

# Comparative effectiveness of cisplatin-based and carboplatin-based chemotherapy for treatment of advanced urothelial carcinoma

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**Background:** Cisplatin-based chemotherapy is a standard treatment of metastatic urothelial carcinoma (UC), though carboplatin-based chemotherapy is frequently substituted due to improved tolerability. Because comparative effectiveness in clinical outcomes of cisplatin- versus carboplatin-based chemotherapy is lacking, a meta-analysis was carried out.

**Methods:** PubMed was searched for articles published from 1966 to 2010. Eligible studies included prospective randomized trials evaluating cisplatin- versus carboplatin-based regimens in patients with metastatic UC. Individual patient data were not available and survival data were inconsistently reported. Therefore, the analysis focused on overall response (OR) and complete response (CR) rates. The Mantel–Haenszel method was used for combining trials and calculating pooled risk ratios (RRs).

**Results:** A total of 286 patients with metastatic UC from four randomized trials were included. Cisplatin-based chemotherapy was associated with a significantly higher likelihood of achieving a CR [RR = 3.54; 95% confidence interval (CI) 1.48–8.49;  $P = 0.005$ ] and OR (RR = 1.34; 95% CI 1.04–1.71;  $P = 0.02$ ). Survival end points could not be adequately assessed due to inconsistent reporting among trials.

**Conclusions:** Cisplatin-based, as compared with carboplatin-based, chemotherapy significantly increases the likelihood of both OR and CR in patients with metastatic UC. The impact of improved response proportions on survival end points could not be assessed.

**Key words:** bladder cancer, carboplatin, chemotherapy, cisplatin, meta-analysis, urothelial cancer

## introduction

Urothelial carcinoma (UC) is a neoplasm sensitive to treatment with chemotherapeutic agents. With cisplatin-based combination chemotherapy utilized in the first-line metastatic setting, ~50%–60% of patients achieve an objective response and complete responses (CRs) occur in 10%–20% of patients. Methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) and gemcitabine plus cisplatin have emerged as first-line treatment standards, based on evidence from randomized phase III trials [1–5]. However, for reasons of tolerability and ease of

administration, multiple phase II trials have explored regimens substituting carboplatin for cisplatin [6–10].

A large proportion of patients with UC are considered cisplatin ineligible, based on impaired renal function and other comorbidities [11]. For the cisplatin-ineligible subset of patients, carboplatin-based regimens are frequently utilized [12]. However, the National Comprehensive Cancer Center Network Guidelines recommend cisplatin-based combination chemotherapy as the preferred first-line chemotherapy regimen for patients with metastatic urothelial cancer and state, ‘carboplatin should not be substituted for cisplatin in patients with normal renal function’ (www.nccn.org). Yet, there is no level I evidence available comparing cisplatin- versus carboplatin-based chemotherapy in this patient population. To assess clinical outcomes in patients with metastatic UC treated with cisplatin- versus carboplatin-based regimens, we carried out a systematic review and meta-analysis of published randomized trials.

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## methods

### data source

An independent review of citations from PubMed published from January 1966 to January 2010 was conducted. Search terms included cisplatin, carboplatin, bladder cancer, and randomized clinical trial. The search strategy also used the text terms urothelial cancer and UC. The search was limited to articles published in the English language. In addition, abstracts presented at the American Society of Clinical Oncology Annual Meeting held between January 2000 and January 2010 were searched to identify relevant clinical trials using the same key words as described above. We reviewed each publication and only the complete report was included when duplicate publications were identified.

### study selection

The goal of this study was to determine the clinical outcomes of patients with metastatic urothelial cancer treated with cisplatin- versus carboplatin-based regimens. Therefore, only randomized trials with a direct comparison between these regimens were included for analysis. Phase I trials and single-arm phase II trials were excluded due to lack of controls. Clinical trials that met the following criteria were included in the meta-analysis:

(i) prospective randomized phase II trials and (ii) prospective randomized phase III clinical trials.

### data extraction and clinical end points

We first contacted all authors of the selected studies in an effort to obtain individual patient data. However, individual patient data were only available for one of the selected studies. Therefore, we extracted details from the study publications including study characteristics, patient characteristics, treatment regimens, adverse events, and clinical outcomes (response rate, progression-free survival, and overall survival). Two reviewers (MDG and GS) extracted the data independently. Any discrepancies between reviewers were resolved by consensus.

### statistical analysis

Individual patient data were not available from three of the four studies identified as the studies were old, data were not stored in an electronic format, and/or investigators were no longer working at the institution where the trial was conducted. In addition, progression-free survival and overall survival data were not consistently reported with one study reporting only disease-related survival [13], two studies reported progression-free survival and overall survival [2, 14], and one study reported median survival in only a subset of patients [15]. Therefore, the analyses were focused on events of overall response (OR, partial + complete) and CR. The numbers of events were extracted for each outcome of OR and CR from each individual study. Adverse events, when reported consistently, were also extracted. A fixed-effects model using the Mantel-Haenszel method was utilized for combining trials. The weighted Mantel-Haenszel pooled risk ratios (RRs) and 95% confidence interval (CI) for each outcome of interest were calculated. The heterogeneity of effects across studies was tested by using chi-square and I-squared statistics. The possibility of publication bias was examined by visual inspection of funnel plots. All statistical analyses were carried out by using Stata 10 (Stata, College Station, TX).

## results

Our search revealed 12 potentially relevant clinical studies in the literature (Figure 1). A total of four randomized clinical trials were included for the analysis, three randomized phase II trials and one randomized phase III trial (Table 1).

### study quality

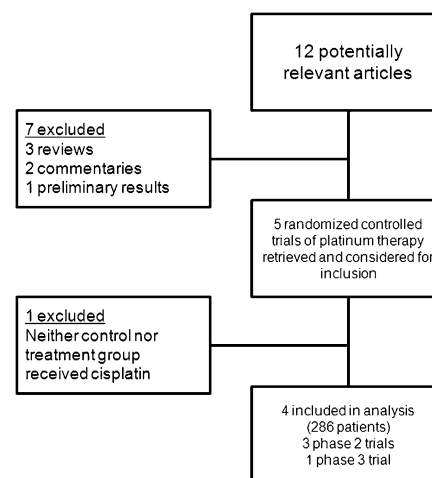
None of the selected studies were blinded or placebo controlled, as would be difficult with comparisons of cisplatin- versus carboplatin-based therapy given the differing requirements for hydration and infusion times. In two of the studies, the use of carboplatin versus cisplatin was the only difference between the treatment regimens whereas in two studies, the regimens differed more substantially including other chemotherapeutic agents (Table 1). The systems for classifying response differed among the studies, including use of the World Health Organization (WHO) criteria in two studies [13, 14], Eastern Cooperative Oncology Group criteria [16] in one study [2], and an older bladder cancer-specific system [17] in one study [15]. However, aside from minor variations, each of these systems defines a partial response as a 50% reduction in the bidimensional tumor measurements and CR as a resolution of radiographic abnormalities. Three of the studies utilized the WHO toxicity criteria while one study utilized the Common Toxicity Criteria for Adverse Events version 2.

### patients

A total of 286 patients from three randomized phase II studies and one randomized phase III study were included. The baseline characteristics of patients in the four studies are listed in Table 2. All four studies enrolled patients who had not previously received chemotherapy for metastatic UC, although one study [15] allowed enrollment of patients who had received prior adjuvant chemotherapy provided the treatment had been discontinued at least 1 year before study entry. The majority of patients on both the cisplatin- and carboplatin-containing regimens had a performance status of zero to one and there was a similar distribution of patients with visceral metastases among the treatment arms.

### OR and CR

A total of 256 patients from the four studies with available tumor response data were identified. Among patients receiving cisplatin-based chemotherapy, the OR and CR rates ranged



**Figure 1.** Selection process for randomized controlled trials included in the meta-analysis.

**Table 1.** Characteristics of randomized clinical trials included in the meta-analysis

Study	Phase	Number of patients	Cisplatin-based treatment arm	Carboplatin-based treatment arm
Petrioli et al. [15]	II	55	M-VEC: methotrexate 30 mg/m <sup>2</sup> days 1, 15, 22; vinblastine 3 mg/m <sup>2</sup> days 2, 15, 22; epirubicin 50 mg/m <sup>2</sup> day 2; cisplatin 70 mg/m <sup>2</sup> day 2; repeated every 28 days	M-VECa: methotrexate 30 mg/m <sup>2</sup> days 1, 15, 22; vinblastine 3 mg/m <sup>2</sup> days 2, 15, 22; epirubicin 50 mg/m <sup>2</sup> day 2; carboplatin 250 mg/m <sup>2</sup> day 2; repeated every 28 days
Bellmunt et al. [13]	II	47	MVAC: methotrexate 30 mg/m <sup>2</sup> days 1, 15, 22; vinblastine 3 mg/m <sup>2</sup> days 2, 15, 22; doxorubicin 30 mg/m <sup>2</sup> day 2; cisplatin 70 mg/m <sup>2</sup> day 2; repeated every 28 days	M-CAVI: methotrexate 30 mg/m <sup>2</sup> days 1, 15, 22; vinblastine 3 mg/m <sup>2</sup> days 2, 15, 22; carboplatin 300 mg/m <sup>2</sup> day 2; repeated every 28 days
Dreicer et al. [2]	III	80	MVAC: methotrexate 30 mg/m <sup>2</sup> days 1, 15, 22; vinblastine 3 mg/m <sup>2</sup> days 2, 15, 22; doxorubicin 30 mg/m <sup>2</sup> day 2; cisplatin 70 mg/m <sup>2</sup> day 2; repeated every 28 days	CP: paclitaxel 225 mg/m <sup>2</sup> day 1; carboplatin AUC 6 day 1; repeated every 21 days
Dogliotti et al. [14]	II	110	GP: gemcitabine 1250 mg/m <sup>2</sup> days 1, 8; cisplatin 70 mg/m <sup>2</sup> day 2; repeated every 21 days	GC: gemcitabine 1250 mg/m <sup>2</sup> days 1, 8; carboplatin AUC 5 day 2; repeated every 21 days

MVAC, methotrexate, vinblastine, doxorubicin and cisplatin; AUC, area under the curve.

**Table 2.** Baseline patient characteristics

Characteristic	Cisplatin regimens, <i>n</i> = 148 (%)	Carboplatin regimens, <i>n</i> = 144 (%)
Male	125 (84.5)	119 (82.6)
Performance status 0–1	114 (77.0)	100 (69.4)
Visceral metastases <sup>a</sup>	44 (29.7)	44 (30.6)

<sup>a</sup>Information could not be abstracted from study by Dogliotti et al. [14].

from 36% to 71% and 13% to 25%, respectively. Among patients receiving carboplatin-based chemotherapy, the OR and CR rates ranged from 28% to 56% and 0% to 11%, respectively. Using the Mantel–Haenszel method for combining trials, the pooled RR for achieving an objective response with cisplatin- versus carboplatin-based chemotherapy was 1.34 (95% CI 1.04–1.71; *P* = 0.02), Table 3. The pooled RR for achieving a CR with cisplatin- versus carboplatin-based chemotherapy was 3.54 (95% CI 1.48–8.49; *P* = 0.005), Table 4.

## survival

Due to the heterogeneous methods of reporting survival outcome measures in the four randomized trials included in the meta-analysis, only data regarding overall mortality at 12 months could be extracted and this information was limited to only the trials reported by Dreicer et al. [2] and Dogliotti et al. [14]. The Mantel–Haenszel pooled RR for overall mortality at

12 months with cisplatin- versus carboplatin-based chemotherapy was 0.775 (95% CI 0.56–1.07; *P* = 0.12).

## discussion

The comparative effectiveness in clinical outcomes of cisplatin-based combination chemotherapy relative to carboplatin-based regimens was examined in this study. Though cisplatin-based combination chemotherapy is considered standard first-line treatment of ‘cisplatin-eligible’ patients with metastatic UC, there have been no completed randomized phase III trials comparing cisplatin- with carboplatin-based regimens in this disease. Three small randomized phase II trials have been reported, although only one previously demonstrated a significant difference in objective response rates with cisplatin- versus carboplatin-based chemotherapy [15]. A single large phase III trial was attempted, comparing MVAC with paclitaxel plus carboplatin; however, this trial closed early due to poor accrual [2]. Importantly, our current meta-analysis of these randomized trials demonstrates a significantly higher likelihood of achieving an objective response, and in particular, a CR, with cisplatin-based therapy. These results lend further support to the notion that cisplatin-based regimens are favored for the first-line treatment of metastatic UC.

There are several limitations to the current analysis. Foremost, only four randomized trials were available resulting in a pooled population of only 286 patients. Two of the

**Table 3.** Likelihood of achieving an objective response: cisplatin- versus carboplatin-based chemotherapy

Source	Cisplatin-based		Carboplatin-based		Weight (%)	RR (95% CI)	P value
	Events	Total	Events	Total			
Petrioli et al. [15]	12	23	9	23	20.64	1.75 (1.05–2.93)	0.02
Bellmunt et al. [13]	20	28	11	27	16.58	1.33 (0.70–2.54)	
Drecier et al. [2]	14	36	12	39	21.23	1.26 (0.68– 2.36)	
Dogliotti et al. [14]	27	41	22	39	41.55	1.17 (0.82–1.66)	
Overall (Mantel–Haenszel method)	73	128	54	128		1.34 (1.04–1.71)	

Heterogeneity chi-square test = 1.68 (d.f. = 3);  $P = 0.642$ ; I-squared test (variation in RR attributable to heterogeneity) = 0.0%.

RR, risk ratio; CI, confidence interval.

**Table 4.** Likelihood of achieving a complete response: cisplatin- versus carboplatin-based chemotherapy

Source	Cisplatin-based		Carboplatin-based		Weight (%)	RR (95% CI)	P value
	Events	Total	Events	Total			
Petrioli et al. [15]	7	28	3	27	51.80	2.25 (0.65–7.18)	0.005
Bellmunt et al. [13]	3	23	0	23	14.54	1.17 (0.07–18.58)	
Drecier et al. [2]	5	36	1	39	16.28	5.42 (0.66–44.12)	
Dogliotti et al. [14]	8	41	1	39	17.38	7.61 (0.10–58.06)	
Overall (Mantel–Haenszel method)	23	128	5	128		3.54 (1.48–8.49)	

Heterogeneity chi-square test = 1.83 (d.f. = 3);  $P = 0.609$ ; I-squared test (variation in RR attributable to heterogeneity) = 0.0%.

RR, risk ratio; CI, confidence interval.

included trials closed early, one due to poor accrual [2] and the other due to loss of funding [14]. For a variety of reasons, the field of urothelial cancer has been plagued by small underpowered studies. However, because more pressing clinical questions will take priority in the allocation of limited patient and financial resources, there will likely never be an adequately powered trial comparing cisplatin- versus carboplatin-based chemotherapy in metastatic urothelial cancer. In this context, the current meta-analysis may be the largest available analysis with which to gain additional insights into the relative benefits of cisplatin- versus carboplatin-based therapy in this disease.

Individual patient data could not be obtained from the four trials included in this meta-analysis. Therefore, data were abstracted directly from the publications. While individual patient data are preferred when available, extracting data directly from publications is an accepted method of analysis and appears to parallel results of individual patient level meta-analyses [18]. A consequence of the lack of individual patient data was the inability to pool data regarding survival outcomes and instead, the analysis focused on proportions of the response to treatments. Survival data were variably reported and only two trials could be pooled to analyze overall mortality at 12 months. The superior OR and CR rates achieved with cisplatin-based chemotherapy may not translate into a survival benefit in metastatic UC. However, the difference in response proportions was largely attributed to an increase in CRs with cisplatin-based chemotherapy, an outcome measure that has been associated with improved survival in prior analyses of patients with metastatic UC [19].

Substitution of cisplatin for carboplatin was not the only difference in the chemotherapy regimens in two of the studies included in the meta-analysis. Most notably, the trial by Dreicer

et al. [2] compared MVAC with paclitaxel plus carboplatin. The inclusion of additional chemotherapeutic agents may have contributed to the improved response rates in these trials. In this regard, whether adding additional agents to carboplatin-based regimens (e.g. gemcitabine, carboplatin, plus paclitaxel) would offset the improvement in response proportions conferred by a cisplatin-based doublet (e.g. gemcitabine plus cisplatin) is unknown. While the doses of cisplatin (70 mg/m<sup>2</sup>) were the same across the four cisplatin-based chemotherapy trials, the doses of carboplatin differed; two trials utilized body surface area-based dosing [13, 15], one trial utilized an area under the curve (AUC) of 5 [14] and another using an AUC of 6 [2]. Whether inadequate carboplatin dosing contributed to the inferior response proportions with carboplatin-based therapy cannot be determined in this analysis.

A large proportion of patients with metastatic UC are 'unfit' for cisplatin-based chemotherapy [11]. The randomized trials included in this meta-analysis were conducted in cisplatin-eligible patients with adequate baseline renal function and good functional status. In patients with metastatic UC who are 'unfit' for cisplatin-based chemotherapy, carboplatin-based regimens are generally substituted [12]. Also of note, the trials included in this meta-analysis employed cisplatin administered as a single infusion every 3–4 weeks. Weekly cisplatin schedules appear less nephrotoxic, but the impact of alternative cisplatin schedules on the efficacy of treatment of metastatic UC remains incompletely defined limiting extrapolation of the current findings to such regimens [20–23].

The impact of quality of life of cisplatin- versus carboplatin-based therapy must also be considered in this population of patients being treated with palliative intent. In this regard, the

improved response proportions with cisplatin-based chemotherapy, and possibly survival, could potentially be offset by a decrement in quality of life. An adequately powered randomized phase III trial, with quality-of-life assessments, would be required to definitively address this issue; however, as noted, such a trial is unlikely to occur.

In conclusion, the current meta-analysis demonstrates a significantly higher likelihood of achieving an objective response, and particularly, a CR, with cisplatin- versus carboplatin-based therapy as first-line treatment of metastatic urothelial cancer. These findings support current practice guidelines recommending cisplatin-based combination chemotherapy as standard first-line treatment of cisplatin-eligible patients with metastatic UC.

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