original article

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Gemcitabine and oxaliplatin combination: a multicenter phase II trial in unfit patients with locally advanced or metastatic urothelial cancer

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Background: Up to 50% of patients with bladder cancer cannot be treated with cisplatin because they are considered unfit due to poor renal function. Gemcitabine and oxaliplatin are active, nonnephrotoxic therapies with nonoverlapping toxicity profiles that provide an alternative therapy for this group of patients.
Patients and methods: In a multicenter study, patients received gemcitabine 1200 mg/m^2 on days 1 and 8 and oxaliplatin 100 mg/m^2 on day 8 every 21 days. Eligible criteria were creatinine clearance >30 ml/min and/or Eastern Cooperative Oncology Group (ECOG) performance status of two or less.
Results: Forty-six patients were assessable for response and toxicity. Median age was 69 years (range 52–85), median ECOG two (range 0–2). Median number of metastatic sites was 2 (range 1–6). Median creatinine clearance was 50.73 ml/min (range 30–87). A total of 187 cycles were given with a median of 5 (range 1–6). Hematological toxicity was mild with grade 3–4 peripherical neuropathy occurring in 4% of patients. Overall response rate was 48% (three complete response, 19 partial response, seven stable disease and 17 progressive disease). Median time to disease progression was 5 months.
Conclusion: Gemcitabine–oxaliplatin is an active and tolerable combination with response rate that merits further study in patients with impaired renal function but good performance status.
Key words: bladder cancer, gemcitabine, oxaliplatin, unfit patients

introduction

The standard chemotherapy for metastatic or locally advanced transitional cell carcinoma of the urothelium during the last 15 years has been a combination of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) which has an overall response rate of between 40% and 72%. Although the combination is superior to cisplatin alone or other cisplatin-based combinations [1, 2], the median survival time is only 13 months. Moreover, MVAC is toxic with a treatment-related death rate of up to 3% and a neutropenic sepsis rate of 25%. Because of all theses reasons MVAC is not recommended for patients who are elderly, and those who have impaired performance status (PS) or renal function.

Gemcitabine (Eli Lilly, Alcobendas, Spain) is a nucleoside analogue that has shown good activity in transitional cell carcinoma (TCC) of the urothelium [3, 4] and is well tolerated, providing an ideal candidate as an alternative therapy for combination with other active agents for elderly and unfit patients. A phase III trial comparing gemcitabine and cisplatin with MVAC showed no significant differences in overall survival (OS) or response rates [5]. The cisplatin and gemcitabine arm had significantly better safety profile and tolerability, prompting a call for this combination to become the standard of care for these patients.

Oxaliplatin (Sanofi-Aventis, Barcelona, Spain) is a water-soluble derivative of 1,2-diamino-cyclohexane platinum that has several advantages over cisplatin and carboplatin in relation to activity and toxicity. One of the main advantages is that it can be administered to patients with renal impairment [6]. Oxaliplatin is active against cell lines resistant to cisplatin and one of the great advantage is that it could be administered in patients with renal impairement [6]. This study was designed to examine the efficacy and toxicity of oxaliplatin in combination with gemcitabine (Gemox) in patients with metastatic TCC of

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the urothelium who are considered unfit for standard treatment due to poor renal function.

patients and methods

patients

This was a multicenter phase II study of patients who had locally advanced or metastatic transitional cell carcinoma of the bladder, ureter or renal pelvis. Patients were required to have histologically or cytologically proven TCC and measurable disease. Prior cytotoxic treatment in the adjuvant setting was permitted if the treatment had been completed at least 6 months before enrollment in the study. Prior radiotherapy was permitted but had to have been completed at least 6 weeks before enrollment. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) of two or less and have adequate bone marrow reserve (white blood cell count $>3.5 \times 10^9$/l, platelets $>100 \times 10^9$/l and hemoglobin >10 g/dl), and a creatinine clearance of >30 ml/min calculated by the Cockcroft method [7]. Exclusion criteria included known central nervous system metastases, pregnancy and prior malignancy (except *in situ* carcinoma of the cervix or treated basal cell carcinoma of the skin) within 5 years. The study was approved by the Institutional Review Board according to Institutional rules.

treatment schedule

Patients were treated on an outpatient basis. Gemcitabine (Eli Lilly Co. Alcoberdas. Spain) 1200 mg/m^2 was given by i.v. infusion >30 min on days 1 and 8 of a 21-day cycle. Oxaliplatin Sanofi-Aventis. Barcelona. Spain 100 mg/m^2 was given as an i.v. infusion >2 h on day 8 of a 21-day cycle. Day 8 Gemox were omitted if the neutrophil count was $<1.0 \times 10^9$/l or platelet count $<70 \times 10^9$/l and reduced to 50% if the neutrophil count was between 1.0 and 1.5×10^9/l or platelet count was between 70 and 100×10^9/l. Patients were monitored every 3 weeks for toxicity. All toxicity was recorded according to common toxicity criteria 2.1. A complete blood count was carried out on days 1 and 8 of all cycles. Cycles were delayed 1 week if the absolute neutrophil count was $<1.5 \times 10^9$/l or platelets $<100 \times 10^9$/l. The worst grade (G) of toxicity was recorded for each cycle. In case of hematological (G ≥2) or non-hematological toxicity (G >2), treatment was interrrupted until symptoms resolved. Blood transfusions, antiemetics and analgesics were administered as appropriate. Patients received a maximum of six cycles unless they developed progressive disease or toxicity unacceptable to the patient.

outcome evaluation

Patients were evaluated for response after every three cycles with physical examination, computed tomography of chest or abdomen and bone scintigraphy as appropriate. All patients who received at least one dose were assessable for toxicity and those receiving at least one cycle were assessable for response. OS was measured from the date of study entry until death, and time to progression (TtP) was measured from the date of study entry until progression or death.

Standard Response Evaluation Criteria in Solid Tumors (RECIST) criteria [8] were used to assess response. Response criteria were as follows: (i) complete response (CR) was defined as the disappearance of all known disease, (ii) partial response (PR) was defined as a decrease of 30% of the greater diameter of measurable lesions compared with baseline and (iii) progressive disease was defined as a 20% or greater increase in the greater diameter of measurable lesions compared with baseline. (iv) Stable Disease (SD) neither sufficients shrinkage to qualify for PR nor sufficient increase to qualify for PD. Patients who achieved a response were rescanned after a further three cycles of chemotherapy to confirm their response. Criteria for stopping treatment included tumor progression, serious toxicity or patient request. Following completion of treatment, patients were assessed every 3 months until disease progression or death.

The primary end point was the objective response rate. The secondary end points were the duration of response, OS and safety. All patients included in the study were included in the analysis of response and of survival, and all treated patients were included in the evaluation of toxicity.

statistical methods

The aim of this trial was to determine whether the Gemox combination should be investigated further in locally advanced or metastatic urothelial cancer based on the following criteria: (i) if the results of the trial were compatible with a 50% response rate in the population under study, the combination would be further investigated, (ii) if the results were unable to demonstrate at least a 25% response rate in the population under study, the combination would be rejected for further investigation.

Treatment results are expressed as percentages with 95% confidence intervals (CIs) or as medians and ranges. TtP, OS and progression-free survival (PFS) were estimated by the Kaplan–Meier method and calculated from the day treatment started with Rothman's CIs.

results

patient characteristics

Baseline characteristics for all 46 assessable patients are shown in Table 1. The median age of the group was 68.6 years (range 52–85). Only six (13%) patients were female. The median ECOG PS of the group was two (range 0–2). Seven patients had received adjuvant or neo-adjuvant chemotherapy and five previous treatments with radiotherapy. The median number of metastatic sites was 2 (range 1–6). Median creatinine clearance was 50.73 ml/min (range 30–87). Seventy-five percent of patients had relatively poor renal function (Creatinine Clearance

Table 1. Patient characteristics

No. of patients	46
Median age, years (range)	69 (52–85)
Sex (male/female)	40/6
ECOG performance status	
0	7
1	16
2	23
Mean creatinine clearance (range)	50.73 (30–87)
Clinical stage	
Locoregional advanced disease	9
Metastatic disease	37
Prior therapy	
Adjuvant chemotherapy	7
Radiotherapy	5
Metastatic sites	
Median number (range)	2 (1–6)
Lymph nodes	40
Liver	18
Bone	1
Pelvis	16
Lung	22

ECOG, Eastern Cooperative Oncology Group.

<60 ml/min), 53% had visceral metastases and half of the patients had a PS of two.

study treatment

Of the 46 patients entered into the study, 20 completed six cycles of treatment. The majority of patients completed only the first course of treatment (10 patients) due to rapid disease progression. Two patients stopped treatment (during the first course) due to disease progression, two due to patient refusal and six patients died. All patients were evaluated for disease progression.

The day 8 dose of Gemox was omitted on 17 out of a total of 187 cycles due to neutropenia or thrombocytopenia. Fourteen patients had a cycle delay: three due to neutropenia, one due to thrombocytopenia, two due to toxicity and eight for other reasons. Dose reductions were required in 19 patients due to neutropenia (17 patients) or/and thrombocytopenia (three patients). Twenty-five patients (54.3%) received at least 85% of the planned dose of gemcitabine and 25 patients (54.3%) received at least 85% of the planned dose of oxaliplatin.

tumor response

In the 46 patients assessable for response, there were three (6.5%) CRs and 19 (41.5%) PRs for an overall response rate of 48% (95% CI: 33.4% to 62.2%). In addition, seven patients (15.2%) had stable disease and 17 patients (36.9%) had progressive disease.

Twenty patients completed the six cycles. At the end of study, most of the patients (90%) had progressive disease.

During the median follow-up period of 8.5 months (range 2–19 months), there was only one patient still alive and free of disease. This patient had resection of residual disease in the bladder following a PR to chemotherapy. The estimated median time to disease progression was 5 months (95% CI: 3–6.6 months) (Figure 1). The Kaplan–Meier estimate of the median OS was 6.5 months (95% CI: 5–11.3 months) (Figure 2).

toxicity

The worst adverse event encountered with this regimen was a hematological toxicity. Table 2 contains a list of the worst toxicity encountered for each patient. Patients received a median number of five cycles of chemotherapy (range 1–6) for a total of 187 cycles. Hematological toxicity was mild: G 3 anemia was reported in 11% of the patients; G 3 thrombopenia in 9% and G 3–4 neutropenia in 22%. G 3–4 non-hematological toxic effects were fatigue in 11%, nausea in 4%, vomiting in 9% and peripheral neuropathy in 4%. There was no renal toxicity.

discussion

This multicenter phase II study demonstrates that Gemox has significant activity against advanced TCC of the urothelium with manageable toxicity in a group of patients with relatively poor prognostic factors. We choose this combination based on a phase I study where the authors reported a very few hematological and non-hematological toxicity. G 3–4 neutropenia was reported in only 9% of cycles (without febrile neutropenia) and G 3–4 thrombocytopenia in only 5% of cycles [9]. One of the major problems of this study was that many patients had developed rapid progressive disease after the first treatment. This was due to the poor prognostic factors—especially low PS—in our series. The majority of patients had relatively poor renal function (75%) (median creatinine clearance 50 ml/min), while a significant proportion had visceral metastases (53%) and poor PS (50% ECOG 2). In a previous study combining gemcitabine and carboplatin, we observed that patients with

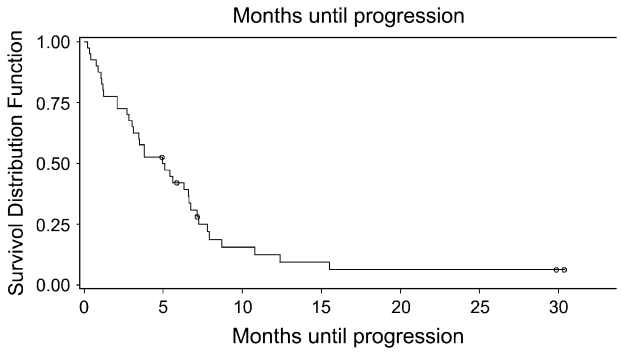

Figure 1. Time to progression.

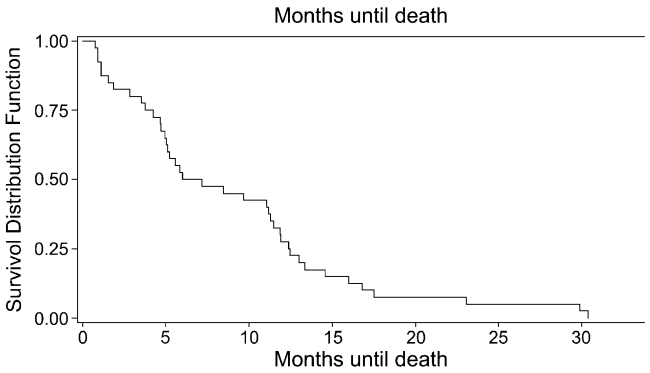

Figure 2. Overall survival.

Table 2. Hematological and non-hematological toxicity

Toxicity	I (%)	II (%)	III (%)	IV (%)
Anemia	21 (45.6)	14 (30.4)	5 (10.9)	0
Neutropenia	3 (6.5)	8 (17.4)	7 (15.2)	3 (6.5)
Thrombocytopenia	5 (10.9)	1 (2.2)	4 (8.7)	0
Vomiting	4 (8.7)	8 (17.4)	3 (6.5)	1 (2.2)
Nausea	9 (19.5)	7 (15.2)	2 (4.3)	0
Hepatotoxicity	0	2 (4.3)	0	0
Alopecia	2 (4.3)	1 (2.2)	0	0
Astenia	7 (15.2)	10 (21.7)	3 (6.5)	2 (4.3)
Peripheral neuropathy	9 (19.5)	1 (2.2)	1 (2.2)	1 (2.2)

(PS) of two had a response rate of only 14% [10]. Others studies combining gemcitabine and carboplatin demonstrated similar activity with manageable toxicity when they were used as first-line treatment of advanced bladder carcinoma in the elderly and those unfit for cisplatin-based chemotherapy. Therefore, it may be concluded that this combination of Gemox represents a reasonable choice for the treatment of such patients [11, 12].

Despite the relatively poor clinical characteristics, the treatment was well tolerated. Although a significant proportion of patients had some hematological toxicity, there were few clinical sequelae. Only one patient was admitted as a result of toxicity, attesting to the practicality of using this schedule in the outpatient setting. There were no cases of neutropenic sepsis. The median number of cycles given was five and 36 patients had at least two cycles of treatments. These data indicate that the doses selected for this combination were suitable for this group of patients.

A recent study [13] using a different schedule of administration in fit patients demonstrated a response rate of 47% with a median OS of 15 months and a median PFS of 7 months. However, patient characteristics of this study were very different from the present study, with most having a good PS without renal insufficency and only five out of 30 having visceral metastases and poor PS.

The median survival of our study was lower than expected but, as already mentioned, most of the patients included in the study had a poor PS, visceral metastases and a creatinine clearance <60 ml/min. PS and visceral metastases are the two major factors for poor prognosis in this disease as has been reported previously [14]. Our study population presented no favorable prognostic factors and this may have affected the results. We do not know if differences in schedule used might also explain the limited results on survival.

The results with Gemox are similar to published phase II response rates using other combination of the newer agents such as carboplatin/paclitaxel (Taxol) (20.7%–52%) or gemcitabine/paclitaxel (53%–60%) [15–17]. Although survival for the Gemox combination is disappointing, the high level of activity and good toxicity profile of the regimen holds promise for the treatment of advanced bladder.

In conclusion, this pilot study demonstrates that Gemox is an active and tolerable combination in unfit patients with response rates that merits further study in patients with impaired renal function but good PS.

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