A multicentre phase II trial was undertaken to evaluate the activity and toxicity of docetaxel plus cisplatin as first-line chemotherapy in patients with urothelial cancer. Thirty-eight patients with locally advanced or metastatic transitional-cell carcinoma of the bladder, renal pelvis or ureter received the combination of docetaxel 75 mg m\(^{-2}\) and cisplatin 75 mg m\(^{-2}\) on day 1 and repeated every 21 days, to a maximum of six cycles. The median delivered dose-intensity was 98% (range 79 – 102%) of the planned dose for both drugs. There were seven complete responses and 15 partial responses, for an overall response rate of 58% (95% CI, 41 – 74%). Responses were even seen in three patients with hepatic metastases. The median time to progression was 6.9 months, and the median overall survival was 10.4 months. Two patients who achieved CR status remain free of disease at 4 and 3 years respectively. Grade 3 – 4 granulocytopenia occurred in 27 patients, resulting in five episodes of febrile neutropenia. There was one toxic death in a patient with grade 4 granulocytopenia who developed acute abdomen. Grade 3 – 4 thrombocytopenia was rare (one patient). Other grade 3 – 4 toxicities observed were anaemia (three patients), vomiting (five patients), diarrhoea (four patients), peripheral neuropathy (two patients) and non-neutropenic infections (seven patients). Docetaxel plus cisplatin is an effective and well-tolerated regimen for the treatment of advanced urothelial cancer, and warrants further investigation.

Keywords: urothelial cancer; docetaxel; cisplatin; bladder carcinoma
follows: normal baseline haematologic parameters, creatinine clearance of 60 ml min$^{-1}$ or more, a normal bilirubin level, a alkaline phosphatase level of less than six times the upper normal limit, and transaminase levels of less than 3.5 times the upper normal limit or less than 1.5 times in case of association with alkaline phosphatase greater than 2.5 times the norm. Patients with known CNS metastases, pre-existing grade 1 peripheral neuropathy, history of prior malignancy, or significant cardiac disease were not eligible for this study. Written informed consent was obtained from all patients before study entry. The study was carried out with ethical committee approval at each participating hospital.

### Treatment schedule

Docetaxel was administered at a dose of 75 mg m$^{-2}$, diluted in 250 ml of 5% glucose, as a 1 h infusion. Cisplatin 75 mg m$^{-2}$ was infused in 500 ml of normal saline over 30–60 min, with adequate pre- and post-hydration and mannitol. Both drugs were given on day 1 and repeated every 3 weeks. Premedication included dexamethasone, 8 mg orally b.i.d., the day before and four consecutive days following chemotherapy. Antiemetic treatment consisted of intravenous ondansetron or granisetron in combination with dexamethasone 20 mg on day 1. Cycles were not started unless the granulocyte count was $>1500$ mm$^{-3}$ and platelets were $>100 000$ μl$^{-1}$. Prophylactic use of growth factors (G-CSF) was not routinely recommended. However, if grade 4 granulocytopenia or febrile neutropenia was present, prophylactic Lenograstim, 263 55 mg m$^{-7}$ over 10 days, was administered in subsequent cycles. The docetaxel dose was reduced to 55 mg m$^{-2}$ if patients experienced grade 4 thrombocytopenia, febrile neutropenia despite prophylactic administration of G-CSF, or grade 2 hepatotoxicity. Doses of both agents were reduced by 25% if patients experienced grade 2 peripheral neuropathy. Patients were taken off the study if creatinine clearance decreased to less than 50 ml min$^{-1}$. Patients received treatment for a maximum of six cycles unless they developed progressive disease or experienced excessive toxicity as judged by the investigator or the patient.

### Outcome evaluation

National Cancer Institute common toxicity criteria were used to analyze toxicity. Response evaluation was performed every three cycles using standard WHO criteria. Even patients receiving just one cycle were considered evaluable for response and toxicity assessment. Patients were followed for survival and disease progression every 3 months until death or loss to follow-up. The method of Kaplan–Meier was used to estimate duration of response, time to progressive disease and overall survival. The planned sample size was 35 patients, using a two-stage sequential design, with the assumption that the regimen would not be of interest if it had a response rate of less than 30% but would be of considerable interest if it had a response proportion of 50% or more (Fleming, 1982).

### RESULTS

From February 1997 to August 1999, 38 patients were entered into the study at seven centres. All patients were eligible for the study, and all assessable for toxicity and response. Pre-treatment characteristics of the patients are summarized in Table 1. Twenty (53%) patients had locally advanced or metastatic lymph node disease, and the remaining 18 (47%) had metastatic visceral or soft tissue disease. Six patients had received prior systemic adjuvant chemotherapy with cisplatin or carboplatin-containing regimens.

A total of 166 cycles of chemotherapy were administered. The median number of cycles received per patient was six (range, 1–6 completed cycles). Of the 38 patients, 35 (92%) received at least two cycles of chemotherapy. The median delivered dose-intensity was 98% (range, 79–102%) of the planned dose for both drugs. Fifteen patients received G-CSF in a total of 48 cycles of chemotherapy. G-CSF was administered prophylactically in 42 cycles, and as a treatment of febrile neutropenia in six cycles. Overall, all patients were ultimately withdrawn from therapy due to progressive disease (nine patients), adverse events (six patients), stable disease (three patients), or request (one patient). Twenty-two of the 38 assessable patients obtained an objective response, for an overall response rate of 58% (95% confidence interval (CI), 41–74%), with seven patients obtaining a radiological complete response (CR, 18%) and 15 a partial response (PR, 39.5%). An additional four patients (10.5%) had stable disease, and 11 patients had progressive disease. Responses were seen in three out of the six patients who had received prior adjuvant chemotherapy. Fifteen of the 22 patients who achieved a response had locally advanced or metastatic lymph node disease exclusively. However, five patients had visceral metastases, including three with liver and two with lung disease, and two additional patients had soft tissue metastases. The median duration of response was 10.5 months (95% CI, 7.6 to 16.8). The median time to progressive disease was 6.9 months (95% CI, 6.2 to 10.5), and the median overall survival time for all patients was 10.4 months (95% CI, 6.3 to 17.4 months). At the time of the report, two patients who had achieved CR status remain alive and free of recurrence at 48 and 36 months respectively. Both had exclusively locally advanced and lymph node disease before the chemotherapy. One of them underwent salvage cystectomy after chemotherapy, and no viable tumour was found at pathological study.

Table 2 lists the maximum grade of common toxicities observed in each patient. Grade 3 and 4 toxicities were primarily haematological. Twenty-seven (71%) patients experienced grade 3 or 4 granulocytopenia; however, only five (13%) patients in five of the total cycles experienced febrile neutropenia. Three patients developed grade 3 anaemia. Clinically significant thrombocytopenia was observed in one patient. There was one toxic death in a patient.
Table 2  Worst toxicity by patient

| Toxicity          | Grade |
|-------------------|-------|
|                   | 1     | 2     | 3     | 4     |
| Granulocytopenia  | 2     | 5     | 12    | 15    |
| Thrombocytopenia  | 3     | 1     | –     | –     |
| Anaemia           | 15    | 10    | 3     | –     |
| Vomiting          | 6     | 12    | 5     | –     |
| Mucositis         | 8     | 2     | –     | –     |
| Diarrhoea         | 4     | 10    | 3     | 1     |
| Fatigue           | 6     | 14    | 13    | –     |
| Alopecia          | 5     | 25    | 2     | –     |
| Peripheral neuropathy | 15  | 1     | 2     | –     |
| Hypersensitivity reaction | 2   | 3     | –     | –     |
| Fluid retention   | 5     | 2     | –     | –     |
| Skin changes      | 6     | 1     | –     | –     |
| Nephrotoxicity    | 3     | 2     | –     | –     |
| Infection         | 5     | 6     | 4     | 3     |

with grade 4 granulocytopenia who developed acute abdomen. Grade 3 and 4 nonhaematologic toxicity was experienced by five (13%) patients with nausea and vomiting, four patients (10%) with diarrhoea, two patients (5%) with peripheral neuropathy, and one patient with renal toxicity. A total of seven patients had severe non-neutropenic infections, that consisted of four urinary tract infections, two pneumonia, and one candida lung abscess in a patient with concurrent corticosteroid treatment. One patient died on study due to gastrointestinal haemorrhage without thrombocyto- penia. Two patients experienced episodes of cardiac arrhythmias, and one patient had a myocardial infarction. Most patients had some degree of fatigue with this therapy that did not lead to dose modification. Hair loss was common and 27 (71%) patients had total alopecia. Infusion-related hypersensitivity reactions were seen in five patients and all were mild (grade 1 and 2). Severe bronchoospasm was not observed. Grade 1 and 2 fluid retention occurred in five and two patients respectively, and it was generally noted after four or five cycles of treatment.

DISCUSSION

The initial experience with docetaxel in the treatment of urothelial cancer demonstrated single-agent activity in a series of patients previously treated with chemotherapy (McCaffrey et al., 1997). One trial performed on 30 chemotherapy-naïve patients showed a response rate of 31% (de Wit et al, 1998), suggesting that docetaxel could be among the drugs with high activity against urothelial cancer. In addition, docetaxel can be administered safely to patients with impaired renal function (Dimopoulos et al, 1998), a condition frequently associated with bladder carcinoma.

The present study evaluated docetaxel in combination with cisplatin which is generally considered to be the most active agent against urothelial cancer. Prior phase I studies showed the feasibility of this combination and its activity on different tumours (Pronk et al, 1997). The response rate observed for urothelial cancer in our study is within the range of the responses seen with other conventional (Sternberg et al, 1989) and newer schedules (Von der Maase et al., 1999; Dreicer et al, 2000) which are considered highly active. Responses were even seen in patients with visceral metastases, traditionally considered resistant to M-VAC chemotherapy, and also in patients previously treated with adjuvant chemotherapy, where the proportion of responses was similar to the whole group. It should be noted that two patients in our series have achieved long-term survival. At the time of the report, they remained alive and free of disease, at 4 and 3 years from the treatment.

The toxicity of this regimen was generally acceptable and manageable. The most common toxicity was haematological, mainly granulocytopenia. However, most episodes of granulocytopenia were brief and did not cause clinical repercussion, since only 13% of the patients experienced febrile neutropenia. Nevertheless, there was a toxic death associated with acute abdomen and severe granulo- cytopenia. This rare and serious complication has been reportedly associated with different chemotherapy schedules, including docetaxel (Cardenal et al, 1996). Also, several episodes of severe non-neutropenic infections were observed. They were probably linked to comorbidities and complications due to the neoplasm rather than to the treatment itself. In spite of the potential neurotoxicity of cisplatin and docetaxel, there was not a significantly high incidence of severe peripheral neuropathy. The incidence of thrombocytopenia and mucositis, two complications that may cause important morbidity and are frequently seen with other common regimens (Von der Maase et al, 2000), was very low.

Recently, two studies that used the same regimen in bladder carcinoma have been reported (Sengelov et al, 1998; Dimopoulos et al, 1999) (Table 3). The results of these three studies confirm the efficacy of this regimen. Variations in the distribution of pre-treatment prognostic features and the multicentre nature of two studies could justify the differences in the results between them. The toxicity profile observed was similar in the three studies, the side effects being generally of mild to moderate intensity.

Two additional studies have evaluated docetaxel in other combinations in the treatment of urothelial cancer. One of them evaluated the three-drug combination with cisplatin and etoposide (Cavallari et al, 2000). The response rate was 66.7% and the median overall survival was 14.5 months. Nevertheless, more than half of the patients required dose reductions due to haematological toxicity, despite the frequent use of G-CSF. The other study assessed the association of docetaxel and ifosfamide after failure of cisplatin-based chemotherapy (Krege et al, 2001). This combination showed activity with acceptable tolerability.

In the last few years, several clinical trials aimed at identifying polychemotherapy regimens with new drugs active against urothe- lial cancer have been initiated. The objective has been to find combinations that demonstrate improved efficacy and a better toxicity profile compared with that of M-VAC. The most extensively studied drugs have been gemcitabine (Moore et al, 1999; Von der Maase et al., 1999; Kaufman et al, 2000) and paclitaxel (Redman et al, 1998; Vaughn et al, 1998; Zielinski et al, 1998; Dreicer et al, 2000; Small et al, 2000), each in combination with cisplatin or carboplatin. These studies have usually shown an elevated activity with a favourable toxicity profile (Table 3). However, comparing results of different phase II trials is unreliable, because they are very dependent on the prognostic features of the patients included in the trials (Bajorin et al, 1999). At the moment, there is only one phase III trial available comparing gemcitabine plus cisplatin to standard M-VAC (Von der Maase et al, 2000). Four hundred and five patients were included, and no differences in activity in both regimens were found. However, the tolerance profiles were different, showing a significantly lower incidence of serious granulocytopenia and mucositis in the patients treated with gemcitabine plus cisplatin.

A few trials with three-drug regimens containing two new drugs have performed in recent years. The combination of paclitaxel, gemcitabine and cisplatin (Bellmunt et al, 2000; the one with ifosfamide, paclitaxel and cisplatin (Bajorin et al, 1998); and one with paclitaxel, gemcitabine and carboplatin (Hussain et al, 2001) showed promising activity with acceptable tolerability and haematological toxicity. The last study was comprised of patients with normal and poor renal function (Hussain et al, 2001). The association of paclitaxel, vinblastine and cisplatin, however, resulted in a poor efficacy (Mulatero et al, 2000). Another new approach studied, with preliminary encouraging results, consisted of a sequential schedule with doxorubicin and gemcitabine followed by ifosfamide, paclitaxel and cisplatin (Dodd et al, 2000). In summary, the present study shows that the association of docetaxel and cisplatin is an effective regimen in the treatment.
of advanced urothelial cancer. The results also show that a small number of patients, who would otherwise succumb to disease, can achieve long-term disease-free survival after this chemotherapy regimen. Although the toxicity of this regimen was not insignificant, it was tolerable considering that the severe toxicity observed was in general reversible and manageable. These results, added to the other recent studies that included docetaxel in their treatment regimens, indicate the interest in this drug in the treatment of urothelial cancer as an alternative to conventional therapeutic regimens. Further studies aimed at determining more accurately the potential of docetaxel are warranted together with investigation into new strategies that will introduce it into three-drug regimens or in combinations without cisplatin.

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REFERENCES

Bajorin DF, McCaffrey J, Hilton S, Mazumdar M, Kelly WK, Scher HI, Spencer J, Herr H, Higgins G (1998) Treatment of patients with transitional cell carcinoma of the urothelial tract with ifosfamide, paclitaxel and cisplatin: a phase II trial. J Clin Oncol 16: 2722–2727

Bajorin DF, Dodd PM, Mazumdar M, Fazzari M, McCaffrey JA, Scher HI, Herr H, Higgins G, Boyle MG (1999) Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. J Clin Oncol 17: 3173–3181

Bellmunt J, Guillem V, Paz-Ares L, Gonzalez Larriba JL, Carles J, Batiste Bellmunt J, Gómez C, Zincke H (2001) Phase II study of docetaxel and gemcitabine in advanced transitional-cell carcinoma of the urothelium. J Clin Oncol 18: 3247–3255

Cardenal F, Montes A, Llort G, Seguí J, Mesia R (1996) Typhlitis associated with docetaxel treatment. J Natl Cancer Inst 88: 1078–1079

de Wit R, Kruit WH, Stoter G, de Boer M, Kezer J, Verweij J (1998) Docetaxel: an active agent in metastatic urothelial cancer, results of a phase ii study in non-chemotherapy-pretreated patients. Br J Cancer 78: 1342–1345

Dimopoulos MA, Deliveliotis C, Moulopoulos LA, Papadimitriou C, Mitropoulos D, Anagnostopoulos A, Athanassiades P, Dimopoulos C (1998) Treatment of patients with metastatic urothelial carcinoma and impaired renal function with single-agent docetaxel. Urology 52: 56–60

Dimopoulos MA, Bakoyannis C, Georgoulis V, Papadimitriou C, Moulopoulos LA, Deliveliotis C, Karayannis A, Varkarakis I, Aravantinos G, Zervas A, Pantazopoulos D, Fountzilas G, Bamias A, Kyriakakis Z, Anagnostopoulos A, Giannopoulos A, Kosmidis P (1999) Docetaxel and cisplatin combination chemotherapy in advanced carcinoma of the urothelium: a multicenter phase II study of the Hellenic Cooperative Oncology Group. Ann Oncol 10: 1385–1388

Dreicer R, Manola J, Roth BJ, Cohen MB, Hattfels AK, Wilding G (2000) Phase II study of cisplatin and paclitaxel in advanced carcinoma of the urothelium: an Eastern Cooperative Oncology Group Study. J Clin Oncol 18: 1058–1061

Dodd PM, McCaffrey JA, Herr H, Mazumdar M, Bacik J, Higgins G, Boyle MG, Scher HI, Bajorin DF (1999) Outcome of chemotherapy surgery after treatment with methotrexate, vinblastine, doxorubicin and cisplatin in patients with resectable or metastatic transitional cell carcinoma. J Clin Oncol 17: 2546–2552

Dodd PM, McCaffrey J, Hilton S, Mazumdar M, Herr H, Kelly WK, Icasiano E, Boyle MG, Bajorin DF (2000) Phase I evaluation of sequential doxorubicin + gemcitabine then ifosfamide + paclitaxel + cisplatin for patients with unresectable or metastatic transitional-cell carcinoma of the urothelial tract. J Clin Oncol 18: 840–846

Fleming TR (1982) One-sample multiple testing procedure for phase II clinical trials. Biometrics 38: 143–149

Fossa SD, Sternberg C, Scher H, Theodore CH, Mead B, Dearnaley D, Roberts JT, Skovlund E (1996) Survival of patients with advanced urothelial cancer treated with cisplatin-based chemotherapy. Br J Cancer 74: 1655–1659

Hussain M, Vaishampayan U, Du W, Redman B, Smith DC (2001) Combination paclitaxel, carboplatin and gemcitabine is an active treatment for advanced urothelial cancer. J Clin Oncol 19: 2527–2533

Kaufman D, Raghavan D, Carducci M, Levine EG, Murphy B, Aisner J, Kuzel T, Nicol S, Oh W, Stadler W (2000) Phase II trial of gemcitabine plus cisplatin in patients with metastatic urothelial cancer. J Clin Oncol 18: 1921–1927

Krege S, Rembrink V, Börgermann CH, Otto T, Rubben H (2001) Docetaxel and ifosfamide as second line treatment for patients with advanced or metastatic urothelial cancer after failure of platinum chemotherapy: a phase II study. J Urol 165: 67–71

McCaffrey JA, Hilton S, Mazumdar M, Sadan S, Kelly WK, Scher HI, Bajorin DF (1997) Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. J Clin Oncol 15: 1853–1857

Moore MJ, Winquist EW, Murray N, Tannock IF, Hsu S, Bennett K, Walsh W, Seymour L (1999) 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 17: 2876–2881

Table 3 Cisplatin and carboplatin-based two drug regimens including either paclitaxel, gemcitabine or docetaxel in urothelial carcinoma

| Reference                  | Regimen         | N° patients | PS 0–1 (%) | Visceral metastases (%) | RR (%) | OS (months) |
|----------------------------|-----------------|-------------|------------|-------------------------|--------|-------------|
| Dreicer et al, 2000       | Cis+Doc         | 38          | 81         | 47          | 58     | 10.4        |
| Redman et al, 1998        | Carbo+Doc       | 66          | 64         | –           | 52     | 8           |
| Vaughan et al, 1998       | Carbo+Doc       | 38          | 58         | 71          | 42     | 12.5        |
| Small et al, 2001         | Carbo+Doc       | 25          | 88         | –           | 60     | 13.6        |
| von der Maase et al, 1999 | Cis+Doc         | 46          | 33         | 33          | 41     | 14.3        |
| Moore et al, 1999         | Cis+Gem         | 29          | 93         | 76          | 21     | 9           |
| Kaufman et al, 2000       | Cis+Gem         | 38          | 91         | 37          | 51     | 9.5         |
| Sengelow et al, 1998      | Cis+Doc         | 29          | 85         | 45          | 50     | 8.5         |
| Dimopoulos et al, 1999    | Cis+Doc         | 38          | 85         | 45          | 50     | 8.5         |

Abbreviations: PS, performance status; RR, response rate; OS, overall survival; Cis, cisplatin; Carbo, carboplatin; Pac, paclitaxel; Gem, gemcitabine; Doc, docetaxel.
Mulatero C, McClaren BR, Mason M, Oliver RTD, Gallagher CJ (2000) Evidence for a schedule-dependent deleterious interaction between paclitaxel, vinblastine and cisplatin in the treatment of advanced transitional cell carcinoma. *Br J Cancer* 83: 1612–1616

Pectasides D, Visvikis A, Aspropotamotis A, Halikia A, Karvounis N, Dimitriadi M, Athanassiou A (2000) Chemotherapy with cisplatin, epirubicin and docetaxel in transitional cell urothelial cancer. Phase II trial. *Eur J Cancer* 36: 74–79

Pronk LC, Schellens JH, Planting AS, van den Bent MJ, Hilkens PH, van der Burg ME, de Boer-Dennert M, Ma J, Blanc C, Hartevel M, Bruno R, Stoter G, Verweij J (1997) Phase I and pharmacologic study of docetaxel and cisplatin in patients with advanced solid tumors. *J Clin Oncol* 15: 750–758

Redman BG, Smith DC, Flaherty L, Du W, Hussain M (1998) Phase II trial of paclitaxel and carboplatin in the treatment of advanced urothelial carcinoma. *J Clin Oncol* 16: 1844–1848

Saxman SB, Propert KJ, Einhorn LH, Crawford ED, Tannock I, Raghavan D, Loehrer PJ, Trump D (1997) 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* 15: 2564–2569

Sengelov L, Kamby C, Lund B, Engelholm SA (1998) Docetaxel and cisplatin in metastatic urothelial cancer: a phase II study. *J Clin Oncol* 16: 3392–3397

Small EJ, Lew D, Redman BG, Petrylak DP, Hammond N, Gross HM, Eastham JA, Crawford ED (2000) Southwest Oncology Group study of paclitaxel and carboplatin for advanced transitional cell carcinoma: the importance of survival as a clinical trial end point. *J Clin Oncol* 18: 2537–2544

Sternberg C, Yagoda A, Scher H, Watson RC, Geller N, Herr H, Morse MJ, Segani PC, Vaughan ED, Bander N (1989) Methotrexate, vinblastine, doxorubicin and cisplatin for advanced transitional cell carcinoma of the urethelium: Efficacy and patterns of response and relapse. *Cancer* 64: 2448–2458

Vaughn DJ, Malkowicz SB, Zollick B, Mick R, Ramchandani P, Holroyde C, Armstead B, Fox K, Wein A (1998) Paclitaxel plus carboplatin in advanced carcinoma of the urethelium: an active and tolerable outpatient regimen. *J Clin Oncol* 16: 255–260

Von der Maase H, Andersen L, Crino L, Weinknecht S, Dogliotti L (1999) Weekly gemcitabine and cisplatin combination therapy in patients with transitional cell carcinoma of the urethelium: a phase II clinical trial. *Ann Oncol* 10: 1461–1465

Von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, Bodrogi I, Albers P, Knuth A, Lippert CM, Kebrat P, Sanchez-Rovira P, Wersall P, Cleall SP, Roychowdhury DF, Tomlin I, Visseren-Grul CM, Conte PF (2000) 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* 17: 3068–3077

Zielinski CC, Schnack B, Grbovic M, Brodowicz T, Wilschke C, Steger G, Pfliiger H, Marberger M (1998) Paclitaxel and carboplatin in patients with metastatic urothelial cancer: results of a phase II trial. *Br J Cancer* 78: 370–374