Gemcitabine plus docetaxel as first-line biweekly therapy in locally advanced and/or metastatic urothelial carcinoma: a phase II study

Bruno Neri[a], Laura Vannini, Clara Giordano[a], Raffaella Grifoni[a], Pietro Pantaleo, Valentina Baldazzi[b], Alfonso Crisci[a,b], Alberto Lapini[b], Andrea Raugei[b] and Marco Carini[b]

The purpose of the study was to evaluate objective response rate, survival and toxicity of the combination of gemcitabine–docetaxel administered on a biweekly schedule as first-line treatment in advanced/relapsed or metastatic urothelial carcinoma. Treatment consisted of the sequenced administration of gemcitabine 1500 mg/m^2 and docetaxel 60 mg/m^2 (2 h intravenous infusion) on days 1, 14 of a 28-day cycle for 6 months. A total of 33 patients, 22 men and 11 women, were enrolled, aged 41–75 years (median 64 years). The majority of patients had a good performance status (94%; status < 2). Thirteen patients had locally advanced disease (39%) and 20 metastasic disease (41%). A total of 178 treatment cycles were administered with a median number of 5.4 cycles for a patients (range 2–8). Toxicity was primarily hematologic with the most frequent grade > 2 being neutropenia (11%), with three episodes of febrile neutropenia. Anemia and thrombocytopenia were milder and had a lower incidence. The most frequent nonhematological toxicities were alopecia, followed by asthenia. Cardiac and pulmonary toxicity was minimal. No toxic deaths were recorded during study and follow-up. Overall response rate was 53.1%, including four complete responses (12.5%) and 13 partial responses (40.6%), whereas six patients (18.8%) had disease stabilization. Median time to progression was 10.2 months (95% confidence interval: 5.1–13.7), with a median survival of 14.8 months (95% confidence interval: 9.4–20.2) after an observation of 30 months (range 4–30+). The results of this study suggested that combination therapy with gemcitabine and docetaxel administered twice a week is particularly active and well tolerated as first-line treatment in advanced and/or metastatic urothelial carcinoma. Once data are confirmed in a larger study and longer follow-up, the favorable toxicity profile of this regimen may offer an interesting alternative to the cisplatin-based regimen. ***Anti-Cancer Drugs*** **18:1207–1211 © 2007 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2007, **18**:1207–1211

Keywords: chemotherapy, docetaxel, gemcitabine, urothelial carcinoma

[a]Department of Oncology, Centre of Experimental and Clinical Oncology and [b]Department of Urology, University of Florence, Italy

Correspondence to Professor Bruno Neri, MD, Department of Oncology, Centre of Experimental and Clinical Oncology, University of Florence, Azienda Ospedaliero Universitaria, Careggi, Viale Pieraccini 17, 50139 Florence, Italy
Tel: +39 055 7949748; fax: +39 055 7948237;
e-mail: bruno.neri@unifi.it

Received 30 March 2007 **Revised form accepted** 5 June 2007

Introduction

Urothelial carcinoma (UC) is the fourth most frequent malignancy in Europe, accounting for about 7% of all human neoplasms. About new 136 000 cases are recorded each year with an incidence of 32 instances out of every 100 000 men and nine out of 100 000 women. Overall, about 49 000 deaths in Europe are related to this neoplasm [1]. To date, a cure is not possible for the majority of patients with locally advanced/recurrent or metastatic disease. The standard therapy for patients affected by invasive cancer of the bladder is radical cystectomy preceded or followed by chemotherapy. As with surgery alone the survival rate is particularly low, systemic chemotherapy appears to be the only treatment potentially capable of lengthening survival. In the past 10 years, the most widely employed regimens in advanced and/or metastatic UC have been cisplatin-based combinations like cisplatin–methotrexate–vinblastine or methotrexate–vinblastine–adriamicina–cisplatin (M-VAC) [2], which offer a high rate of objective responses (40–70%) although at the expense of major toxicities, mainly myelosuppression, nausea, vomiting and nephrotoxicity [3]. Furthermore, only 5% of patients achieve a survival of more than 5 years [4–6]. More recently, a phase III study has demonstrated that the combination gemcitabine–cisplatin could achieve the standard of care of M-VAC, but with a significantly lower toxicity [7]. This result is particularly significant if we consider that symptom palliation is one of the major goals in advanced UC. In the meantime, oncological research has focused on newer agents and combinations potentially capable of increasing response rates and survival time with acceptable toxicity grades. Over the past several years clinical studies have shown that taxanes (paclitaxel–docetaxel) are among the

most active agents in UC both as single agents [8] and especially in combinations with other drugs [9–11]. In particular, some authors have assessed the validity of the combination gemcitabine–docetaxel in UC. In the light of these results, the purpose of this study was to assess if the treatment schedule with the combination of gemcitabine plus docetaxel administered twice a week can offer equally high response rates while providing a more favorable therapeutic index.

Patients and methods

Patient selection

The study was conducted on patients with histologically proven UC. All patients had measurable disease and met the following criteria: performance status Eastern Cooperative Oncology Group ≤ 2, life expectancy of at least 3 months and age ≤ 75 years. Laboratory acceptance parameters included a white blood cell count above 4000 cells/μl, a hemoglobin level ≥ 9.5 g/dl, a platelet count $\geq 100\,000$/μl, serum transaminase $< 3\times$ the upper normal limit (UNL), and bilirubin and creatinine values of $< 1.5 \times$ UNL. Contraindication to entry included an active infectious process, an active heart disease, central nervous system involvement or any concomitant second primary cancer. All patients gave written informed consent and entered the study after being thoroughly informed of the study design, benefits and risks according to the guidelines of 'Local Ethic Committee' and the 'Helsinki declaration'.

Treatment schedule

All the enrolled patients received chemotherapy in a day-hospital setting, with a gemcitabine dose of 1500 mg/m^2 (intravenously over 30 min) plus docetaxel 60 mg/m^2 (intravenously over 60 min). The two agents were administered in sequence on days 1, 14 of a 28-day cycle. All patients received an antiemetic premedication with ondansetron 4 mg intravenously and metilprednisolone 8 mg administered intramuscularly during the 12 h before chemotherapy. Granulocyte colony-stimulating growth factors (G-CSFs) were not used prophylactically, whereas supportive care like blood transfusions or erythropoietin administration and analgesics were administered as appropriate. The planned overall duration of chemotherapy treatment was 6–8 months; however, the therapy was stopped in case of disease progression, unacceptable toxicity or patient refusal.

Toxicity-related dose reduction

Toxicity was assessed before each treatment cycle according to the World Health Organization (WHO). criteria [12]. As a result, any dose reduction was calculated based on hemochrome level, liver, renal, cardiac and pulmonary function tests. Full doses of the anticancer drugs were given if granulocyte count was > 1500 μl and platelet count was $> 100\,000$ μl. In the case of grade 2 or more toxicity, excepting alopecia, chemotherapy was discontinued for a week and than restarted after full recovery. During the study, leukocyte-stimulating growth factors were allowed in patients showing grade 3 or more neutropenia. Reduction of 25% in all the drugs dose was performed in the event of a second consecutive occurrence of grade > 2 toxicity. Patients with unsolved grade 2 or more toxicity after two consecutive treatment delays or experiencing grade 3–4 nonhematological toxicity except alopecia went off study.

Response evaluation

Baseline evaluation before treatment start included complete past medical history, thorough physical examination, ECG, standard chest radiograph and/or, when appropriate, computed tomography (CT) scan of the chest, a complete abdominal CT scan, and 'total body' bone scintigraphy. At the same time, complete blood counts, hematochemical tests, and renal and liver function tests were performed. These tests were repeated before any subsequent cycle. Target lesions were reevaluated after the first 3 months and at the end of treatment, through ecographic evaluation and/or CT scan, whereas the scintigraphy, when appropriate, was performed only after completion of the planned cycles. According to protocol provisions, also patients who had received at least two applications of the planned treatment (one cycle) were considered evaluable for toxicity, response and survival. Patients who withdrew from treatment before reevaluation were considered nonrespondent. Response evaluation was performed according to WHO [12] criteria. After completion of the treatment all patients underwent a periodical check-up every 3 months until disease progression or death.

Statistical methods

The study was a nonrandomized, phase II study. The primary end point included objective response, survival, time to disease progression (TTP) and toxicity. The sample size was calculated on the assumption that a percentage of objective response variable between 20 and 40% could be detected. According to the optional Simon two-step design, if a minimum objective response rate $> 40\%$ was observed in the first 15 patients, an additional 15 patients should be enrolled, and if > 12 responses were observed in 30 patients (40%), the regimen was considered active to be submitted for further evaluation [13]. Descriptive statistics was reported as proportions and medians. TTP was defined as the interval between initial treatment and the time of disease progression or death. Survival time was calculated from the date of treatment initiation until the date of the last follow-up evaluation or death. TTP and overall survival were analyzed according to the Kaplan–Meier method [14]. The confidence intervals (CIs) for response rates, TTP and overall survival were calculated using methods for exact binominal CIs [15]. Survivors were censored on the date they were last known to be alive.

Results

Patient characteristics

Between January 2002 and December 2004, 33 patients with locally advanced/relapsed or metastatic UC were enrolled in the study. One patient could not be evaluated for response because he refused to continue treatment after the second cycle and was lost at follow-up. Final data analysis was performed in February 2007. Patient clinical characteristics are reported in Table 1. The majority of patients (94%) had Eastern Cooperative Oncology Group performance status ≤ 2 at study entry. Twenty out of 33 patients (61%) had metastases, whereas the remaining 13 patients (39%) had locally advanced or recurrent disease. Study treatment (gemcitabine–docetaxel) was administered as first-line therapy to all patients, of whom 20 (61%) had not previously received any treatment, whereas 13 patients had prior surgery (33%) or radiotheraphy (6%).

Treatment

A total of 178 treatment cycles were administered, with a median number of 5.4 cycles per patient (minimum 2 to maximum 8). Treatment was discontinued in one patient who refused to continue the cure after the second cycle (3%), in five patients (15%) due to disease progression and in one patient (3%) due to hematological toxicity during the fifth cycle. A significant hematological toxicity was observed in this study that required G-CSF for 13 patients. In other three patients a dose reduction of 25% was necessary for both drugs (gemcitabine–docetaxel) in 8 cycles, amounting to 4.8% of the total number of administered cycles. Thus, at the end of study, the dose intensity actually administered was 91% of that planned.

Table 1 Patient characteristics

Characteristics	*N* patients (%)
Total	33 (100)
Age (years)	
Median	64
Range	41–75
Sex	
Female	11 (33)
Male	22 (67)
Performance status (ECOG)	
0	11 (33)
1	20 (61)
2	2 (6)
Prior treatment	
None	20 (61)
Surgery	11 (33)
Radiotherapy	2 (6)
Sites of disease	
Lymph nodes	15 (45)
Soft tissues	12 (36)
Liver	7 (21)
Lungs	6 (18)
Skeleton	10 (30)
Bladder	10 (30)
No. of sites of disease	
1	10 (40)
2	17 (52)
3	6 (18)

ECOG, Eastern Cooperative Oncology Group.

Toxicity

All the 33 patients were evaluable for toxicity. Toxicity was primarily hematologic with neutropenia being the most prominent with 16 occurrences of grade 3 and three episodes of febrile neutropenia, one of which required hospitalization. Less significant and frequent were anemia and thrombocytopenia. No chemotherapy-related deaths occurred, nor episodes of cardiac toxicity or changes in the lung and renal function. Among non-hematological toxicities the most frequent was alopecia, however, reversible after the end of treatment, and asthenia. Overall toxicities with details on type and grade are listed in Table 2.

Treatment response

Of 33 patients enrolled in the study, 32 were evaluable for response, TTP and survival. Response results are reported in Table 3. Four patients achieved a complete response (CR = 12.5%) and 13 patients achieved a partial response (PR = 40.6%) giving an overall response of 53.1% (CR + PR). In addition, six patients achieved disease stabilization (18.8%), whereas the remaining nine patients had rapid progression (28.1%). Responses are referred to measurable lesions. Skeletal lesions were not included in the response assessment because all of them were treated with pamidronate.

After a follow-up of 30 months (range 4–30 +), 26 patients died (81.2%), whereas the other six patients

Table 2 Toxicity type and grade (total no. of treatment cycles 178)

Toxicity	Grade 1–2 [*N* (%)]	Grade 3–4 [*N* (%)]
Hematologic		
Anemia	173 (97)	5 (3)
Neutropenia	159 (89)	19 (11)
Thrombocytopenia	168 (94)	10 (6)
Nonhematologic		
Alopecia	178 (100)	–
Asthenia	176 (99)	2 (1)
Diarrhea	178 (100)	–
Mucositis	176 (99)	2 (1)
Nausea/vomiting	178 (100)	–
Cardiac	178 (100)	–
Neurologic	178 (100)	–
Pulmonary	178 (100)	–

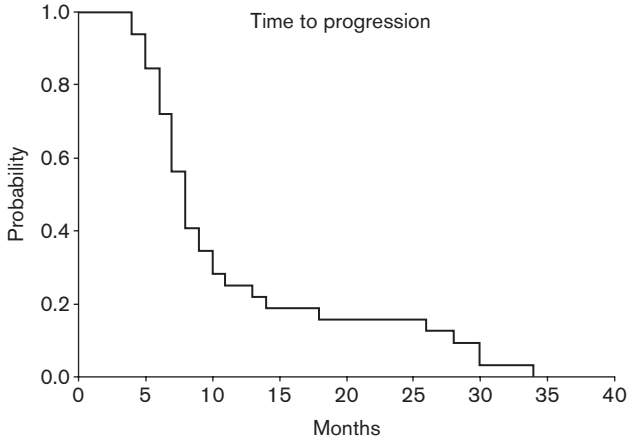
Table 3 Response and survival (no. of patients 32)

Response	*N*	%
Complete responses	4	12.5
Partial responses	13	40.6
Stable disease	6	18.8
Disease progression	9	28.1
Overall response	17	53.1

	Median	95% CI
Time (months)		
Progression time (TTP)	10.2	5.1–13.7
Overall survival (OS)	14.8	9.4–20.2

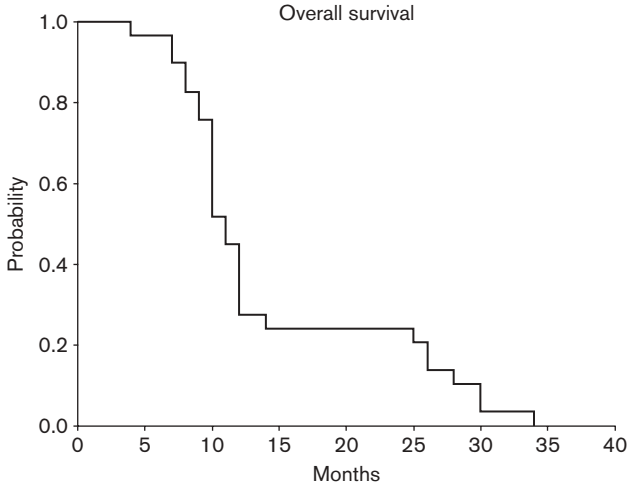
CI, confidence interval.

Fig. 1



Kaplan–Meier estimates of time to progression among patients with urothelial carcinoma treated with the gemcitabine–docetaxel regimen.

Fig. 2



Kaplan–Meier estimates of overall survival among patients with urothelial carcinoma treated with the gemcitabina–docetaxel regimen.

(18.7%) were still alive. Figures 1 and 2 report the curves of median time to progression (TTP) that was 10.2 months (range 4–30 + 95% CI: 5.1–13.7) and the median survival time that was 14.8 months (range 4–30 + 95% CI: 9.4–20.2).

Discussion

Despite significant progress of antiblastic chemotherapy in the treatment of advanced and/or metastatic urothelial cancer, the latter remains a rapidly fatal disease for the majority of patients. Randomized studies have indicated the M-VAC [2] regimen as the standard treatment for survival compared with cisplatin alone or with other combination schedules with cyclophosphamides, anthracyclines and platinoids. In this regimen, however, toxicity, particularly hematologic [3], was high and only 5% of treated patients survived more than 5 years [4–6]. Hence the interest for newer combinations and treatment schedules that may offer high efficacy and good tolerability. Since 1994 many studies have demonstrated the efficacy of taxanes in this disease [16,17] and, later, that the combination with gemcitabine improved the overall response rates [18,19]. More recently, it has been found that in the combination gemcitabine–docetaxel, the two agents *in vivo* have a synergetic action in the treatment of some solid tumors [20,21]. In this phase II study, we report on the efficacy and toxicity of the biweekly treatment with gemcitabine–docetaxel regimen used as first-line treatment in advanced or metastatic UC. Overall, 53.1% of patients achieved an objective response (CR + PR), with a definitely better response on lymph nodes (78.7%) compared with visceral sites (49.2%). After a follow-up of 30 months, the median survival was 13.8 months, with six patients still alive at the time of assessment (18.7%). Among the side effects, the primary toxicity was hematologic, particularly thrombocytopenia, although well manageable through the use of leukocyte growth factors. The episodes of lung and/or cardiac toxicity reported by other authors for other oncological diseases with the combination gemcitabine–paclitaxel [22,23] were not found in this study in the combination gemcitabine–docetaxel. Moreover, this biweekly regimen was particularly well tolerated and effective compared both with the reference cisplatin-based schedules and other weekly schedules with gemcitabine and taxanes [24,25]. In conclusion, it is reasonable to consider that also in this pathology the high rate of objective responses achieved with the combination gemcitabine–docetaxel may be related to the synergetic action of the two agents, while the improved toxicity profile compared with previous studies may be due to the biweekly administration. Thus, if survival and response rates will be confirmed in longer follow-ups and larger studies, the gemcitabine–docetaxel regimen might be indicated as first-line treatment in advanced and/or metastatic UC.

Acknowledgements

The authors acknowledge the assistance of Professor Grazia Cini for editing the manuscript.

The study was partially funded by the 'Associazione Toscana Ricerche e Cure Oncologiche' of Florence, Italy.

References

1 Ferlay J, Bray F, Pisani P, Parkin DM. *Cancer incidence, mortality and prevalence wordwide*. Lyon: IARC Press; 2001.

2 Von der Maase H. Current and future prospectives in advanced bladder cancer: is there a new standard?. *Semin Oncol* 2002; **29**:3–14.

3 Vaughn DJ. Review and outlook for the role of paclitaxel in urothelial carcinoma. *Semin Oncol* 1999; **26**:117–122.
4 Sternberg CN, Yagoda A, Scher HI, Waston RC, Geller N, Herr HW, *et al*. Methotrexate, vinblastine doxorubicin and cisplatin for advanced transitional cell carcinoma of the urothelium. Efficacy and patterns of response and relapse. *Cancer* 1989; **64**:2448–2458.
5 Loeher PJ, Einhorn LH, Elson PJ, Crawford Ed, Kubler P, Tannok I, *et al*. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *J Clin Oncol* 1992; **10**:1066–1073.
6 Saxman SB, Propert KJ, Einnhorn LH, Crawford ED, Tannock I, Raghavan D, *et al*. Long-term follow-up of a phase III Intergroup study of cisplatin alone or in combination with methotrexate, vinblastine and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *J Clin Oncol* 1997; **15**:2564–2569.
7 Von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, *et al*. Gemcitabine and cisplatin vs. methotrexate, vinblastine doxorubicin, and cisplatin in advanced or metastatic bladder cancer: result of a large randomized, multinational multicenter phase II study. *J Clin Oncol* 2000; **18**:3068–3077.
8 Galsky MD. The role of taxanes in the management of bladder cancer. *Oncologist* 2005; **10**:792–798.
9 Pectasides D, Visvikis A, Aspropotamitis A, Halikia A, Karvounis N, Dimitriadis M, Athanassiou A. Chemotherapy with cisplatin, epirubicin, and docetaxel in transitional cell urothelial cancer. Phase II trial. *Eur J Cancer* 2000; **36**:74–79.
10 Gitlitz BJ, Baker C, Chapman Y, Allen HJ, Bosserman LD, Patel R, *et al*. A phase II study of gemcitabine and docetaxel in patients with advanced urothelial carcinoma. *Cancer* 2003; **98**:1863–1869.
11 Hainsworth JD, Meluch AA, Litchy S, Schnell FM, Bearden JD, Yost K, Greco FA. Paclitaxel, carboplatin and gemcitabine in the treatment of patients with advanced transitional cell carcinoma of the urothelium. *Cancer* 2005; **103**:2298–2303.
12 Miller AB, Hoogstraten B, Staquet M, Wikler A. Reporting results of cancer treatment. *Cancer* 1981; **72**:207–214.
13 Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989; **10**:1–10.
14 Kaplan E, Meier P. Non-parametric estimation from incomplete observation. *J Am Stat Assoc* 1958; **53**:457–481.
15 Lentner C. Exact Confidence Limits. In Geigy Scientific Tables 89–102. Ciba-Geigy, Switzerland, 1982.
16 Roth BJ, Einhorn LH. Significant activity of paclitaxel in advanced transitional cell carcinoma of the urothelium: a phase II trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 1994; **12**:2264–2270.
17 McCafferyb JA, Hilton S, Mazumdar M. Phase II trial of docetaxel in patients with advanced or metastatic transitional cell carcinoma. *J Clin Oncol* 1997; **15**:589–593.
18 Rothenberg ML, Sharma A, Weiss GR, Villalona-Calero MA, Eckardt JR, Aylesworth C. Phase I trial of paclitaxel and gemcitabine administered every two weeks in patients with refractory solid tumors. *Ann Oncol* 1998; **19**:733–738.
19 Stemberg CN, Calabrò F, Pizzocaro G, Marini L, Schnetzer S, Sella A. Chemotherapy with an every 2 weeks regimen of gemcitabine and paclitaxel in patients with transitional cell carcinoma who have received prior cisplatin-based therapy. *Cancer* 2001; **92**:2993–2998.
20 Sherman WH, Fine RL. Combination gemcitabine and docetaxel therapy in advanced adenocarcinoma of the pancreas. *Oncology* 2001; **60**: 313–321.
21 Alexopuolos A, Tryfonopoulos D, Karamouzis MV, Gerasimidis G, Karydas I, Kandilis K, *et al*. Evidence for *in vivo* synergism between docetaxel and gemcitabine in patients with metastatic breast cancer. *Ann Oncol* 2004; **15**:95–99.
22 Roychowdhury DF, Cassidy CA, Peterson P. A report on serious pulmonary toxicity associated with gemcitabine-based therapy. *Invest New Drugs* 2002; **20**:311–315.
23 Shord SS, Faucette SR, Gillenwater HH. Gemcitabine pharmacokinetics and interaction with paclitaxel in patients with advanced non-small-cell lung cancer. *Cancer Chemother Pharmacol* 2003; **51**:328–336.
24 Li J, Juliar B, Yiannoutsos C, Ansari A, Fox E, Fisch MJ, *et al*. Weekly paclitaxel and gemcitabine in advanced transitional-cell carcinoma of the urothelium: a phase II Hoosier oncology group study. *J Clin Oncol* 2005; **23**:1185–1191.
25 Ardavanis A, Tryfonopuolos D, Alexopoulos A, Kandylis A, Lainakis G, Rigatos G. Gemcitabine and docetaxel as first-line treatment for advanced urothelial carcinoma: a phase II study. *Br J Cancer* 2005; **92**:645–650.