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ORIGINAL RESEARCH

# Efficacy of methotrexate/vinblastine/doxorubicin/cisplatin combination in gemcitabine-pretreated patients with advanced urothelial cancer: a retrospective analysis

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**Objective:** Second-line treatment options in advanced urothelial cancer are limited. We investigated the efficacy of a methotrexate/vinblastine/doxorubicin/cisplatin (MVAC) combination after failure of gemcitabine/platinum chemotherapy.

**Patients and methods:** Twenty-five patients with advanced urothelial cancer, who received second-line MVAC after first-line gemcitabine/cisplatin (n = 9) or gemcitabine/carboplatin (n = 16), were included in this retrospective analysis.

**Results:** Twenty-two patients (88%) relapsed within 6 months after first-line treatment. Following MVAC, there were 5 (20%) objective responses. Median follow-up was 20.2 months. Median progression-free survival (PFS) was 3.8 months (95% CI: 2.3–5.2), and median overall survival (OS) was 9 months (95% CI: 6.6–11.4). Eastern Cooperative Oncology Group performance status 0.1 versus 2 was associated with longer PFS (5 months versus 3.3 months, $P = 0.049$). Response or stabilization of disease during second-line chemotherapy predicted for a significantly longer PFS and OS (7.4 versus 3.5, $P = 0.005$; 15.5 versus 7, $P = 0.046$).

**Conclusions:** Second-line MVAC chemotherapy may result in prolonged survival in some patients with refractory disease. Further research in this field is necessary.

**Keywords:** MVAC, second line, bladder cancer

## Introduction

Urothelial cancer is a common malignancy. Cisplatin-based chemotherapy is the standard of care in initially metastatic, unresectable, or recurrent after cystectomy disease.[1] Until recently, the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) has been the standard of care in advanced urothelial cancer. Following the results of a randomized study, the combination of gemcitabine/cisplatin (GC) has been substituted for MVAC by many centers due to noninferiority and a more favorable toxicity profile.[2] Almost half of the patients with inoperable or recurrent urothelial cancer are unfit to receive cisplatin in the first-line setting. In this setting, carboplatin-based chemotherapy has been used.[1] Specifically, carboplatin/gemcitabine (CaG) combination has shown considerable efficacy in several studies in unfit as well as in fit-for-cisplatin patients.[3–6] High response rates (RRs) and prolongation of survival have been achieved with systemic chemotherapy in advanced urothelial cancer, but eventually most patients will relapse and therefore long-term disease-free survival remains infrequent. It is imperative that improvement of the prognosis of

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these patients will require the development of effective therapies following relapse after first-line treatment.

There are limited data on second-line chemotherapy in advanced urothelial cancer (Table 1). One of the main reasons is the fact that after progressing following first-line treatment, there is frequently a significant deterioration in performance status (PS) and/or renal function, which makes the enrolment of patients in clinical studies or the administration of systemic chemotherapy outside the context of a clinical trial difficult. In most studies, nonplatinum agents or combinations have been used. Combinations containing gemcitabine, mostly combined with taxanes, represent the most studied therapy.[7–11,19] The efficacy of this treatment is limited with RRs averaging 20% and median overall survival (OS) of 7–11 months. More importantly, the clinical relevance of this treatment has been limited by the emergence of GC as a new standard, as many of the patients on progression will have been exposed to gemcitabine. Equally modest activity has been reported with novel agents, such as pemetrexed, piritrexim, and vinflunine.[12,13,20–22] Therefore, there is a need for more effective treatment in relapsed advanced urothelial cancer.

The percentage of unfit-for-cisplatin patients is high at relapse after first-line chemotherapy. Nevertheless, given the efficacy of platinum-based chemotherapy, a retrial has been attempted in those patients who can tolerate it (Table 1).[14–18] Specifically, MVAC has been proposed as an option in patients treated with this regime and relapsing after more than 12 months.[23] Nevertheless, there is limited information on the efficacy of cisplatin-based combination chemotherapy following gemcitabine-based first-line chemotherapy.

We attempted to retrospectively study the efficacy of MVAC combination as second-line therapy in advanced or recurrent urothelial cancer following first-line gemcitabine-based chemotherapy.

## Patients and methods

### Patients

The patients included in this analysis were retrieved from the advanced urothelial cancer database of the Oncology/Haematology Unit of the Department of Clinical Therapeutics, University of Athens, Greece, and were treated at Alexandra and Attikon Hospitals, Athens, Greece. Criteria for inclusion in the analysis were histologically confirmed urothelial cancer, first-line treatment with GC or CaG, and second-line MVAC chemotherapy. The medical records of patients fulfilling these criteria were reviewed regarding the following information: first-line chemotherapy; response; progression-free survival (PFS); time to second-line therapy and treatment-free interval (TFI) after first-line chemotherapy; baseline characteristics (primary site, histological type, sites of metastases, and PS) prior to second-line MVAC; and response, toxicity, PFS, and OS following MVAC.

**Table 1** Selected studies of second-line combination chemotherapy in patients with advanced urothelial cancer who received first-line cisplatin-based chemotherapy

| Treatment | Prior regime | No. | RR | Median OS (mos) |
|---|---|---|---|---|
| Nonplatinum-containing second-line chemotherapy | | | | |
| Gemcitabine/paclitaxel[7] | MVAC | 15* | 27% | – |
| Gemcitabine/paclitaxel[8] | MVAC, MCaVI | 10* | 30% | – |
| Gemcitabine/paclitaxel[9] | MVAC | 20 | 30% | 11.5 |
| Gemcitabine/paclitaxel[10] | MVAC, MVEC | 14* | 14% | – |
| Gemcitabine/paclitaxel[11] | MVAC, MEC | 33 | 33% | 11.3 |
| Pemetrexed[12] | NR | 29* | 27% | 9.2 |
| Vinflunine[13] | NR | 253 | NR | 6.9 |
| Cisplatin-containing second-line chemotherapy | | | | |
| Paclitaxel/methotrexate/cisplatin[14] | MVAC | 25 | 40 | 3.7 |
| Fluorouracil, interferon, cisplatin[15] | MVAC, CMV | 43 | 13 | 4.9 |
| Gemcitabine, ifosfamide, cisplatin[16] | MVAC, FAP, CMV, TMP, CaP | 51 | 41 | 9.5 |
| MVAC[17] | GC | 30 | 30 | 10.9 |
| Cisplatin, paclitaxel[18] | GC | 28 | 36 | 10.3 |
| MVAC (this study) | GC, CaG | 20 | 25 | 9 |

**Note:** *Subanalysis excluding patients who received first-line chemotherapy as adjuvant or neoadjuvant treatment from a total of 41, 54, 23, and 47, respectively.
**Abbreviations:** RR, response rate; OS, overall survival; MVA(E)C, methotrexate, vinblastine, adriamycin (epirubicin), cisplatin; MCaVI, methotrexate, carboplatin, vinblastine; NR, not reported; CMV, cyclophosphamide, methotrexate, vinblastine; FAP, 5-fluorouracil, adriamycin, cisplatin; TMP, paclitaxel, methotrexate, cisplatin; CaP, carboplatin, paclitaxel; GC, gemcitabine, cisplatin; CaG, carboplatin, gemcitabine.

## Methods

### Treatment and efficacy evaluation

Patients were treated with MVAC with granulocyte-colony stimulating factor (G-CSF) support or high-dose (HD) MVAC. Details of these regimens have been reported in the literature.[24,25] The duration of treatment was decided by the treating physician. In general, the policy of both centers participating in this analysis is to continue treatment until maximum response or unacceptable toxicity.

All patients who received at least one cycle of chemotherapy were analyzed for toxicity. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI CTC, Version 3.0). In each case, we report the worst toxicity quoted in the medical files. Toxicity was managed similarly in both centers. Provided that the absolute neutrophil count was $\geq 1.5 \times 10^9$/L and the platelets $\geq 100 \times 10^9$/L, chemotherapy was given on schedule; otherwise, it was delayed for 1 week. All agents were reduced by 25% in the case of thrombocytopenia Grade 3/4 or neutropenic fever. Assessment of response was based on Response Evaluation Criteria In Solid Tumors (RECIST) criteria.[26] In an intention-to-treat analysis, patients who could not be evaluated for response were regarded as nonresponders.

### Statistical analysis

Patients were stratified into three groups according to baseline PS (0 and 1 versus 2 and 3) and the presence or absence of visceral metastases according to the Memorial Sloan Kettering Cancer Center (MSKCC) prognostic model.[27] The chi-square test was used for comparisons of proportions across levels of categorical variables, while the nonparametric Mann–Whitney test was used to compare medians of continuous variables. PFS was calculated from the initiation of treatment to the time of objective progression, death from disease, or last follow-up. Patients who received subsequent treatment without disease progression were censored at the time of the initiation of subsequent treatment. Time to second-line therapy was calculated from the date of the first course of first-line treatment to the date of the first course of second-line treatment. TFI was calculated from the date of the last course of first-line treatment to the date of the first course of second-line treatment. Survival was calculated from the time of the initiation of second-line treatment until the date of last contact or the date of death. The Kaplan–Meier method was used to calculate survival curves, and survival functions were compared across different groups with the log-rank test. The independent prognostic significance of various baseline factors was assessed by Cox regression analysis. Data analysis was performed using SPSS 11.1 software (SPSS, Inc., Chicago, IL, USA).

## Results

### Demographics

From a total of 502 patients included in our database, 25 (Alexandra Hospital: 19, Attikon Hospital: 6) fulfilled the prespecified criteria and were included in the analysis. The baseline characteristics of these patients are shown in Table 2. This analysis had appropriate Institutional Review Board approval, and all patients had consented to the administration of chemotherapy.

The histological type in most patients (92%) was transitional cell. As expected, all patients had a creatinine clearance $>50$ mL/min calculated according to the Cockroft–Gault formula[28] prior to the initiation of second-line treatment, and no patient had pre-existing neuropathy. PS was $<3$ in all cases, and 64% had PS 1. The majority of patients (72%) had visceral metastases, and 64% were categorized in the intermediate group according to the MSKCC classification.

Nine patients had received first-line treatment with GC and 16 with CaG.[6] Ten patients (40%) experienced partial response (PR) to first-line therapy, 3 (12%) stable disease (SD), and 12 (48%) progression of disease (PD). The median PFS after first-line chemotherapy was 4.5 months, median time to second-line therapy was 5 months (range 2–14), and the median TFI between the end of first line and initiation of second line was 1 month (range 0–16). TFI was longer than 6 months only in three cases. Seventeen patients (68%) experienced progression and received second-line chemotherapy while on first-line chemotherapy.

### Second-line chemotherapy and toxicity

The most commonly used treatment (24 patients, 96%) was classic MVAC with G-CSF support, and only 1 patient (4%) was treated with HD-MVAC. The median number of cycles given was 4, with a range between 1 and 7.

Worst reported toxicities, affecting at least 10% of the patients (apart from alopecia), are shown in Table 3. Toxicity data for one patient were missing; therefore, 24 patients were included in the toxicity analysis. No Grade 4 toxicity was reported. The most frequent toxicities were nausea and vomiting (53.3%), while the most frequent Grade 3 toxicities were anemia (6.7%) and thrombocytopenia (6.7%). Neurotoxicity was reported in 16.6% of cases, but it was Grade 3 in only one case.

**Table 2** Baseline characteristics of 25 patients receiving second-line MVAC

| Characteristics | Patients | |
|---|---|---|
| | No. | % |
| No. of patients included in the analysis | 25 | – |
| Age, median (range) | 68 (42–84) | – |
| Gender | | |
| Male | 23 | 92 |
| Female | 2 | 8 |
| Primary site | | |
| Bladder | 24 | 96 |
| Renal pelvis | 1 | 4 |
| Histological type | | |
| Transitional | 23 | 92 |
| Squamous | 1 | 4 |
| Adenocarcinoma | 1 | 4 |
| ECOG PS | | |
| 0 | 2 | 8 |
| 1 | 16 | 64 |
| 2 | 7 | 28 |
| Disease status at diagnosis | | |
| Locoregional only | 11 | 44 |
| Visceral metastases | 14 | 56 |
| Disease sites | | |
| Lymph nodes | 17 | 68 |
| Lung | 7 | 28 |
| Bone | 3 | 12 |
| Liver | 6 | 24 |
| Brain | 1 | 4 |
| Number of metastatic sites | | |
| 1 | 17 | 68 |
| 2 | 7 | 28 |
| 3 | 1 | 4 |
| MSKCC risk stratification | | |
| Good | 7 | 28 |
| Intermediate | 16 | 64 |
| High | 2 | 8 |
| First-line regime | | |
| Gemcitabine/CDDP | 9 | 36 |
| Gemcitabine/carboplatin | 16 | 64 |
| Response to first-line therapy | | |
| CR | 0 | 0 |
| PR | 10 | 40 |
| SD | 3 | 12 |
| PD | 12 | 48 |
| PFS after first-line chemo median (range) | 4.5 months (1.5–12.8) | |
| Treatment-free interval median (range) | 1 month (0–16) | |

**Abbreviations:** MVAC, methotrexate, vinblastine, adriamycin, cisplatin; ECOG, eastern cooperative oncology group; PS, performance status; MSKCC, Memorial Sloan Kettering Cancer Center; CDDP, cisplatin; CR, complete response; PR, partial response;SD, stable disease; PD, progressive disease; PFS, progression-free survival.

## Response to second-line chemotherapy and survival

Twenty patients were assessable for response. Tumor response had not been assessed in the remaining five cases (two early deaths and re-evaluation not performed in three cases). There were 1 CR, 4 PRs, 2 SD, and 13 cases of PD. In an intention-to-treat analysis, the respective percentages were 4%, 16%, 8%, and 72%. Two of the responders had received GC, while the remaining three had received CaG.

**Table 3** Toxicity reported for 24 patients treated with second-line cisplatin-based chemotherapy

| Toxicity | Grade 1 | Grade 2 | Grade 3 |
|---|---|---|---|
| Neutropenia | 6 (20) | 4 (13.3) | 1 (3.3) |
| Anemia | 7 (23.3) | 9 (30) | 2 (6.7) |
| Thrombocytopenia | 0 (0) | 1 (3.3) | 2 (6.7) |
| Nausea/vomiting | 13 (43.3) | 2 (6.7) | 1 (3.3) |
| Neurotoxicity | 4 (13.3) | 0 (0) | 1 (3.3) |
| Stomatitis | 3 (10) | 1 (3.3) | 0 (0) |
| Renal | 7 (23.3) | 1 (3.3) | 0 (0) |

Median follow-up for the entire cohort following initiation of second-line chemotherapy was 20.2 months (range 3.5–36). Median PFS was 3.8 months (95% CI: 2.3–5.2), and median OS was 9 months (95% CI: 6.6–11.4) (Figure 1A), while 1-year survival rate was 29%. At the time of analysis, one patient was alive with progressive disease 20 months after the start of second-line therapy, but all remaining patients had died from progressive disease.

Response to second-line chemotherapy and OS did not correlate with age, type of first-line chemotherapy (cisplatin versus carboplatin), response to first-line chemotherapy, PFS after first line (continuous and categorical), TFI from first line (continuous and categorical), MSKCC risk classification (0 versus 1.2), Eastern Cooperative Oncology Group (ECOG) PS (0.1 versus 2), disease (locoregional versus visceral), or

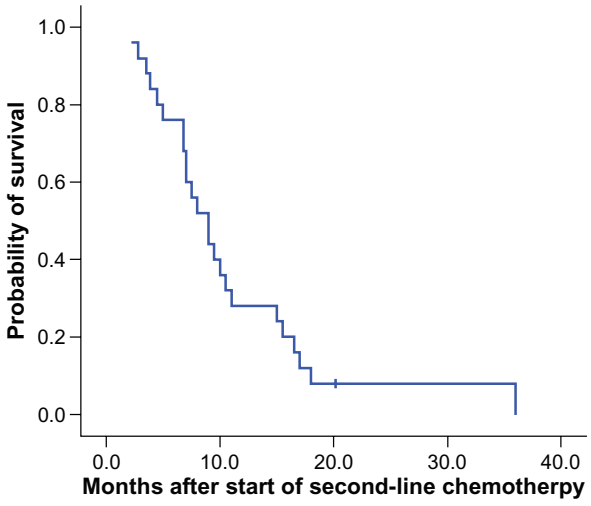


**Figure 1 A**) Overall survival Kaplan–Meier curve of 25 patients who received second-line MVAC for advanced urothelial carcinoma. **B**) Stratification according to response to second-line MVAC.
**Abbreviation:** MVAc, methotrexate, vinblastine, adriamycin, cisplatin.

number of metastatic sites (1 versus 2.3). PFS after second line was correlated with ECOG PS (0.1 versus 2) (5 months versus 3.3 months, $P = 0.049$). Response or stabilization of disease during second-line chemotherapy predicted for a significantly longer PFS and OS (Figure 1B) (7.4 versus 3.5, $P = 0.005$; 15.5 versus 7, $P = 0.046$). Seven patients survived at least 1 year following second-line chemotherapy. Again only response to second-line therapy was associated with 1-year survival: 5 of 7 patients (71.4%) with PR or SD survived at least 1 year, in contrast to only 2 of 18 (11.1%) progressing patients ($P = 0.007$).

## Discussion

Second-line therapy in advanced bladder cancer after first-line combination chemotherapy represents an unmet medical need. In contrast to the first-line setting, data on second-line therapy are limited, mainly due to the fact that only a small percentage of patients can be offered further treatment. In addition, there is lack of effective therapies. Both limitations are reflected by the lack of guidelines for second-line therapy in metastatic bladder cancer.[29] In the few prospective studies, nonplatinum agents or combinations have been mainly used (Table 1). In a phase II study, pemetrexed, a multitargeted antifolate, produced a 27% RR and a median survival of 9.6 months in patients selected for ECOG PS 0 or 1.[12] Nevertheless, these results were not confirmed by a subsequent study.[30] Gemcitabine and paclitaxel combination has also been studied in a second-line setting.[7–11] This combination is theoretically attractive, as it employs two agents with considerable activity, in patients not previously exposed to them. All these studies combined first- and second-line treatment. Although impressive, RRs were observed in a first-line setting, and the corresponding RRs for a second-line setting were considerably lower (14%–30%). Finally, a new vinca alkaloid, vinflunine, has been assessed in a randomized study compared with best supportive care.[13] A survival advantage was demonstrated after adjusting for an imbalance in ECOG PS in favor of vinflunine. In spite of this important finding, median OS was only 6.9 months for patients who received vinflunine.

Cisplatin-based combination chemotherapy represents the most effective treatment in advanced urothelial carcinoma. It is therefore reasonable to test the efficacy of this treatment in a second-line setting. Several combinations of cisplatin with taxanes, fluorouracil, interferon, and gemcitabine have been reported.[14–18] In spite of high RRs in some of them, median OS was modest, ranging from 3.2 to 10.3 months. Most of the published studies included patients previously treated with MVAC. On the contrary, data on second-line therapies following the most recent standard GC are lacking. This is only the second report of second-line MVAC (standard or intensified) in patients who had received first-line treatment consisting of gemcitabine and cisplatin or carboplatin. Several limitations may be associated with retrospective studies, more importantly regarding the evaluation of toxicity, RR, and PFS, although a detailed review of each case was performed in order to limit inaccuracies on the estimation of these parameters. For this reason, our conclusions are based on the OS data, which are not affected by the retrospective nature of our analysis. First-line therapy was only considered in the advanced and not perioperative setting, thus avoiding the inclusion of patients not truly in second-line therapy, which represents a disadvantage of several previous studies.[7–9,13] Our efficacy results showed a numerically lower RR of 20%, but the median PFS of 3.8 months and median OS of 9 months are in concert with those of previous studies. It should be taken into consideration that our population mainly consisted of platinum-refractory disease, as only three patients had a TFI longer than 6 months, while most patients (68%) received second-line therapy experiencing progression while on first-line treatment. In this context, the fact that five patients responded (irrespective of prior platinum compound) is encouraging and indicates that the substitution of MVAC for GC can partially reverse refractoriness to platinum compounds. Nevertheless, it should be pointed out that 64% of our patients received carboplatin, which is considered inferior to cisplatin. There are no data suggesting that mechanisms of resistance differ between these compounds. Response to second-line chemotherapy was highly predictive of a more favorable outcome. Patients who responded had a median OS of 15 months, while response or disease stabilization was associated with a 70% chance of surviving at 1 year.

Up to now, there are only 2 studies specifically including patients who received first-line GC chemotherapy.[17,18] The first study, by Han et al[17] also used MVAC in 30 patients with baseline characteristics similar to ours. They report similar median OS, although their RR was in the range of 30% and median PFS 5.3 months. Their TFI from first line was 2 months, as opposed to our 1 month, suggesting that sensitivity to cisplatin was probably maintained in more patients than in our study. Unfortunately, further analyses based on TFI were not reported in that study. In the second study, 28 patients received second-line paclitaxel/cisplatin, and 36% overall RR was reported. Nevertheless, median OS was similar to ours at 10.3 months, and 1-year survival rate was 45%. More importantly, that study did not predominantly

include patients with refractory disease, as only 10 patients had a PFS <6 months following first-line treatment, while the respective RR was 71% compared with 40% in our population.

In spite of the undisputed benefit that a limited number of patients will derive from second-line chemotherapy, rapid progression and death from the disease will occur in most cases. It is therefore important to attempt to select patients likely to benefit from this treatment. Several investigators have attempted to identify predictive and prognostic factors for patients with advanced urothelial cancer treated in a second-line setting. These efforts are hampered predominantly from the small number of patients included in these studies. Sensitivity to first-line therapy,[17,31]stratification according to Bajorin criteria,[7] PS,[8] site of metastases,[11] and prior therapy[7] have all been reported as predicting outcome. In our analysis, PFS was associated with PS, but we did not find any of these factors to be associated with OS. This is probably due to the fact that our population was predominantly platinum refractory; all our patients had received chemotherapy for advanced disease, while the low number included in this analysis may have obscured such an association.

The results of second-line therapy in urothelial cancer so far indicate that the development of an effective treatment in this setting remains an elusive goal. Novel chemotherapeutic agents have failed to demonstrate promising results. Recently, targeted therapies have been studied in urothelial carcinoma. Two inhibitors of the tyrosine kinases of the epithelial growth factor receptor and HER-2 receptor are currently being evaluated in clinical studies.[32,33] In the only published study, the addition of trastuzumab to a combination of paclitaxel, gemcitabine, and carboplatin resulted in a 70% RR, suggesting a synergistic effect between trastuzumab and chemotherapy. Although this agent was used in first-line therapy, these results indicate that targeted therapies alone or in combination with chemotherapy may prove useful after failure of first-line chemotherapy, especially due to their favorable toxicity profile for chemotherapy-pretreated patients.

In conclusion, second-line cisplatin-based chemotherapy may benefit a minority of patients, but this is a setting with no standard treatment, underlining the necessity for expanding clinical research in this area. The development of effective second-line treatment may result in further improvement of prognosis in patients with advanced bladder cancer.

## Disclosure

The authors report no conflicts of interest in this work.

## References


1. Bamias A, Tiliakos I, Karali MD, Dimopoulos MA. Systemic chemotherapy in inoperable or metastatic bladder cancer. *Ann Oncol*. 2006;17:553–561.
2. von der Maase H, Hansen SW, Roberts JT, et al. 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*. 2000;18: 3068–3077.
3. Dimopoulos MA, Deliveliotis C, Moulopoulos LA, et al. Treatment of patients with metastatic urothelial carcinoma and impaired renal function with single-agent docetaxel. *Urology*. 1998;52:56–60.
4. Shannon C, Crombie C, Brooks A, Lau H, Drummond M, Gurney H. Carboplatin and gemcitabine in metastatic transitional cell carcinoma of the urothelium: effective treatment of patients with poor prognostic features. *Ann Oncol*. 2001;12:947–952.
5. Linardou H, Aravantinos G, Efstathiou E, et al. Gemcitabine and carboplatin combination as first-line treatment in elderly patients and those unfit for cisplatin-based chemotherapy with advanced bladder carcinoma: Phase II study of the Hellenic Co-operative Oncology Group. *Urology*. 2004;64:479–484.
6. Bamias A, Moulopoulos LA, Koutras A, et al. The combination of gemcitabine and carboplatin as first-line treatment in patients with advanced urothelial carcinoma. A Phase II study of the Hellenic Cooperative Oncology Group. *Cancer*. 2006;106:297–303.
7. Sternberg CN, Calabro F, Pizzocaro G, Marini L, Schnetzer S, Sella A. Chemotherapy with an every-2-week regimen of gemcitabine and paclitaxel in patients with transitional cell carcinoma who have received prior cisplatin-based therapy. *Cancer*. 2001;92:2993–2998.
8. Meluch AA, Greco FA, Burris HA 3rd, et al. Paclitaxel and gemcitabine chemotherapy for advanced transitional-cell carcinoma of the urothelial tract: a phase II trial of the Minnie Pearl Cancer Research Network. *J Clin Oncol*. 2001;19:3018–3024.
9. Kanai K, Kikuchi E, Ohigashi T, et al. Gemcitabine and paclitaxel chemotherapy for advanced urohtelial carcinoma in patients who received prior cisplatin-based chemotherapy. *Int J Clin Oncol*. 2008;13: 510–514.
10. Takahashi T, Higashi S, Nishiyama H, et al. Biweekly paclitaxel and gemcitabine for patients with advanced urothelial cancer ineligible for cisplatin-based regimen. *Jpn J Clin Oncol*. 2006;36:104–108.
11. Suyama T, Ueda T, Fukasawa S, et al. Combination of gemcitabine and paclitaxel as second-line chemotherapy for advanced urothelial carcinoma. *Jpn J Clin Oncol*. 2009;39:244–250.
12. Sweeney CJ, Roth BJ, Kabbinavar FF, et al. Phase II study of pemetrexed for second-line treatment of transitional cell cancer of the urothelium. *J Clin Oncol*. 2006;24:3451–3457.
13. Bellmunt J, Von der Maase H, Theodore C, et al. Randomised phase III trial of vinflunine (V) plus best supportive care (B) vs B alone as 2nd line therapy after a platinum-containing regimen in advanced transitional cell carcinoma of the urothelium (TCCU). *J Clin Oncol*. 2008;26 Suppl 15:5028.
14. Tu SM, Hossan E, Amato R, Kilburn R, Logothetis CJ. Paclitaxel, cisplatin and methotrexate combination chemotherapy is active in refractory urothelial malignancies. *J Urol*. 1995;154:1719–1722.
15. de Mulder PH, Theodore C, Sella A, et al. Phase II EORTC trial with 5-fluorouracil, cisplatin and interferon-aloha as second-line treatment of advanced transitional cell cancer of the urothelial tract. *Ann Oncol*. 2000;11:1391–1394.
16. Pagliaro LC, Millikan RE, Tu SM, et al. Cisplatin, gemcitabine, and ifosfamide as weekly therapy: a feasibility and phase II study of salvage treatment for advanced transitional-cell carcinoma. *J Clin Oncol*. 2002; 20:2965–2970.
17. Han KS, Joung JY, Kim TS, et al. Methotrexate, vinblastine, doxorubicin and cisplatin combination regimen as salvage chemotherapy for patients with advanced or metastatic transitional cell carcinoma after failure of gemcitabine and cisplatin chemotherapy. *Br J Cancer*. 2008; 98:86–90.

18. Uhm JE, Lim HY, Kim WS, et al. Paclitaxel with cisplatin as salvage treatment for patients with previously treated advanced transitional cell carcinoma of the urothelial tract. *Neoplasia*. 2007;9:18–22.
19. Pectasides D, Aravantinos G, Kalofonos H, et al. Combination chemotherapy with gemcitabine and ifosfamide as second-line treatment in metastatic urothelial cancer. A phase II trial conducted by the Hellenic Cooperative Oncology Group. *Ann Oncol*. 2001;12:1417–1422.
20. Paz-Ares L, Bezares S, Tabernero JM, Tabernero JM, Castellanos D, Cortes-Funes H. Review of a promising new agent – pemetrexed disodium. *Cancer*. 2003;97 Suppl 8:2056–2063.
21. Vaughn DJ, Srinivas S, Stadler WM, et al. Phase II study of single-agent vinflunine in platinum-refractory transitional cell carcinoma of the urothelium (TCCU) [Abstract 15543]. *J Clin Oncol*. 2007;18S:391.
22. Lassiter LK, Tummala MK, Hussain MH, Stadler WM, Petrylak DP, Carducci MA. Phase II open-label study of oral piritrexim in patients with advanced carcinoma of the urothelium who have experienced failure with standard chemotherapy. *Clin Genitourin Cancer*. 2008;6:31–35.
23. Bellmunt J, Albiol S, Suarez C, Albanell J. Optimizing therapeutic strategies in advanced bladder cancer: update on chemotherapy and the role of targeted agents. *Crit Rev Oncol/Haematol*. 2009;69:211–222.
24. Bamias A, Aravantinos G, Deliveliotis C, et al. Docetaxel and cisplatin with granulocyte colony-stimulating factor (G-CSF) versus M-VAC with G-CSF in advanced urothelial carcinoma: a multicenter, randomized, phase III study conducted by the Hellenic Cooperative Oncology Group. *J Clin Oncol*. 2004;22:220–228.
25. Sternberg CN, de Mulder PHM, Schornagel JH, et al. Randomized phase III trial of high-dose-intensity methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy and recombinant human granulocyte colony-stimulating factor versus the classic MVAC in advanced urothelial tract tumors: European Organization for Research and Treatment of Cancer protocol no. 30924. *J Clin Oncol*. 2001;19:2638–2646.
26. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst*. 2000;92(3):205–216.
27. Bajorin DF, Dodd PM, Mazumdar M, et al. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. *J Clin Oncol*. 1999;17:3173–3181.
28. Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31–41.
29. Stenzl A, Cowan NC, de Santis M, et al. The updated EAU guidelines on muscle-invasive and metastatic bladder cancer. *Eur Urol*. 2009;55:815–825.
30. Galsky MD, Mironov S, Iasonos A, Scattergood J, Boyle MG, Bajorin DF. Phase II trial of pemetrexed as second-line therapy in patients with metastatic urothelial carcinoma. *Invest New Drugs*. 2007;25:265–270.
31. Albers P, Siener R, Härtlein M, et al. German TCC Study Group of the German Association of Urologic Oncology: Gemcitabine monotherapy as second-line treatment in cisplatin-refractory transitional cell carcinoma – prognostic factors for response and improvement of quality of life. *Onkologie*. 2002;25:47–52.
32. Philips G, Halabi S, Sanford B, Bajorin D, Small E. Phase II trial of cisplatin (C), fixed-dose rate gemcitabine (G) and gefitinib for advanced transitional cell carcinoma (TCC) of the urothelial tract: Preliminary results of CALGB 90102 [Abstract 4540]. *J Clin Oncol*. 2004;22:14S (391s).
33. Hussain MH, MacVicar GR, Petrylak DP, et al. Trastuzumab, paclitaxel, carboplatin, and gemcitabine in advanced human epidermal growth factor receptor-2/neu-positive urothelial carcinoma: results of a multicenter phase II National Cancer Institute trial. *J Clin Oncol*. 2007;25:2218–2224.