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ORIGINAL ARTICLE

Chemotherapy with gemcitabine, cisplatin, and docetaxel in the treatment for patients with muscle-invasive bladder cancer: a multicenter phase II study of the Hellenic Oncology Research Group (HORG)

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Abstract
Purpose To assess the antitumor activity and toxicity of gemcitabine, cisplatin, and docetaxel (GCD) regimen in patients with locally advanced or metastatic urothelial cancer.
Patient and methods Chemotherapy-naïve patients, aged ≤70 years with measurable or evaluable disease and a performance status (PS) of 0–2 were treated with sequential cisplatin 80 mg/m^2 (d1), gemcitabine 1,100 mg/m^2 (d1 and d14), and docetaxel 80 mg/m^2 (d14) every 28 days.
Results Sixty patients with an ECOG PS of 0–2 were enroled. Most (71.7%) patients had stage IV disease. A median number of 4 chemotherapy cycles per patient (range, 1–9) was administered. Eight (13.3%) patients achieved a CR and 16 (26.7%) a partial response (PR) (intention-to-treat: ORR 40%; 95% CI 27.6–52.4%). Thirteen (21.7%) and 23 (38.3%) patients experienced stable and progressive disease, respectively. The median time to progression (TTP) was 7.7 months (range, 0.7–43.4), and the median overall survival 21.4 months (range, 0.7–68.6). Grade 3 and 4 neutropenia occurred in 27 (45%) patients and grade 3 and 4 thrombocytopenia in five (8.3%). Three (5%) patients developed febrile neutropenia. There were no treatment-related deaths. Severe non-haematological toxicity was infrequent.
Conclusions The GCD combination is an active and well-tolerated regimen in patients with chemotherapy-naive locally advanced or metastatic TCC and merits to be further investigated.

Keywords Gemcitabine · Platinums · Docetaxel · Bladder cancer

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Introduction

The rate of new diagnoses of muscle-invasive transitional cell carcinoma (TCC) is steadily increasing. Although TCC is a chemo-sensitive neoplasm, the prognosis is poor, with low 5-year survival rates in patients with advanced or metastatic disease. Chemotherapy with M-VAC (methotrexate/vinblastine/doxorubicin/cisplatin) or GC (gemcitabine/cisplatin) is currently recommended by the National Comprehensive Cancer Network [1] and the European Society for Medical Oncology [2] for the treatment of patients with locally advanced or metastatic disease. However, clinical researchers are trying to develop combinations of newer agents that are more effective and have a reduced toxicity profile.

M-VAC and GC have been shown to have similar response rates (49.4 and 45.7%, respectively) and median overall survival rates (15.2 and 14 months, respectively); yet, GC has a more favourable toxicity profile [3, 4]. The use of M-VAC produces significant toxicity, including toxic death rates of 3–4% [5, 6]. Both regimens include cisplatin,

since it has been shown to have a synergistic effect with drugs with dissimilar mechanisms of action [7, 8].

Several phase II studies have shown that 3-drug combinations (triplets) with a taxane plus GC (gemcitabine with carboplatin) produce higher overall response rates (ORR) than M-VAC or GC alone and may be associated with an improved median survival time [9–13]. The mode of action of taxanes is different from the mechanism of gemcitabine, cisplatin/carboplatin. Taxanes bind to distinct sites on the β-tubulin subunit, inducing microtubule assembly and subsequent cell death [14].

Among the different taxanes, docetaxel has been shown to be 1.9-fold higher in affinity for tubulin and is a more potent inducer of microtubule assembly than paclitaxel [15]. Several studies have explored various paclitaxel-based triple combinations, all with promising results but with increased toxicity, which, in some cases, included toxic deaths. However, the number of trials investigating docetaxel-based triple combinations is very limited. Our group has recently shown in a phase II in a study [16] that the sequential administration of 4 cycles of a gemcitabine/cisplatin (GC) regimen followed by 4 cycles of docetaxel in chemo-naive patients with locally advanced or metastatic TCC is an active regimen with an acceptable toxicity profile. The logical next step of this work was to explore in a phase II study the association of the three drugs by adding docetaxel in the GC regimen (GCD regimen) in an effort to investigate whether this could lead to better efficacy results in the first line setting of locally advanced or metastatic TCC.

Patients and methods

Patient selection

Chemotherapy-naïve patients aged $\leq$70 years, with histologically confirmed locally advanced, recurrent or metastatic transitional cell carcinoma were enroled into the study. Patients had to have measurable disease and a performance status (PS) [Eastern Cooperative Oncology Group (ECOG)] of $\leq$2. Previous neoadjuvant or adjuvant treatment was allowed as long as there was at least a 6-month treatment-free interval. Patients with a history of a second primary tumour (other than a non-melanoma skin cancer or radically excised in situ carcinoma of the uterine cervix), severe heart failure, arrhythmias, or acute myocardial infection within the previous 6 months and patients with renal or liver failure (creatinine >1.5 mg/dl or creatinine clearance $\leq$60 ml/min, bilirubin >3 mg/dl, transaminases 2 times the upper normal limit) were excluded from the study. Other exclusion criteria were pregnancy, abnormal bone marrow function (neutrophils $\leq$1,500/dl and platelets $\leq$100.000/dl), active infections, or other serious underlying medical or mental conditions, which would impair patients' compliance to the protocol. The protocol was approved by the ethic and scientific committees of the participating institutions, and signed informed consent was obtained from all patients before entry to the study.

Treatment schedule

Cisplatin (Platinol; Bristol-Myers Squibb, NJ) 80 mg/m^2 was administered to patients on day 1 after appropriate hydration. Gemcitabine (Gemzar; Elli Lilly, Indianapolis, IN) was administered at a dose of 1,100 mg/m^2 by a 30-min i.v. infusion on days 1 and 14. Docetaxel (Taxotere; Sanofi-Aventis, Bridgewater, NJ) was administered on day 14, at a dose of 80 mg/m^2 as a 1-h i.v. infusion, after appropriate standard premedication with corticosteroids. Omission of day 8, gemcitabine was due to concern of worrisome toxicities. The prophylactic use of hematopoietic growth factors [granulocyte colony-stimulating factor (G-CSF)] was not allowed. Supportive care, including blood transfusions, analgesics, and antiemetics, was administered as appropriate. Each patient received a total of six 28-days chemotherapy cycles, unless disease progression or unacceptable toxicity occurred. Patients who developed renal dysfunction during treatment (defined as a calculated creatinine clearance (CrCl) <60 ml/min by the Cockroft-Gault equation) were subsequently treated with carboplatin (5 AUC) instead of cisplatin.

Dose modifications

Toxicity was evaluated before each treatment cycle according to the National Cancer Institute Common Toxicity Criteria (NCI CTC version 2.0). Dosage adjustments were made before each treatment on the basis of haematological and non-haematological toxicity. Patients requiring dose reductions were treated with reduced doses for all subsequent cycles. In cases of grade 3 or 4 neutropenia, patients received the subsequent cycles of chemotherapy with prophylactic administration of G-CSF (Granocyte; 15 μg/m^2; Sanofi-Aventis) from day 2 to day 8. This policy was chosen in order to maintain dose intensity of active drugs since it has been shown in randomized trials that survival may be associated with clinical complete responses [17]. If grade 3 or 4 neutropenia occurred despite the subsequent administration of G-CSF, a 25% dose reduction was performed. This 25% dose reduction was also carried out for patients who developed febrile neutropenia, grade 4 thrombocytopenia, and grade 3 or 4 non-haematologic toxicity. In cases of nephrotoxicity, treatment was postponed until renal function was recovered. If treatment delay was more than 2 weeks, the patients were off study.

Pre-treatment and response evaluation

Before treatment, all patients were required to have a baseline assessment with complete medical history, physical examination, complete blood cell counts (with differential and platelet counts), chemistry profile, and urinalysis. In addition, patients underwent computed tomography scans of the chest and abdomen, with appropriate tumour measurements.

Before each treatment cycle, renal and liver function tests were performed. Complete blood cell counts with differential and platelet counts and serum creatinine levels were performed weekly. Tumour assessment was performed after the administration of 2 cycles, unless earlier evaluation was clinically required. Dose intensity was defined as the total amount of the drug (mg/m^2) given per week. All adverse events resulting in treatment discontinuation were followed closely until resolution or stabilization. After treatment completion, all patients were followed-up at least every 3 months with biochemical and imaging studies until disease progression or death. All patients were analysed on an intention-to-treat basis. Patients were assessed for response using RECIST criteria [18]. Patients who discontinued treatment before tumour assessment or those who were lost to follow-up were considered as non-responders.

Statistical analysis

The primary end point study was to measure is the efficacy of the GCD regimen in terms of objective response rate (complete + partial response). Secondary end points include the assessment of toxicity, time to progression, and overall survival of patients. The Simon's two-stage model [19] was applied in order to ascertain the total number of patients required for the study. The sample size required for the first phase of the study was calculated as 51 patients, based on the assumption that a 40% response rate would be detected and the minimum acceptable response rate would be 25%. A total of 60 patients would then be accrued if a minimum of 17 responses were observed. Survival rates were calculated as the time from the initiation of treatment to the date of last contact or death. The Kaplan–Meier method [20] was used to calculate survival curves. Data analysis was performed using SPSS 11.0 (SPSS, Inc., Chicago, IL).

Results

Patient characteristics

Between April 2004 and November 2007, 60 chemotherapy-naive patients with locally advanced, relapsed, or metastatic TCC were enroled onto this multicentre phase II study. Final data analysis was performed 5 months after the last patient was enroled. The main patient baseline characteristics are summarised in Table 1. Fifty-eight patients were male with a median age of 65.5 years. More than 90% of patients had an ECOG PS of 0–1 and 43 (71.7%) had stage IV disease, the rest had locally advanced disease. Additionally, 17 (28%) patients presented with both local

Table 1 Demographic Data

	$N = 60$	%
Age	65.5	
Median (min–max)	48–77	
Sex		
Male	58	96.7
Female	2	3.3
Performance status		
0	32	53.3
1	23	38.3
2	5	8.3
Histology		
Transitional cell	55	91.6
Adeno carcinoma	1	1.7
Large cell	1	1.7
Unknown	3	5.0
Stage		
III	17	28.3
IV	43	71.7
Grade		
II	10	16.7
III	37	61.7
IV	1	1.7
Unknown	12	20.0
Prior treatment		
Surgery	33	55.0
RT[a]		
Adjuvant	3	5.0
RT + Chemotherapy	1	1.7
RT locally advanced	1	1.7
None	55	91.7
Previous chemotherapy		
Adjuvant	3	5.0
None	57	95.0
No of organs involved		
0	1	1.7
1	25	41.7
2	17	28.3
3	13	21.7
4	4	6.7
Median	2 (1–4)	

[a] Radiotherapy

and distant disease and 34 (56.7%) with multiple site involvement. Visceral disease (liver, lung, bones) had 26 patients (43.3%). The impact on survival of PS and visceral sites of metastasis (Bajorin risk criteria) was not analysed due to small number of patients with PS 2. Thirty-three (55%) patients had prior surgery and five (8.4%) had received prior adjuvant chemotherapy or/and radiotherapy.

Compliance with the treatment

A total of 258 chemotherapy cycles were administered with a median of 4 cycles per patient (range, 1–9). The main reasons for treatment discontinuation was disease progression or recurrence ($n = 17$ patients; 28.3%). Doses were reduced in 16.3% of patients because of haematological toxicity (42.9%), non-haematological toxicity (9.5%), and both haematological and non-haematological toxicity (4.8%). Treatment delay was necessary in 71.3% of cycles because of haematological (32.4%) and non-haematological (4.1%) toxicity or other reasons (63.5%) not related to treatment or toxicity. Nine (15%) patients shifted to carboplatin due to impaired renal function and increased serum creatinine levels. The median dose intensity delivered for cisplatin, gemcitabine, and docetaxel was 88.5% (17.7 mg/m^2/week), 82.7% (455.2 mg/m^2/week), and 80.5% (16.1 mg/m^2/week) of the protocol-planned dose, respectively.

Toxicity

All patients who received at least one cycle of chemotherapy were included in the toxicity analysis. Toxicity was evaluated using the National Cancer Institute Common Toxicity Criteria. All enroled patients were evaluable for toxicity (Table 2). Severe (grade 3 and 4) neutropenia occurred in 27 (45%) patients, and three (5%) patients were hospitalised due to febrile neutropenia. All patients were uneventfully recovered. A total of 30 (50%) patients received G-CSF during treatment due to neutropenic episodes. Grades 3 and 4 thrombocytopenia occurred in five (8.3%) patients; however, no patient required platelet transfusions or hospitalisation for bleeding problems. There were no toxic deaths. The incidence of severe (grade 3 or 4) non-haematological toxicity was unusually low (<5%). There was one grade IV event—typhlitis—requiring operation. Diarrhoea, fatigue, vomiting, and neurotoxicity were the most prominent side effects.

Efficacy

All patients were evaluated for response (intention-to-treat analysis). Objective responses were seen in 24 patients (overall response rate: 40%; 95% CI: 27.6–52.4%). Eight (13.3%) patients achieved a complete response (CR) and 16 (26.7%) a partial response (PR). Additionally, stable disease (SD) was observed in 13 (21.7%) patients and progressive disease in 23 (38.3%). Twenty-four patients (40%) received second-line chemotherapy, and 5 patients (8.3%) received radiation therapy.

The median time to progression (TTP) was 7.7 months (range, 0.7–43.4 months; Fig. 1a). After a median follow-up period of 33.3 months (range, 0.7–68.6 months), the median overall survival was 21.4 months (range, 0.7–68.6) and the 1-year survival rate 73.3% (Fig. 1b).

Table 2 Adverse events possibly/probably related to study treatment

	GrI *n* (%)	GrII *n* (%)	GrIII *n* (%)	GrIV *n* (%)
Neutropenia	7 (12.0)	6 (10.0)	22 (37.0)	5 (8.0)
Febrile neutropenia	–	–	2 (8.0)	1 (2.0)
Anaemia	39 (65.0)	17 (28.0)	3 (5.0)	–
Thrombocytopenia	21 (35.0)	2 (3.0)	2 (3.0)	3 (5.0)
Nausea	14 (23.0)	4 (7.0)	1 (2.0)	–
Vomiting	2 (8.0)	1 (4.0)	2 (8.0)	–
Diarrhoea	4 (7.0)	2 (3.0)	1 (2.0)	1 (2.0)
Mucositis	2 (3.0)	1 (2.0)	–	1 (2.0)[a]
Constipation	4 (7.0)	6 (10.0)	–	–
Neurotoxicity	2 (3.0)	2 (3.0)	1 (2.0)	–
Allergy	1 (2.0)	–	–	–
Fatigue	16 (27.0)	11 (18.0)	–	1 (2.0)
Edema	–	1 (2.0)	–	–
Nail disorder	1 (2.0)	1 (2.0)	–	–
Fever in the absence of infection	1 (2.0)	–	–	–
Infection	1 (2.0)	–	–	–

[a] Typhlitis

Discussion

Data from several phase II studies and a landmark phase III study have confirmed the clinical benefit of the GC regimen in metastatic transitional cell carcinoma [2, 3, 21]. In this phase II study, we aimed to improve the efficacy of the standard GC regimen by adding docetaxel, while reducing the toxicity profile of cisplatin by allowing substitution with carboplatin if nephrotoxicity occurred.

In the context of the current study, 60 patients with locally advanced or metastatic urothelial cancer were treated with GCD for a mean of 4 cycles. In an intention-to-treat (ITT) analysis, the objective response rate was 40% with 13.3% complete responses. Although this response rate seems to be lower than the 52–78% response rates achieved by other taxane-containing triplets [23], the observed median overall survival time with the GCD was

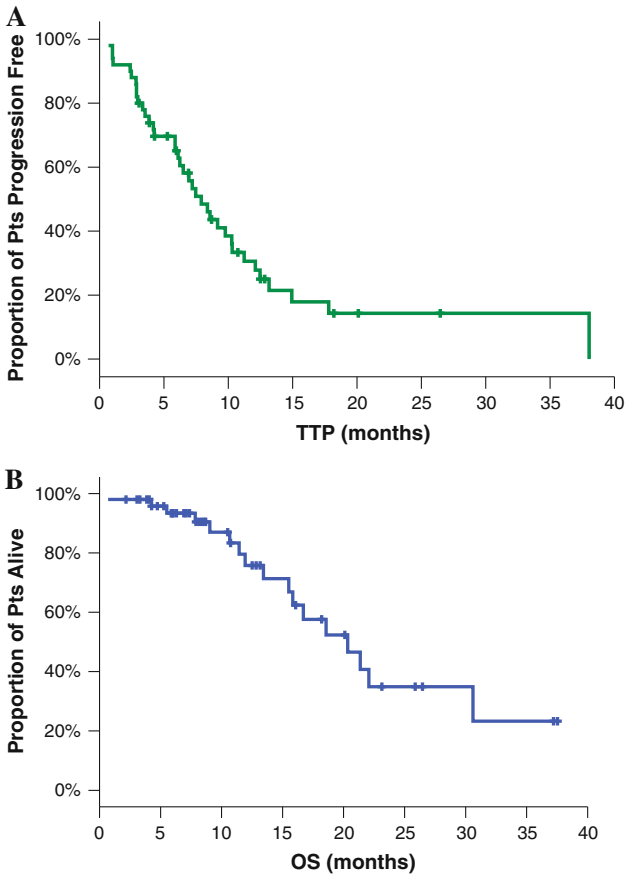

Fig. 1 Kaplan–Meier curves for PFS (**a**) and OS (**b**)

among the best reported results for any chemotherapeutic combination for patients with advanced/metastatic TCC. Indeed, the median overall survival time was 21.4 months (range, 0.7–68.6 months), which compares favourably with the median overall survival of 14.7–24 months observed with other taxane-containing triplet combinations [9, 10, 12] (Table 3). Moreover, the median overall survival of patients treated with GCD was higher than that of GC (15.2 months; 4). The likely rationale for the long median survival in the presence of a low ORR seen in this study reflects the fact that 62% of patients had a disease control and 40% of patients received second-line chemotherapy.

A possible explanation for the lower response rates seen in the present study may be related to the substitution of carboplatin for cisplatin in 9 (15%) of the patients. Although there is some debate over the comparative efficacies of the two drugs, carboplatin has been shown to be associated with lower objective responses compared to cisplatin [24]. Nevertheless, this substitution was allowed as cisplatin-containing regimens are contraindicated in patients with impaired renal function and carboplatin is often used for these patients in everyday clinical practice [22, 25]. In the current study, this switch was decided as being in the clinical best interest of the patients who developed impaired renal function. Furthermore, this measure allowed for an increase in number and frequency of chemotherapy cycles, which is correlated with clinical complete responses [17]. An additional rational for the observed relatively low response rates may be related to the fact that 83.7% of patients received reduced doses of the GCD regimen and 71.3% of chemotherapy cycles were delayed. This hypothesis could be supported by the findings of another study in a small number of patients where the GCD regimen was used with lower doses; in this particular study, an ORR of 65.6%, with 28.5% CRs and a median survival time of 15.5 months, was observed [13]. In addition, the median TTP was 8.9 months with a median time to progression of 10.2 months [13]. There are a number of key methodological differences between the aforementioned study and the present study, which could possibly explain the reduced efficacy of the present study. In the study by Pectasides et al. [13], a reduced dose combination of all drugs were given on a weekly basis, on days 1 and 8 of 21-day cycle, as opposed to the alternating biweekly administration of a 28-day cycle as in the current study. In addition, the patients received a median of 5 chemotherapy cycles instead of 4 given in our study.

These results were obtained with an acceptable toxicity profile. The incidence of severe non-haematological toxicity was unusually low, while the incidence of haematological toxicity was consistent with other regimens. Moreover, there were no toxic deaths and the need for hospitalisations was low. Indeed, grade 3 and 4 neutropenia were seen in 27 (45%) patients but only three (5%) of them required hospitalisation because of febrile neutropenia. The prophylactic use of G-CSF support after the neutropenic episodes could probably explain the low incidence of febrile neutropenia observed in the current study. Grade 3 and 4 thrombocytopenia was only seen in five (8.3%) patients, and nephrotoxicity was controlled by cessation of cisplatin and switching to carboplatin for subsequent doses. Compared with Bellmunt study [9], neutropenia grade 3/4 and febrile

Table 3 Selected phase II trials with triplet combinations

Author	Type of chemotherapy	No of pts	RR (%)	OS (months)
Bellmunt [9]	Paclitaxel/cisplatin/gemcitabine	61	77.6	24
Bajorin [10]	Ifosfamide/paclitaxel/cisplatin	44	68	20
Edelman [17]	Paclitaxel/carboplatin/methotexate	33	56	15.5
Hussain [12]	Paclitaxel/carboplatin/gemcitabine	49	68	14.7

neutropenia were lesser (45% vs. 55% and 10% vs. 20%, respectively). Thrombocytopenia grade 3/4 was less prominent in our study than Hussain study [12] (8% vs. 21%).

In conclusion, the current study demonstrated that the GCD regimen is feasible, well tolerated, and resulted in a favourable patients' clinical outcome. These results are practically comparable with those obtained with other taxane-containing triple combinations, but does not clearly offer a benefit compared with other non-sequential, cisplatin-based regimens. Although we do not recommend this particular sequence of chemotherapy for further study, the superior median survival and reduced toxicity observed suggests that GCD is a feasible strategy for patients with poor renal function.

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Conflict of interest None.

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