PERGAMON

European Journal of Cancer 36 (2000) 74–79

European Journal of Cancer

www.elsevier.com/locate/ejconline

Chemotherapy with cisplatin, epirubicin and docetaxel in transitional cell urothelial cancer. Phase II trial

D. Pectasides*, A. Visvikis, A. Aspropotamitis, A. Halikia, N. Karvounis, M. Dimitriadis, A. Athanassiou

1st Department of Medical Oncology, Metaxa's Memorial Cancer Hospital, 51 Botassi Street, 185 37 Piraeus, Greece

Received 15 March 1999; received in revised form 14 June 1999; accepted 28 June 1999

Abstract

Cisplatin (CDDP), epirubicin (EPI) and docetaxel have single agent activity against urothelial transitional cell carcinoma (TCC). We evaluated the efficacy and toxicity of this combination in locally advanced or metastatic urothelial TCC. Patients with urothelial TCC who had no prior chemotherapy (prior adjuvant chemotherapy >6 months allowed) were eligible for entry the study. Eligibility criteria were performance status 0–3, granulocyte count (AGC) $\geqslant 1.5$ (10^9/l), platelet count $\geqslant 100$ (10^9/l), clearance creatine $\geqslant 60$ ml/min and total bilirubin level $\leqslant 1.5$ mg/dl. Treatment consisted of EPI 40 mg/m^2 intravenous push, docetaxel 75 mg/m^2 in 1 h infusion with premedication and CDDP 75 mg/m^2 with pre- and posthydration. Treatment was repeated every 21 days. Antiemetics with dexamethasone and 5-HT_3 antagonists were used routinely. Prophylactic haematopoietic growth factors were not used. Patients were evaluated for toxicity weekly and assessed for response every two cycles of treatment. 32 patients were entered into the study and 30 patients (7 with locally advanced and 23 with metastatic disease) were assessable for response. There were 9 (30.0%) complete responses (2, 28.6% in locally advanced and 7, 30.4% in metastatic disease) and 11 (36.7%) partial responses (3, 42.9% in locally advanced and 8, 34.8% in metastatic disease) with an overall response rate (RR) of 66.7% (71.5% in locally advanced, 65.2% in metastatic disease). Overall median survival was 14.5 months (15 months for locally advanced, 12.5 months for metastatic disease). The median duration of response in patients with metastatic disease was 8.5 months. 16 (53.3%) patients required one dose reduction and 5 (16.7%) patients required two dose reductions for a nadir AGC $\leqslant 500$/mm^3. Four episodes of febrile neutropenia and sepsis occurred. No patient had a dose reduction or treatment delay for any other grade 3/4 toxicity. There were no treatment delays due to myelotoxicity. Alopecia was universal. Non-haematological toxicity including mucositis, fluid retention, allergy, cutaneous toxicity, diarrhoea and neurotoxicity were mild and infrequent. The combination of EPI, docetaxel and CDDP is an active regimen for urothelial TCC. The response rate and toxicity were comparable with the M-VAC (methotrexate, vinblastine, doxorubicin, cisplastin) regimen. Phase III trials comparing this regimen with M-VAC are warranted.

Keywords: Urothelical cancer; Locally advanced urothelical cancer; Metastatic disease; Combination chemotherapy; Cisplatin; Epirubicin; Doxetaxel

1. Introduction

Carcinoma of the bladder is the fourth most common cancer in men and the ninth in women [1]. Most would consider transitional cell carcinoma (TCC) of the urothelium a 'chemosensitive tumour'. Of the patients who present with muscle invasive bladder cancer, approximately one-third will be cured by local therapy, while the remainder will develop pelvic recurrence or distant metastases. Only 5–10% of patients with T_4 tumours will survive 5 years, while metastatic cancer is a rapidly fatal disease with a median survival of less than 9 months [2].

A large number of phase II trials of single-agent therapy have been performed in the last 20 years. The most active drugs as single agents are cisplatin (CDDP), and methotrexate (MTX), with more modest activity seen with the use of vinblastine (VLB), doxorubicin (ADR) and 5-fluorouracil (5-FU) [3]. The response rate (RR) with these agents ranged from 20 to 35%. The highest RRs in advanced urothelial TTC have been reported with the use of more intensive regimens that combine three or more active drugs. Cisplatin-based combination chemotherapy has become the standard of

* Corresponding author.

0959-8049/00/$ - see front matter
PII: S0959-8049(99)00187-2

care for patients with advanced urothelial TCC. The combination of CDDP with MTX and VLB (CMV) or these agents with ADR (M-VAC-MTX-VLB-ADR-CDDP) have reported RRs of 56–72% [4, 5]. More recently, a multi-institutional phase III trial of M-VAC compared with CDDP alone showed the superiority of the combination over single-agent CDDP in both RR (39% versus 12%) and survival [6]. However, the toxicity of these regimens was significant despite the dose modifications, including grades 3 and 4 myelosuppression, mucositis, nephrotoxicity, nausea and vomiting as well as drug-related mortality. A comparative study in patients with metastatic urothelial cancer showed that M-VAC was superior to CISCA [7]. CMV and M-VAC have never been compared in randomised trials.

Combination chemotherapy has been also applied as an initial treatment with curative intent to patients with locally advanced disease [8, 9]. In 50 patients with T_2–T_4 tumours treated with M-VAC, significant downstaging was achieved in 70% [8]. However, the toxicity was again significant. Also, when CMV was used in 17 patients with locally advanced cancer, a complete response (CR) was obtained in 11 (64.7%) of them. Complications included neutropenic sepsis with septic deaths and nephrotoxicity [10].

In the last years, there have been changes in the management of locally advanced and metastatic urothelial cancer. Despite the use of haematopoietic growth factors for less myelotoxicity and the intensification of M-VAC chemotherapy, the responses were relatively similar [11, 12]. Thus, it is unlikely that further improvements in therapy will arise from minor manipulation of existing regimens. Those advances will rely on the development of novel combination regimens using some of the new active agents identified over the years. Single-agent data on epirubicin (EPI) are sparse [13], but several combination regimens have substituted this agent for ADR [14, 15]. Although it is difficult to determine the equivalence of efficacy of EPI compared with ADR in these trials, it appears that EPI resulted in less toxicity than comparable ADR-based regimens.

Docetaxel is a novel antimicrotubule agent that has a mechanism of action as a promoter of microtubule assembly, and a stabiliser of tubulin polymers against depolymerisation [16]. In addition, docetaxel generates tubulin polymers that differ structurally from those generated by paclitaxel [17] and does not alter the number of protofilaments in the microtubules whilst paclitaxel does. In a phase II study, docetaxel has shown activity in urothelial cancer [18]. Of the 8 evaluable patients, 4 achieved a partial response (PR). The combination of CDDP and docetaxel has shown significant activity in metastatic urothelial TCC [19, 20]. In addition, the combination of CDDP and docetaxel has demonstrated a significant pathological complete remission in patients with T_2–T_4 NoMo tumours with mild toxicity [21].

Based on the single-agent activity of doxetaxel, EPI and CDDP and their favourable toxicity profiles, we initiated a phase II trial of this combination as first-line chemotherapy in patients with locally advanced or metastatic urothelial TCC. Because of the previously reported sequence interaction of EPI and docetaxel and CDDP and docetaxel in patients with breast and ovarian cancer, we administered EPI before docetaxel and CDDP following docetaxel.

2. Patients and methods

From September 1996 to September 1998, 32 patients (26 men and 6 women) with locally advanced (8 patients) or metastatic (24 patients) urothelial TCC entered this phase II study. All patients required to have histologically proven TCC or positive urine cytology, an ECOG performance status of 0–3, measurable or assessable disease outside prior radiotherapy ports, life expectancy of at least 12 weeks, adequate haematological (white blood cells, WBC) > 4 (10^9/l), neutrophils > 2 (10^9/l), platelets > 100 (10^9/l), haemoglobin > 10 g/dl) renal (serum creatinine < 1.5 mg/dl, creatinine clearance $\geqslant 60$ ml/min) and liver functions (bilirubin $\leqslant 1.5$ mg/dl, γGT (γ-glutamyl-transpeptidase) and alkaline phosphatase < 5 times in patients with known liver metastases). Patients with prior intravesical chemotherapy or immunotherapy were not excluded from the study. Prior adjuvant treatment was allowed if it was completed at least 6 months before protocol treatment. Also, patients who had previously been treated with radiotherapy (DRX) entered the study, providing that measurable disease existed outside the radiation field and if at least 4 weeks had elapsed before the protocol treatment. Patients with brain metastases, history of atrial or ventricular arrhythmias, congestive heart failure even if medically controlled, documented myocardial infarction and pre-existing motor or sensory neurotoxicity grade $\geqslant 2$ according to the WHO scale (intolerance paraesthesias and/or marked motor loss) were excluded from the study. Written informed consent was required from all patients.

Before entering the study all patients underwent physical examination, full blood count (FBC), blood chemistry, chest X-ray, bone scan, abdominal computed tomography (CT) scan and urine cytology. Intravenous urography, bimanual examination under general anaesthesia and cytoscopy were mandatory for patients with locally advanced disease. Thoracic CT scan and other specific tests were performed when indicated. Responses were assessed every two cycles of treatment and included clinical examination, FBC, blood chemistry, chest X-rays, CT scan of the abdomen and pelvis and urine cytology and cystoscopy for patients with locally advanced disease.

Patients with locally advanced or loco-regional disease were scheduled to receive four courses of chemotherapy. Patients who responded completely or partially were advised to have radical cystectomy or DRX. In case of refusal of cystectomy DRX to the bladder was recommended. Patients with metastatic disease were treated with at least six cycles of the same chemotherapy, unless there was evidence of disease progression or unacceptable toxicity occurred during the courses.

Treatment was intended to be administered on an inpatient basis. All patients received the same chemotherapy regimen consisting of EPI 40 mg/m^2 intravenous (i.v.) push, docetaxel 75 mg/m^2 as a 1-h infusion with premedication including dexamethasone, 8 mg orally 12 and 4 h before docetaxel infusion and 8 mg tid for 3 additional days and CDDP 75 mg/m^2 (after docetaxel) with pre- and post-hydration. Treatment was repeated every 3 weeks. Antiemetic treatment with 5-HT$_3$ antagonists and dexamethasone was given before the CDDP administration.

Doses of drugs were adjusted according to WBC and platelet counts as well as creatinine clearance and liver function. Chemotherapy was given if the granulocyte count (AGC) was $>1500/mm^3$ and the platelet count was $>100\,000/mm^3$ on the day of treatment. Patients had a dose reduction of docetaxel to 65 mg/m^2 and EPI to 35 mg/m^2 if they had an AGC nadir $<1000/mm^3$ and/or platelet nadir $<75\,000/mm^3$. If the AGC nadir was $<500/mm^3$ and the platelet nadir $<50\,000/mm^3$, docetaxel was reduced to 55 mg/m^2 and EPI to 30 mg/m^2. The dose of CDDP was adjusted according to the creatinine clearance. If the creatinine clearance was <50 ml/min, treatment was delayed until recovery (no longer than 10 days; otherwise the patient was removed from the study). A 25% dose reduction was performed when the creatinine clearance was between 50 and 59 ml/min. If patients experienced a grade 3 non-haematological toxicity, treatment was held until recovery to grade 1 or less. If a grade 4 non-haematological toxicity was experienced, then treatment was delayed until recovery of grade 1 or less and both drugs were reduced as for myelosuppression.

Patients were monitored weekly for FBC and serum creatinine levels and were evaluated for toxicity on day 15 and just before treatment. The WHO scale was used for toxicity grading. Response assessment was based on the WHO criteria [22]. Pathological CR was defined as the histological absence of tumour at radical cystectomy. Clinical CR was defined as the complete disappearance of all clinically detectable disease for at least 4 weeks. Chemotherapy was continued for two further cycles following CR. Partial response (PR) was defined as a $\geqslant 50\%$ reduction of all measurable or assessable disease or downstaging of invasive to superficial disease in the bladder. It will ideally be confirmed by two evaluations of the disease made not less than 4 weeks apart. Chemotherapy was continued until maximum response was achieved plus two cycles. Stable disease (SD) was defined as a $<50\%$ reduction of all measurable or assessable lesions. Confirmation of SD required two evaluations of the disease, ideally made not less than 4 weeks apart. Chemotherapy was discontinued after a total of six courses had been administered. Progressive disease (PD) was defined as an increase in any lesion or the appearance of new lesions.

Survival was calculated from the day of initiation of chemotherapy to the day of death using the Kaplan–Meier method [23]. Duration of response was calculated from the date the response was documented until the date of first progression.

3. Results

32 patients were registered and treated on this trial. Patient characteristics are shown in Table 1. There were 24 males and 8 females with a median age of 62 years (range: 43–75 years). 8 patients had locally advanced disease and 24 metastatic urothelial cancer. Of the 32 patients all were assessable for toxicity and 30 (7 with locally advanced and 23 with metastatic disease) were assessable for response. One patient with locally advanced disease, removed herself from the treatment

Table 1
Patient characteristics

	Locally advanced disease	Metastatic disease
Total number	8	24
Age (year) median-range	65 (43–73)	64 (44–75)
Sex		
Male/female	6/2	20/4
Previous treatment		
Intravesical chemotherapy	2 (25.0%)	5 (20.8%)
Radiotherapy	0	4 (16.7%)
Cystectomy	0	8 (33.3%)
Adjuvant chemotherapy	0	3 (12.5%)
ECOG performance status		
0	6 (75.0%)	4 (16.7%)
1	1 (12.5%)	5 (20.8%)
2	1 (12.5%)	11 (45.8%)
3	0	4 (16.7%)
Stage		
T_2–T_3 NoMo	5 (62.5%)	
T_4 NoMo	3 (37.5%)	
TxNxM+	0	24 (100.0%)
Sites of metastases		
Lymph nodes		18 (75.0%)
Lymph nodes only		12 (50.0%)
Liver		6 (25.0%)
Lung		6 (25.0%)
Bones		4 (16.7%)

Table 2
Response to chemotherapy

	CR (%)	PR (%)	SD (%)	PD (%)
Locally advanced ($n=7$)	2 (28.6)	3 (42.9)	1 (14.3)	1 (14.3)
Metastatic disease ($n=23$)	7 (30.4)	8 (34.8)	3 (13.0)	5 (21.7)
Total 30	9 (30.0)	11 (36.7)	4 (13.3)	6 (20.0)

Table 3
Response by site of metastases

	CR		PR	
	No	%	No	%
Lymph nodes	5	27.8	7	38.9
Liver	1	16.7	3	50.0
Lung	3	50.0	1	16.7
Bones	0	0	2	50.0

after the first cycle due to nausea and vomiting and severe fatigue. This patient was treated with surgery. The patient with metastatic disease developed an allergic reaction after a few millimetres of the first cycle of docetaxel infusion and elected to discontinue treatment. 12 patients had lymph node disease only, whereas 16 patients had distant metastases. 3 patients had received prior adjuvant therapy with MCNO (methotrexate, carboplatin, novantrone, oncovin) regimen more than 6 months before study entry.

The overall responses to chemotherapy of the 30 treated patients are shown in Table 2. 9 (30%) patients achieved a CR, 11 (36.7%) a PR, with an objective response rate (CR + PR) of 66.7%, 4 (13.3%) patients achieved a SD and 6 (20.0%) a PD. The median survival for the whole group of patients was 14.5 months (range: 3–24+ months). In the subgroup of 7 patients with locally advanced disease, 1 (14.3%) patient achieved a pathological CR, 1 (14.3%) a clinical CR, 3 (42.9%) a PR, 1 (14.3%) a SD and 1 (14.3%) a PD. The overall objective RR was 71.5% and the overall median survival 15 months (range: 5–24+ months). Among the 23 patients with metastatic disease, 7 (30.4%) patients achieved a CR, 8 (34.8%) a PR (CR + PR 65.2%), 3 (13.0%) a SD and 5 (21.7%) a PD. The median duration of response for this subgroup of patients was 8.5 months (range: 2–16+ months) and the overall median survival 12.5 months (range: 3–22.5+ months). Response by site of metastases is demonstrated in Table 3. It is of note that there were CRs in liver and lung metastases; the RR for both sites was 66.6%. Similar responses were obtained in lymph node metastases, while bone metastases responded only partially.

The median number of cycles per patient was 5 (range 1–8 cycles). Myelosuppression was the only toxicity that resulted in dose reduction. No patient had a dose reduction or treatment delay for any other grade 3 or 4 toxicity. Grade 3/4 neutropenia was observed in 17 (53.1%) patients, grade 3/4 thrombocytopenia in 3 (9.4%) and grade 3/4 anaemia in 4 (12.5%). Haematopoietic growth factors were not used routinely, but only in the case of grade 3/4 neutropenia and/or febrile neutropenia. Despite the use of haematopoietic growth factors, 16 (53.3%) patients required a dose reduction due to neutropenia and of these 5 (16.7%) required two reductions. There were 4 (12.5%) episodes of febrile neutropenia that required hospitalisation. Neutropenia recovered quickly and there were no treatment delays due to myelosuppression. Alopecia was universal but reversible. Nephrotoxicity grade 2 was observed in 3 (9.4%) patients. Nausea and vomiting $\geqslant 2$ occurred in 5 (15.6%) patients. Fluid retention was developed in 3 (9.4%) patients and 2 (6.3%) patients experienced grade 1 cutaneous toxicity. 3 (9.4%) patients developed grade 2 diarrhoea. No patient had cardiac problems and no drug-related mortality was observed. Infusion-related allergy occurred in 2 (6.2%) patients evidenced by chest tightness, cough, dyspnoea and flushing during the first or second infusion of docetaxel. All these reactions resolved in 5–10 min. One patient developed a very serious allergic reaction that was treated with antihistamines, corticosteroids and adrenaline and resulted in the discontinuation of treatment. 6 (18.8%) patients reported weakness and fatigue but no grade 2 or 3 neuromotor toxicity was noted. Paraesthesias, loss of vibration sensation and loss of deep tendon reflexes were the most frequent findings in 7 (21.9%) patients. Mucositis grade 2/3 occurred in 5 (15.6%) patients (Table 4).

Discussion

Urothelial TCC is a chemosensitive tumour, as the CMV and M-VAC achieve an overall RR of 50–70% with a CR of 30–40% [4, 5]. The reported median survival with these regimens did not greatly exceed 12 months. Because of the activity reported for M-VAC, it has become the community standard for the treatment of advanced urothelial cancer. However, the use of M-VAC has limitations. Trials that evaluated M-VAC reported a high degree of toxicity, mainly neutropenic fever or sepsis (25% of patients) and grade 3/4 mucositis (17% of patients) [6, 24]. Despite the impressive RRs reported for M-VAC, long-term follow-up shows that the vast majority of patients die of their disease with only 3.7% of long-term disease-free survivors at 6 years from M-VAC alone [24]. This has prompted research for novel active agents which could be incorporated with old active drugs for urothelium. Among these new agents, docetaxel seems to be one of the most promising

Table 4
Toxicity

	WHO grade				
	0 (%)	1 (%)	2 (%)	3 (%)	4 (%)
Neutropenia	1 (3.1)	4 (12.5)	10 (31.3)	9 (28.1)	8 (25.0)
Anaemia	3 (9.4)	10 (31.3)	15 (46.9)	3 (9.4)	1 (3.1)
Thrombocytopenia	8 (25.0)	12 (37.5)	9 (28.1)	2 (6.2)	1 (3.1)
Nephrotoxicity	17 (53.1)	12 (37.5)	3 (9.4)	0	0
Alopecia	0	0	0	8 (25.0)	24 (75.0)
Nausea/vomiting	4 (12.5)	8 (25.0)	15 (46.9)	3 (9.4)	2 (6.2)
Neurosensory	25 (78.1)	4 (12.5)	2 (6.2)	1 (3.1)	0
Fluid retention	29 (90.6)	2 (6.2)	1 (3.1)	0	0
Mucositis	25 (78.1)	2 (6.2)	3 (9.4)	2 (6.2)	0
Allergy	29 (90.6)	1 (3.1)	1 (3.1)	0	1 (3.1)
Diarrhoea	25 (78.1)	4 (12.5)	3 (9.4)	0	0
Cutaneous	30 (93.8)	2 (6.2)	0	0	0

drugs. Although, the other two agents have shown efficacy in urothelial TCC, until now, no study has been carried out using a combination with these agents.

In two small phase II trials from Europe, docetaxel as a single agent at a dose of 100 mg/m^2 demonstrated PRs of only 50% (4/8 patients) and 45.5% (5/11 patients) respectively in chemotherapy-naïve patients with metastatic urothelial TCC [18, 25]. Docetaxel was also given as second-line treatment at a dose of 100 mg/m^2 in 30 assessable patients with advanced or metastatic TCC who had failed to respond to or relapsed after one prior CDDP-containing regimen. It yielded a PR of 13.4% [26]. The combination of CDDP at a dose of 75 mg/m^2 and docetaxel at a dose of 75 mg/m^2 yielded a RR of 59% and 60%, respectively, in metastatic TCC [19, 20]. Based on previous experiences using various combinations of taxanes, CDDP and EPI, we administered the three agents in the following sequence: EPI, docetaxel, CDDP. The present report describes the first phase II study combining EPI, docetaxel and CDDP in the treatment of chemotherapy-naïve patients with locally advanced or metastatic urothelial TCC.

We found that the combination of EPI, docetaxel and CDDP appears to be a safe and effective regimen in locally advanced and metastatic urothelial TCC. The overall RR and survival in the present study were similar to those reported for M-VAC and slightly better from those obtained with the combination of CDDP and docetaxel in this disease. Responses were slightly better for locally advanced disease (CR 28.6%, PR 42.9%, RR 71.5%) and very promising for metastatic disease (CR 30.4%, PR 34.8%, RR 65.2%). This regimen appears to be effective even in patients with visceral (liver, lung) metastases. The responses in locally advanced disease were similar when compared with those reported in two other trials [19, 27]. The first one was a preliminary report of a phase II trial that evaluated docetaxel at a dose of 75 mg/m^2 and CDDP 75 mg/m^2 as a neoadjuvant treatment in 44 patients with T_2–T_4 NoMo tumours. This regimen induced CRs or downstaging in a significant number of patients. The treatment was well tolerated and grade 3/4 neutropenia occurred in 20% of patients with no sepsis or hospitalisation requirements. The second trial evaluated the combination of docetaxel and CDDP on a weekly basis with external radiotherapy in T_1–T_4 NoMo tumours. They concluded that the administration of docetaxel and CDDP weekly as radiosensitisers in combination with external DRX can be safely administered and yielded a high CR rate. The toxicity of this regimen was moderate to severe.

Given that the combination of CDDP and docetaxel administered as neoadjuvant treatment was well tolerated and resulted in 20% grade 3/4 neutropenia, we considered that the addition of EPI to CDDP and docetaxel could be safe in patients with urothelial TCC. However, this regimen appears to be toxic, since 53.1% of patients developed grade 3/4 neutropenia and 12.5% of these patients required hospitalisation due to febrile neutropenia. However, no major infections or treatment-related deaths were observed in this study, compared with 41% febrile neutropenia reported in the study using MVAC [6]. Despite the use of haematopoietic growth factors, 53.3% of patients required a dose reduction and 16.7% required two reductions due to severe neutropenia. Thrombocytopenia grade 3/4 occurred in 9.4% of patients. No serious nephrotoxicity was reported. Nausea and vomiting were moderate but easily managed. Neurotoxicity $\geqslant$ grade 2 was observed in one patient. The neurotoxicity declined in the follow-up period. Cutaneous toxicity and fluid retention were very limited with the use of premedication. The hypersensitivity reactions were generally mild and resolved within 10 min. Premedication was given to reduce the risk of hypersensitivity reactions and the incidence of 6.2% in this study compares favourably with other

studies. The incidence of diarrhoea and mucositis were substantially lower than previously described [20].

In conclusion, the combination of EPI, docetaxel and CDDP seems to be effective in the treatment of locally advanced or metastatic urothelial TCC. The toxicity seen with this combination was similar to that reported with M-VAC. A phase III randomised trial comparing this regimen with a standard treatment combination as MVAC would be required to definitely answer the question of any survival advantage.

References

1. Wingo PA, Tong T, Bolden S. Cancer Statistics. 1995. *CA Cancer J Clin* 1995, **45**, 45–48.
2. Quilty PM, Duncan W, Chisholm GD, Fowler JW, Hargrave TB, Newman JE. Results of surgery following radical radiotherapy for invasive bladder cancer. *Br J Urol* 1986, **58**, 396–405.
3. Yagoda A. Chemotherapy of metastatic bladder cancer. *Cancer* 1980, **45**, 1879–1888.
4. Harker WG, Meyers FJ, Freiha FS, *et al*. Cisplatin, methotrexate and vinblastine (CMV): an effective chemotherapy regimen for metastatic transitional cell carcinoma of the urinary tract. A Northern California Oncology Group Study. *J Clin Oncol* 1985, **3**, 1463–1470.
5. Stenberg CN, Yagoda A, Scher HI, *et al*. M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for advanced transitional cell carcinoma of the urothelium. *J Urol* 1988, **39**, 461–469.
6. Loeher PJ, Einhorn LH, Elson PJ, *et al*. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma. A cooperative groupstudy. *J Clin Oncol* 1992, **10**, 1066–1073.
7. Logothetis CJ, Dexeus FH, Finn L, *et al*. A prospective randomized trial comparing M-VAC and CISCA chemotherapy for patients with metastatic urothelial tumours. *J Clin Oncol* 1990, **8**, 1050–1055.
8. Pectasides D, Mylonakis A, Antoniou F, *et al*. Chemotherapy with methotrexate, carboplatin, mitoxantrone (novantrone) and vincristine (oncovin) in transitional-cell urothelial cancer. *Oncology* 1998, **55**, 139–144.
9. Scher HJ, Yagoda A, Herr HW, *et al*. Neoadjuvant M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) effect of the primary bladder lesion. *J Urol* 1988, **139**, 470–474.
10. Meyers FJ, Palmer JM, Freiha FS, Harker E, Hannigan J, Torti F. The fate of the bladder in patients with metastatic bladder cancer treated with cisplatin, methotrexate, and vinblastine. A Northern California Oncology Group Study. *J Urol* 1985, **134**, 1118–1121.
11. Sternberg CN, de Mulder PH, van Oosterom AT, Fossa SD, Giannarelli D, Soedirman JR. Escalated M-VAC chemotherapy and recombinant human granulocyte-macrophage colony stimulating factor (rhGM-CSF) in patients with advanced urothelial tract tumours. *Ann Oncol* 1993, **4**, 403–407.
12. Seidman AD, Scher HI, Gabrilove JL, *et al*. Dose-intensification of M-VAC with recombinant granulocyte colony stimulating factor as initial therapy in advanced urothelial cancer. *J Clin Oncol* 1993, **11**, 408–414.
13. Goldfarb A, Negro A, Coimbra F, et al. Methotrexate, vindesine, epidoxorubicin and cisplatin (M-VEC) for stage III–IV bladder cancer. Final results. *Am Soc Clin Oncol* 1992, **11**, 210 (abstract).
14. Passalacqua R, Cocconi G, Macaluso G, et al. M-VAC versus the same combination using epirubicin at double dose in locally invasive bladder cancer. A prospective study. *Am Soc Clin Oncol* 1992, **11**, 210 (abstract).
15. Skarlos DV, Aravantinos G, Linardou E, *et al*. Chemotherapy with methotrexate, vinblastine, epirubicin and carboplatin (M-VEC) in transitional cell urothelial cancer. *Eur J Urol* 1997, **31**, 420–427.
16. Ringel I, Horwitz SB. Studies with RP 56976 (Taxotere). A semisynthetic analog of Taxol. *J Natl Cancer Inst* 1991, **83**, 288–291.
17. Fromes Y, Gounon P, Bissery MC, Fellous A. Differential effects of Taxol or Taxotere on Tan and MAP2 containing microtubules. *Proc AACR* 1992, **33**, 511 (abstract).
18. DeWit R, Stoter G, Blanc C, Hubert S, Verweij J. Phase II study of docetaxel (Taxotere) in patients with metastatic urothelial cancer. *Ann Oncol* 1994, **5**(Suppl. 8), 67 (abstract).
19. Dimopoulos AM, Louras G, Pantazopoulos D, et al. Docetaxel and cisplatin (DC) combination chemotherapy for metastatic urothelial cancer. *Eur J Cancer* 1997, **33**(Suppl. 8), 145 (abstract).
20. Sengelov L, Kamby C, Lund B, Engelholm SA. Docetaxel and cisplatin in metastatic urothelial cancer. A phase II study. *J Clin Oncol* 1998, **16**, 3392–3397.
21. Dimopoulos MA, Deliveliotis C, Kyriakakis Z, et al. Neoadjuvant docetaxel and cisplatin for muscle invasive carcinoma of the bladder. *Am Soc Clin Oncol* 1998, **17**, 316a (abstract).
22. *WHO Handbook for Reporting Results of Cancer Treatment*. The Hague, Nijhoff, 1979, No 48.
23. Kaplan EL, Meier P. Non-parametric estimation for incomplete observations. *J Am Stat Assoc* 1958, **53**, 357–481.
24. Saxman SD, Propert KJ, Einhorn LH, *et al*. Long-term follow-up of a phase III intergroup study of cisplatin alone or in combination with methotrexate, vinblastin and doxorubicin in patients with metastatic urothelial carcinoma. *J Clin Oncol* 1997, **15**, 2564–2569.
25. Dimopoulos MA, Deliveliotis C, Moulopoulos LA, *et al*. Treatment of patients with metastatic urothelial carcinoma and impaired renal function with single-agent docetaxel. *Urol* 1998, **52**, 56–60.
26. McCaffrey JA, Hilton S, Mazumdar M, *et al*. Phase II trial of docetaxel in patients with advanced or metastatic transitional-cell carcinoma. *J Clin Oncol* 1997, **15**, 1853–1857.
27. Varveris H, Delakas D, Anezinis H, *et al*. Concurrent platinum and docetaxel chemotherapy and external radical radiotherapy in patients with invasive transitional cell bladder carcinoma. A preliminary report of tolerance and local control. *Anticancer Res* 1997, **17**, 4771–4780.