# Systemic chemotherapy in patients with advanced transitional cell carcinoma of the urothelium and impaired renal function

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**Cisplatin is the backbone of chemotherapeutic regimens used in the treatment of advanced transitional cell carcinoma of the urothelium. However, about 50% of patients cannot be administered cisplatin because of impaired renal functions. A review of the different approaches that have been developed in this patient population was performed through a Medline search from 1 January 1998 to 31 December 2010. Twenty-six studies including 25 phase II and one randomized phase II/III studies were analyzed. All regimens, except one, were based on gemcitabine and/or carboplatin and/or paclitaxel. Only five (20%) out of 25 phase II studies actually include homogeneous patients with an impaired renal function defined by a creatinine clearance below 60 ml/min. One hundred and eight patients with a median creatinine clearance ranging from 28 to 48 ml/min received four different chemotherapy regimens including one to four drugs. The results showed the response rates to vary from 24 to 56% and survival to range from 7 to 15 months. No standard chemotherapy can be recommended from literature data. Future randomized studies will have to solve the following questions: what is the optimal definition of cisplatin eligibility? Which platinum salt should be used? Is a platinum salt necessary? How many drugs should be delivered?** *Anti-Cancer Drugs* **23:143–148 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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## Introduction

Cisplatin is the backbone of chemotherapeutic regimens used in the treatment of advanced transitional cell carcinoma of urothelium (ATCCU). Current standard combinations include cisplatin, methotrexate, vinblastine, and doxorubicin (MVAC) or cisplatin plus gemcitabine (GC). Both regimens yielded similar results in terms of the response rates (49 vs. 46%) and the overall survival (OS) (13.8 vs. 14.8 months) in a randomized trial [1].

However, it has long been recognized that a large proportion of patients with ATCCU (up to 50%) cannot be administered cisplatin because of impaired renal function (IRF) caused by multiple factors including ureteral obstruction, medical comorbidities, and/or age-related decline in glomerular filtration rate. The treatment of these patients is subject to considerable controversy and no general consensus has been reached regarding the optimal regimen to be delivered. In this article, we present a review of the different approaches that have been developed in this patient population.

## Materials and methods

We searched Medline using the following medical headings: chemotherapy, transitional cell carcinoma, advanced and metastatic, and IRF. We selected trials published between 1998 and 2010, containing data on age, histological subtype, renal function, performance status (PS), toxicity, objective response rate (ORR), and OS of front-line chemotherapy in patients with ATCCU. Categorical variables were reported by means of contingency tables. In addition, for continuous variables, the mean, median, and range were computed. All data entered using the Access interface were exported to delimited text file using STATAv11 statistical software (STATA Corp., College Station, Texas, USA) for statistical analyses.

## Results

Our review resulted in 27 phase II and one randomized phase II/III studies. Two trials were excluded because of normal renal function (creatinine clearance of at least 60 ml/min), leaving us with 26 trials, which are discussed in this paper. Eleven (40%) were single institution studies. In phase II studies, the median number of patients included was 32 (range 9–88), with a median age of 67 years (range 62–75). Most patients had ATCCU but four studies also included patients with other histologies (adenocarcinoma, squamous cell carcinoma, or small cell carcinoma). The median number of patients with a PS of 0/1 and 2 was 31 and 5, respectively. Many trials allowed

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patients with both normal and abnormal renal function, and required a threshold of at least 30 ml/min for glomerular filtration rate. All regimens except one were based on gemcitabine and/or carboplatin and/or paclitaxel.

The gemcitabine/carboplatin doublet was studied in nine (35%) trials. The proportion of patients with IRF ranged from 22 to 82% (Table 1). Gemcitabine was used at a dose of 1000 mg/m$^2$ day 1 (d1) and day 8 (d8), except in one study, where the dose was 1200 mg/m$^2$ d1 and d8 was used [9]. Carboplatin was given at an area under the serum concentration–time curve (AUC) of 5, except in one study, where an AUC of 4.5 was used [3]. A total of 371 patients with a median age of 68 years (range 64–75) and a median creatinine clearance ranging from 50 to 56 ml/min were included in these nine phase II studies. An ORR of 34–60% was observed with a median OS of 10–16 months.

Experiences with gemcitabine in combination with oxaliplatin or cisplatin are summarized in Table 2. Two studies used oxaliplatin/gemcitabine doublets. A total of 76 patients were treated with either a biweekly or a 3-week schedule. Fifty-five percent of patients had IRF. An ORR of 46–48% with a median OS of 6–15 months was observed. Cisplatin, using a split dose, was combined with gemcitabine in a total of 49 patients with IRF. An ORR of 47–65% and a median OS of 13–16 months without any worsening of renal function were observed.

Ten (38%) trials used a paclitaxel-based combination, including six with paclitaxel/carboplatin doublets (Table 3). The paclitaxel dose varied between 175 and 225 mg/m$^2$; and the carboplatin was used at AUC 5 or 6 with a 3-week schedule. The median ORR was 39% (range 21–72%), with a median OS of 8.5 months (range 6–10 months). Other trials with paclitaxel are depicted in Table 4. Two trials used the triplet paclitaxel/gemcitabine/carboplatin with an ORR of 43–68% and a median OS of 11–15 months. Galsky *et al.* [24] treated 25 patients with a dose-dense regimen combining doxorubicin and gemcitabine every other week for five cycles, followed by paclitaxel plus carboplatin weekly for 12 cycles. An ORR of 56% with a median OS of 15 months was reported. Calabro *et al.* [25] treated 54 patients with the doublet paclitaxel/gemcitabine. An ORR of 37% and a median OS of 13 months were observed.

Finally, two other trials should be mentioned. A monocentric trial enrolled 11 patients with IRF who received docetaxel 100 mg/m$^2$ every 3 weeks. A 46% ORR was observed with a median OS of 11 months [26]. Thirty-eight patients including 30 patients with IRF were treated with a combination of gemcitabine (1000 mg/m$^2$ d1, d8) and epirubicin (70 mg/m$^2$ d1) every 3 weeks. The ORR was 39% and the median OS was 8 months [27].

The only randomized trial reported so far in patients 'unfit' for cisplatin is a phase II/III European Organization for Research and Treatment of Cancer study, in which randomized patients received either gemcitabine (1000 mg/m$^2$ d1, d8) plus carboplatin (AUC = 4.5) on a 3-week schedule (GCa arm) or methotrexate (30 mg/m$^2$ d1) plus carboplatin (AUC = 4.5 d1) plus vinblastine (3 mg/m$^2$ d1, d15, d22) on a 4-week schedule (M-CAVI arm) [10]. Among 175 eligible patients, 103 (59%) had IRF. Statistically significant differences favoring the GCa arm were observed (42 vs. 30% and 14 vs. 23% regarding response rates and severe acute toxicities, respectively). However, in a subgroup analysis, patients with both IRF and poor PS clearly did not benefit from either regimen. Preliminary results of the phase III part on 238 patients did not show any statistical difference between the two arms, with a median survival of 9.3 and 8.1 months, respectively [28].

## Discussion

This literature review highlights the great heterogeneity that is observed in studies dedicated to patients with IRF. However, in most studies, the eligibility criteria did not distinguish patients who are ineligible for cisplatin because of IRF from those who are ineligible for other reasons, mainly poor PS. Only five out (20%) of 25 phase II studies actually include homogeneous patients with an IRF defined by a creatinine clearance below 60 ml/min (Table 5). One hundred and eight patients with a median creatinine clearance ranging from 28 to 48 ml/min received four different chemotherapy regimens including

**Table 1 Results with gemcitabine/carboplatin doublets**

| Author | Trial | Number of patients | Median age (years) | Patients with impaired renal function (%) | Median creatinine clearance (ml/min) | Objective response rate (%) | Median overall survival (months) |
|---|---|---|---|---|---|---|---|
| Shannon *et al.* [2] | Phase II | 17 | 69 | 82 | 56 | 58 | 15 |
| Bellmunt *et al.* [3] | Pilot study | 16 | 68 | 81 | Not reported | 43 | Not reported |
| Nogué-Aliguer *et al.* [4] | Phase II | 41 | 66 | 54 | Not reported | 55 | 10 |
| Linardou *et al.* [5] | Phase II | 55 | 75 | 68 | 50 | 34 | 11 |
| Hoschke *et al.* [6] | Phase II | 23 | 68 | Not reported | 56 | 60 | 15 |
| Bamias *et al.* [7] | Phase II | 60 | 69 | 22 | Not reported | 37 | 16 |
| Helke *et al.* [8] | Phase II | 30 | 68 | 50 | Not reported | 50 | Not reported |
| Xu *et al.* [9] | Phase II | 41 | 64 | 20 | Not reported | 45 | 13 |
| De Santis *et al.* [10] | Randomized phase II | 88 | 71 | 59 | 50 | 38 | Not reported |

**Table 2 Results with gemcitabine in combination with oxaliplatin or cisplatin**

| | Chemotherapy | Number of patients | Median age (years) | Patients with impaired renal function (%) | Median creatinine clearance (ml/min) | Objective response rate (%) | Median overall survival (months) |
|---|---|---|---|---|---|---|---|
| Théodore *et al.* [11] | Gemcitabine 1500 mg/m$^2$ d1<br>Oxaliplatin 85 mg/m$^2$ d1<br>2-Week schedule | 30 | 65 | 27 | 70 | 47 | 15 |
| Carles *et al.* [12] | Gemcitabine 1200 mg/m$^2$ d1, d8<br>Oxaliplatin 100 mg/m$^2$ d1<br>3-Week schedule | 46 | 69 | 75 | 51 | 48 | 6.5 |
| Hussain *et al.* [13] | Gemcitabine 1000 mg/m$^2$ d1, d8<br>Cisplatin 35 mg/m$^2$ d1, d8<br>3-Week schedule | 32 | 66 | 59 | Not reported | 65 | 16 |
| Carles *et al.* [14] | Gemcitabine 2500 mg/m$^2$<br>Cisplatin 35 mg/m$^2$<br>2-Week schedule | 17 | 69 | 100 | 48 | 47 | Not reported |
| Als *et al.* [15] | Gemcitabine 1000 mg/m$^2$ d1, d8, d15<br>Cisplatin 35 mg/m$^2$ d1, d2<br>3- or 4-week schedule | 13 | 63 | 100 | Not reported | 46 | 13 |

**Table 3 Results with paclitaxel/carboplatin doublets**

| Author | Chemotherapy | Number of patients | Median age (years) | Patients with impaired renal function (%) | Median creatinine clearance (ml/min) | Objective response rate (%) | Median overall survival (months) |
|---|---|---|---|---|---|---|---|
| Zielinski *et al.* [16] | Paclitaxel 175 mg/m$^2$<br>Carboplatin AUC=5 | 20 | 67 | Not reported | Not reported | 45 | 9 |
| Vaughn *et al.* [17] | Paclitaxel 225 mg/m$^2$<br>Carboplatin AUC=6 | 33 | 70 | 24 | 52 | 33 | 8 |
| Redman *et al.* [18] | Paclitaxel 200 mg/m$^2$<br>Carboplatin AUC=5 | 36 | 66 | Not reported | Not reported | 50 | 10 |
| Pycha *et al.* [19] | Paclitaxel 175 mg/m$^2$<br>Carboplatin AUC=5 | 32 | 67 | Not reported | Not reported | 72 | 6 |
| Small *et al.* [20] | Paclitaxel 200 mg/m$^2$<br>Carboplatin AUC=5 | 29 | 68 | Not reported | 61 | 21 | 9 |
| Vaughn *et al.* [21] | Paclitaxel 225 mg/m$^2$<br>Carboplatin AUC=6 | 42 | 70 | 100 | 35 | 24 | 7 |

AUC, area under the serum concentration–time curve.

one to four drugs. The results indicated that the ORR ranged from 24 to 56% and from 7–15 months for OS. The remaining 20 studies included a mixed population of patients with or without IRF. In addition, classical prognostic factors for survival such as visceral metastases and poor PS may be differently distributed. This issue clearly confounds comparisons of outcomes across trials. Therefore, no standard chemotherapy can be recommended for this patient group. Many issues remain to be solved: what is the optimal definition of cisplatin eligibility? Which platinum salt should be used? Is a platinum salt necessary? How many drugs should be delivered?

**Table 4 Results with other regimens including paclitaxel**

| Author | Chemotherapy | Number of patients | Median age (years) | Patients with impaired renal function (%) | Median creatinine clearance (ml/min) | Objective response rate (%) | Median overall survival (months) |
|---|---|---|---|---|---|---|---|
| Hussain *et al.* [22] | Paclitaxel 200 mg/m$^2$<br>Carboplatin AUC=5<br>Gemcitabine 800 mg/m$^2$ d1, d8 | 49 | 63 | Not reported | 78 | 68 | 15 |
| Hainsworth *et al.* [23] | Paclitaxel 200 mg/m$^2$<br>Carboplatin AUC=5<br>Gemcitabine 1000 mg/m$^2$ d1, d8 | 60 | 63 | Not reported | Not reported | 43 | 11 |
| Galsky *et al.* [24] | Doxorubicin 50 mg/m$^2$ d1<br>Gemcitabine 2000 mg/m$^2$ d1<br>Biweekly-five cycles<br>Paclitaxel 65 mg/m$^2$ d1<br>Carboplatin AUC=1.7 d1<br>Weekly 12 cycles | 25 | 67 | 100 | 47 | 56 | 15 |
| Calabro *et al.* [25] | Paclitaxel 150 mg/m$^2$ d1<br>Gemcitabine 2500 mg/m$^2$ d1<br>2-Week schedule | 54 | 67 | Not reported | 62 | 37 | 13 |

AUC, area under the serum concentration–time curve.

**Table 5 Results in a homogeneous series of patients with impaired renal function**

| Author | Chemotherapy | Number of patients | Median creatinine clearance (ml/min) | Objective Response rate (%) | Median overall survival (months) |
|---|---|---|---|---|---|
| Dimopoulos *et al.* [26] | Docetaxel | 11 | 28 | 46 | 11 |
| Vaughn *et al.* [21] | Taxol/carboplatin | 42 | 35 | 24 | 7 |
| Carles *et al.* [14] | Gemcitabine/cisplatin | 17 | 48 | 47 | Not reported |
| Als *et al.* [15] | Gemcitabine/cisplatin | 13 | Not reported | 46 | 13 |
| Galsky *et al.* [24] | Doxorubicin/gemcitabine followed by carboplatin/docetaxel | 25 | 47 | 56 | 15 |

A calculated creatinine clearance greater than or equal to 60 ml/min is the usual cutoff for cisplatin eligibility. A first issue refers to the optimal equation to be used to estimate the creatinine clearance. The Cockroft–Gault formula is obviously the most widely used equation. However, a study comparing the Cockroft–Gault formula with the Jelliffe formula and the Modification of Diet in Renal Disease equation has pointed out that all three tests had a 64% concordance; that is, approximately one-third of patients with ATCCU would receive cisplatin on the basis of one formula but not on the basis of another [29]. A better selection of patients who may safely receive standard dose cisplatin is required.

Which platinum salt should be used? Because of a better toxicity profile including a lack of nephrotoxicity, carboplatin has been widely studied in patients with IRF. However, 18 (72%) of the 25 studies selected in our literature review did include carboplatin. Overall, a median ORR of 45% and a median OS of 10.5 months were observed. Although promising, these results are limited by the lack of a randomized trial dealing with the precise role of carboplatin in patients with IRF. In addition, carboplatin should not be routinely substituted for cisplatin in patients without IRF. Indeed, three randomized phase II trials comparing cisplatin with carboplatin in patients with normal renal function showed a trend toward lower response rates and shorter median survivals in patients treated with carboplatin [30–32]. A recent meta-analysis of randomized trials comparing cisplatin versus carboplatin-based chemotherapy confirmed these data, with a significant improvement in the likelihood of achieving a complete response (relative risk, 3.54, $P = 0.004$) and overall response (relative risk 1.33, $P = 0.025$) [33]. Results with oxaliplatin are limited to two phase II studies. The median OS of 6.5 months observed in the trial that included a majority of patients with IRF may suggest limited efficacy. With regard to cisplatin, two studies have shown that splitting the dose with proper hydration and diuresis was feasible in

patients with IRF without worsening of renal function [13,14]. Therefore, a calculated creatinine clearance greater than or equal to 60 ml/min could not be the optimal cutoff for cisplatin eligibility.

Is a platinum salt necessary? Only two studies have reported the results of combination chemotherapy without a platinum salt. Gemcitabine was combined either with paclitaxel or epirubicin [25,27]. Results suggested that the absence of platinum salt could not be detrimental to efficacy but once again the lack of a randomized trial precludes any firm conclusion.

How many drugs should be delivered? In the phase II/III led by the EORTC, the three-drug regimen M-CAVI did not yield better results than the two-drug regimen gemcitabine/carboplatin and resulted in more severe acute toxicities [10,28]. Whether triplets including gemcitabine could improve these results remain to be proven. In patients eligible for cisplatin, the four-drug regimen MVAC did not appear to add superiority to the two-drug regimen GC [1]. However, an increase in the dose density of drugs within the MVAC regimen has been shown to result in a borderline statistically significant relative reduction in the risk of progression and death [34]. In contrast, studies dealing with monochemotherapy in patients with IRF are limited.

Among other randomized trials dedicated to cisplatin-ineligible patients, a phase III study comparing gemcitabine plus vinflunine versus gemcitabine plus placebo included patients with IRF and/or congestive heart failure and PS of 0–2. Initially designed to accrue 450 patients, the trial was prematurely terminated by the sponsor. The French Genito-urinary Tumor Group recently completed the accrual of 'unfit' patients with IRF and/or poor PS in a randomized phase II trial of gemcitabine alone versus gemcitabine plus oxaliplatin. An ongoing international randomized phase II trial is addressing the question of the optimal combination of vinflunine plus gemcitabine or vinflunine plus carboplatin in patients with IRF or congestive heart failure, therefore excluding patients with a poor PS.

## Conclusion

The question of the optimal chemotherapy regimen remains unanswered because of the heterogeneity of inclusion criteria as well as the small number of patients, and above all, the lack of randomized trials specifically dedicated to patients with IRF. Whether renal dysfunction itself is an independent prognostic factor has to be assessed. Randomized trials dealing with the number and the type of drugs need to be performed according to the consensus definition of patients unfit for cisplatin-based chemotherapy [35,36], along with stratification on classical prognostic factors (PS and visceral metastases). As patients with IRF and poor PS derive little or no benefit from standard chemotherapy, the assessment of new drugs or targeted therapies as front-line treatment is justified.

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### Conflicts of interest

There are no conflicts of interest.

## References

1 Von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, *et al.* Long term survival results of a randomised trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Oncol* 2005; **23**:4602–4608.

2 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.

3 Bellmunt J, DeWit R, Albanell J, Baselga J. A feasibility study of carboplatin with fixed dose of gemcitabine in unfit patients with advanced bladder cancer. *Eur J Cancer* 2001; **37**:2212–2215.

4 Nogué-Aliguer M, Carles J, Arrivi A, Juan O, Alonso L, Font A, *et al.* Gemcitabine and carboplatin in advanced transitional cell carcinoma of the urinary tract. *Cancer* 2003; **97**:2180–2186.

5 Linardou H, Aravantinos G, Efstathiou E, Kalofonos C, Anagnostopoulos A, Deliveliotis C, *et al.* Gemcitabine and carboplatin as first line treatment in elderly patients and those unfit for cisplatin based chemotherapy with advanced bladder carcinoma: phase II study of Hellenic Cooperative Oncology Group. *Urology* 2004; **64**:479–484.

6 Hoschke B, May M, Seehafer M, Helke C. Our experience with 23 consecutive patients on gemcitabine/carboplatin chemotherapy for the treatment of metastatic transitional cell carcinoma of the urothelium. *Int J Urol* 2004; **11**:461–466.

7 Bamias A, Moulopoulos LA, Koutras A, Aravantinos G, Fountzilas G, Pectasides D, *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.

8 Helke C, May M, Hoschke B. Gemcitabine and carboplatin chemotherapy in advanced transitional cell carcinoma in regard to patients with impaired renal function. *Akttuelle Urol* 2006; **37**:363–368.

9 Xu N, Zhang XC, Xiong JP, Fang WJ, Yu LF, Zhang L. A phase II trial of gemcitabine and carboplatin in advanced transitional cell carcinoma of urothelium. *BMC Cancer* 2007; **7**:98–105.

10 De Santis M, Bellmunt J, Mead G, Kerst M, Leahy M, Maroto P, *et al.* Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer 'unfit' for cisplatin based chemotherapy: phase II – results of EORTC study 30986. *J Clin Oncol* 2009; **27**:5634–5639.

11 Théodore C, Bidault F, Bouvet-Forteau N, Abdelatif M, Fizazi K, Di Palma M, *et al.* A phase II monocentric study of oxaliplatin in combination with gemcitabine (GEMOX) in patients with advanced/metastatic transitional cell carcinoma (TCC) of urothelial tract. *Ann Oncol* 2006; **17**:990–994.

12 Carles J, Esteban E, Climent M, Font A, Gonzales-Larriba JL, Berrocal A, *et al.* Gemcitabine and oxaliplatin combination: a multicenter phase II trial in unfit patients with locally advanced or metastatic urothelial cancer. *Ann Oncol* 2007; **18**:1359–1362.

13 Hussain SA, Stocken DD, Riley P, Palmer DH, Peake DR, Geh JI, *et al.* A phase I/II study of gemcitabine and fractionated cisplatin in an outpatient setting using a 21-day schedule in patients with advanced and metastatic bladder cancer. *Br J Cancer* 2004; **91**:844–849.

14 Carles J, Suarez C, Mesia C, Nogué M, Font A, Doménech M, *et al.* Feasibility study of biweekly gemcitabine and cisplatin in patients with advanced urothelial tumors and impaired renal function. *Clin Transl Oncol* 2006; **8**:755–757.

15 Als AB, Sengelov L, Von der Maase H. Gemcitabine and cisplatin in locally advanced and metastatic bladder cancer: 3- or 4-week schedule? *Acta Oncol* 2008; **47**:110–119.

16 Zielinski CC, Schnack B, Grbovic M, Brodowicz T, Wiltschke C, Steger G, *et al.* Paclitaxel and carboplatin in patients with metastatic urothelial cancer: results of a phase II study. *Br J Cancer* 1998; **78**:370–374.

17 Vaughn DJ, Malkowicz SB, Zoltick B, Mick R, Ramchandani P, Holroyde C, *et al.* Paclitaxel plus carboplatin in advanced carcinoma of the urothelium: an active and tolerable outpatient regimen. *J Clin Oncol* 1998; **16**:255–260.

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

19 Pycha A, Grbovic M, Posch B, Schnack B, Haitel A, Heinz-Peer G, *et al*. Paclitaxel and carboplatin in patients with metastatic transitional cell cancer of the urinary tract. *Urology* 1999; **53**:510–515.

20 Small EJ, Lew D, Redman BG, Petrylak DP, Hammond N, Gross HM, *et al*. 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* 2000; **18**:2537–2544.

21 Vaughn DJ, Manola J, Dreicer R, See W, Levitt R, Wilding G. Phase II study of paclitaxel plus carboplatin in patients with advanced carcinoma of the urothelium and renal dysfunction (E2896). A trial of Eastern Cooperative Oncology Group. *Cancer* 2002; **95**:1022–1027.

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

23 Hainsworth JD, Meluch AA, Litchy S, Schnell FM, Bearden JD, Yost K, *et al*. Paclitaxel, carboplatin, and gemcitabine in the treatment of patients with advanced transitional cell carcinoma of urothelium. A phase II trial of the Minnie Pearl Cancer Research Network. *Cancer* 2005; **103**: 2298–2303.

24 Galsky MD, Iasonos A, Mironov S, Scattergood J, Boyle MG, Bajorin DF. Phase II trial of dose dense doxorubicin plus gemcitabine followed by paclitaxel plus carboplatin in patients with advanced urothelial carcinoma and impaired renal function. *Cancer* 2007; **109**:549–555.

25 Calabro F, Lorusso V, Rosati G, Manzione L, Frassineti L, Sava T, *et al*. Gemcitabine and paclitaxel every 2 weeks in patients with previously untreated urothelial carcinoma. *Cancer* 2009; **115**:2652–2659.

26 Dimopoulos MA, Deliveliotis C, Moulopoulos LA, Papadimitriou C, Mitropoulos D, Anagnostopoulos A, *et al*. Treatment of patients with metastatic urothelial carcinoma and impaired renal function with single gent docetaxel. *Urology* 1998; **52**:56–60.

27 Ricci S, Galli L, Chioni A, Iannopollo M, Antonuzzo A, Francesca F, *et al*. Gemcitabine plus epirubicin in patients with advanced urothelial carcinoma who are not eligible for platinum-based regimens. *Cancer* 2002; **95**: 444–450.

28 De Santis M, Bellmunt J, Mead G, Bochner BH. Randomized phase II/III trial comparing gemcitabine/carboplatin and methotrexate/carboplatin/ vinblastine in patients with advanced urothelial cancer unfit for cisplatin-based chemotherapy: phase III results of EORTC study 30986. *J Clin Oncol* 2010; **28 (18s)**:951s.

29 Dash A, Galsky MD, Vickers AJ, Serio AM, Koppie TM, Dalbagni G, *et al*. Impact of renal impairment on eligibility for adjuvant cisplatin-based chemotherapy in patients with urothelial carcinoma of the bladder. *Cancer* 2006; **107**:506–513.

30 Petrioli R, Frediani B, Manganelli A, Barbanti G, De Capua B, De Laurentis A, *et al*. Comparison between a cisplatin-containing regimen and a carboplatin-containing regimen for recurrent or metastatic bladder cancer patients. *Cancer* 1996; **77**:344–351.

31 Bellmunt J, Ribas A, Eres N, Albanell J, Almanza C, Bermejo B, *et al*. Carboplatin-based versus cisplatin-based chemotherapy in the treatment of surgically incurable advanced bladder carcinoma. *Cancer* 1997; **80**: 1966–1972.

32 Dogliotti L, Carteni G, Siena S, Bertetto O, Martoni A, Bono A, *et al*. Gemcitabine plus cisplatin versus gemcitabine plus carboplatin as first-line chemotherapy an advanced transitional cell carcinoma of the urothelium: results of a randomized phase 2 trial. *Eur Urol* 2007; **52**: 134–141.

33 Galsky MD, Chen GJ, Oh WK, Bellmunt J, Roth BJ, Petrioli R, *et al*. Comparative effectiveness of cisplatin-based and carboplatin-based chemotherapy for treatment of advanced urothelial carcinoma. *Ann Oncol* 2011 [In press].

34 Sternberg CN, de Mulder P, Schornagel JH, Théodore C, Fossa SD, Van Oosterom AT, *et al*. Seven-year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. *Eur J Cancer* 2006; **42**:50–54.

35 Galsky MD, Hahn NM, Rosenberg J, Sonpavde G, Hutson T, Oh WK, *et al*. A consensus definition of patients with metastatic urothelial carcinoma who are unfit for cisplatin-based chemotherapy. *Lancet Oncol* 2011; **12**: 211–214.

36 Galsky MD, Hahn NM, Rosenberg J, Sonpavde G, Hutson T, Oh WK, *et al*. Treatment of patients with metastatic urothelial cancer 'unfit' for cisplatin-based chemotherapy. *J Clin Oncol* 2011; **17**:2432–2438.