven patients had an improvement of PS.

Discussion

This single-institution observational study of the combination of gemcitabine plus oxaliplatin in advanced or metastatic urothelial cancer with severe comorbidities shows that in this patient population, chemotherapy may represent effective palliation and that the GO regimen has a favorable toxicity profile. This study was based on the discrepancy between the patient population described in the literature and our daily patient population.

Table 5 Patient baseline, overall efficacy and safety summary in recent studies

	Results of studies					
	MVAC [3]	GC [3]	PCa [7]	GCa [8]	GE [9]	GO [this study]
No. patients	202	203	29	17	38	31
PS ≥ 2	0	0	2	5	9	16
Median creatinine clearance (ml/min)	>60	>60	61	56	54	55
Cardiac comorbidity	0	0	NR	NR	NR	20 (65%)
Median age (years)	63.0	63.0	68.0	69	71.5	71
Median TTP (months)	7.4	7.4	4	4.6	4.8	4.2+
Median survival (months)	14.8	13.8	9	10.5	8.0	9.5+
Response rate (%)	46	49	20.7	58.8	39.5	60[a]
Thrombocytopenia (%)						
grade 3	7.7	28.5	10.3	47	6.5	13
grade 4	12.9	28.5				0
Neutropenia (%)						
grade 3	17.1	41.2	38	70	22.4	16
grade 4	65.2	29.9				0
Neutropenic fever (%)	*6*[b]	*1*[b]	NR	0	5.3	3

Abbreviations: GC, gemcitabine plus cisplatin; PCa, paclitaxel plus carboplatin; GCa, gemcitabine plus carboplatin; GE, gemcitabine plus epirubicin; GO, gemcitabine plus oxaliplatin; NR, not reported.
[a]Six of 10 patients with measurable disease.
[b]Italic = percentage of cycles (other values = percentage of patients).

Indeed, as shown in Table 1, the majority of the patients justifying chemotherapy did not share the patient characteristics reported in phase II and III clinical trials in urothelial cancer.

A reduced incidence of hematologic and non-hematologic toxicities was reported with the GC combination compared with MVAC [3], although only patients with a good PS and normal renal function were included. With the GC regimen, grade 3–4 neutropenia was observed in 71% of patients, anemia in 27%, thrombocytopenia in 57%, mucositis in 22% and neutropenic fever in 2%. Still, 1% of toxic deaths occurred.

The toxicities of the standard regimens is manageable, but only in a very selected patient population [3,4]. In this regard, one phase II trial of docetaxel plus cisplatin was quite unique since PS 3 patients and patients > 75 years were included [25]. In a recent phase III clinical trial, its efficacy and toxicity were compared to MVAC plus G-CSF. The doublet combination appeared less toxic than the MVAC regimen. In this study, patients should be ≤ 75, with adequate creatinine clearance (> 50 ml/min) and no moderate or severe cardiac failure [4].

In view of studies assessing the role of cisplatin plus gemcitabine in 'fit' patients with urothelial cancer, it appeared to us a logical step to assess the efficacy and safety of the combination of gemcitabine plus oxaliplatin in urothelial cancer patients who were 'unfit' for cisplatin-based regimens.

Of note, the so-called 'unfit' population is very different from one study to another, especially regarding median age or PS status (see Table 5). The coexistence of cardiac function impairment was rarely described, whereas it is a risk factor for chemotherapy tolerability in cisplatin-based regimens (because of forced hydration) and epirubicin-based regimens. In addition, anemia induced by most cytotoxics, in particular carboplatin, may alter myocardial oxygenation and cardiac function.

The combination of paclitaxel and carboplatin was evaluated by the Southwest Oncology Group [7] in 29 patients (only two patients had a PS of 2). Significant neurologic and hematologic toxicities were reported, with a low response rate (20.7%). In a study published in 2002 [9], a combination of gemcitabine and epirubicin was administered in 38 'unfit' patients; among them nine had a PS of 2 (see Table 5).

Hence, the optimal treatment of 'unfit' patients remains to be defined. Culine *et al.* [20] recently published a pilot study of gemcitabine and oxaliplatin in urothelial cancer. Twenty patients received bimonthly cycles of gemcitabine 1500 mg/m^2 and oxaliplatin 85 mg/m^2, and a good toxicity profile was observed, apart an early death related to a myocardial infarction in one patient.

The main prognostic factors for poor survival in advanced urothelial cancer are altered PS and the presence of visceral disease (mainly liver metastases) [23]. The median survival in a phase II trial with $> 40\%$ of patients having these two unfavorable characteristics is expected to be 10 months with standard therapy [23,24].

In our population, with more than 50% with PS ≥ 2 and 20% with visceral metastases, the median TTP was 4.2 months and overall survival was 9.5 months. Only six patients (19%) experienced early progression. These

results are similar to previous studies including 'unfit' patients (Table 5).

Our study indicates a favorable risk–benefit ratio of the GO regimen in 'unfit' patients. Since a clear limitation of this report is the relatively small number of patients, a multicenter phase III would be warranted to further evaluate this combination regimen.

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