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Urothelial Cancer

Overall Survival of Patients Receiving Cisplatin or Carboplatin for Primary Metastatic Urothelial Carcinoma of the Bladder: A Contemporary Dutch Nationwide Cohort Study

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Abstract

Background: Cisplatin is preferred to carboplatin when treating metastatic urothelial carcinoma of the bladder (mUCB), despite its greater toxicity. Randomised studies underpinning this have been performed in noncontemporary populations with limitations in sample sizes and analyses, affecting their validity in current clinical practice.
Objective: To estimate overall survival (OS) and assess the benefit of cisplatin-based regimens over carboplatin-based regimens in a contemporary cohort of patients with mUCB.
Design, setting, and participants: A nationwide retrospective cohort study was conducted in patients diagnosed with de novo mUCB in the Netherlands between 2016 and 2019, who underwent first-line treatment with cisplatin- or carboplatin-based chemotherapy, based on the data from the Netherlands Cancer Registry.
Outcome measurements and statistical analysis: A propensity model for receiving cisplatin-based chemotherapy based on age, sex, age-adjusted Charlson Comorbidity Index, renal function, performance status, serum haemoglobin, and the presence of visceral and bone metastases was used to produce inverse probability weighting (IPW) per patient. Unadjusted and IPW-adjusted Kaplan-Meier OS curves of both chemotherapy groups were compared by restricted mean survival time (RMST).
Results and limitations: Of the 1041 patients with mUCB, 359 received either cisplatin (n = 170; 47%) or carboplatin (n = 189; 53%) as first line. The cisplatin group was younger, had fewer comorbidities, and had better performance status and renal function. The median OS in the cisplatin and carboplatin groups was 13.1 and 11.5 mo, respectively. After IPW adjustment, prognostic factors were balanced between the two chemotherapy groups (standardised differences <0.1), and differences in RMST were <2.0 mo and not statistically significant up to 24 mo.
Conclusions: After accounting for all known prognostic factors, we found no significant survival benefit for cisplatin over carboplatin as first-line chemotherapy in mUCB.

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Patient summary: In this study, we compared the survival benefits of cisplatin- and carboplatin-based chemotherapy for patients with metastatic bladder cancer.

1. Introduction

Cisplatin-based chemotherapy is the preferred first-line treatment for metastatic urothelial carcinoma of the bladder (mUCB) in patients with adequate renal function and performance status. By contrast, carboplatin and immune checkpoint inhibitors are indicated for patients ineligible for cisplatin or as second-line treatment [1].

Treatment preferences in current clinical guidelines for mUCB are based on the results of three phase II trials and one phase III trial [2–5], which are summarised by Galsky et al [6] in a meta-analysis. Two of these trials reported overall survival (OS) data for a total of 190 patients: the phase III study by Dreicer et al [4] found no OS benefit, and the phase II study by Dogliotti et al [5] did not formally test OS benefit but did present survival curves. Galsky et al [6] later reported a pooled relative risk of mortality at 12 mo based on these two studies, indicating that cisplatin-based chemotherapy offered no significant survival benefit. However, not only is a pooled relative risk an insensitive summary of the scarce data, but also one of the two trials may have presented biased survival curves by censoring patients from the OS analysis who discontinued treatment due to adverse events [5]. Thus, the preference for cisplatin-based chemotherapy is mostly based on comparisons of response rates, despite the considerably higher toxicity [4] and lack of proven OS benefits [4–6]. Given that rigorous evidence from direct comparisons is scarce, decisions in clinical practice have taken into account indirect comparisons from chemotherapy arms in different trials [7,8], which is clearly hindered by differences in patient populations.

Current guidelines used for mUCB are based on studies that yielded inconclusive results in small populations as long as three decades ago [2–5]. This raises valid concerns that both absolute survival estimates and the relative survival benefit of one treatment over the other may not apply in contemporary populations. Moreover, the increased availability of more effective second-line treatment options could further dilute the purported benefits of cisplatin-based regimens. In the current study, we aimed to estimate the OS of patients with primary mUCB treated with cisplatin- and carboplatin-based regimens in an unselected contemporary population. Second, we aimed to assess the survival benefit of cisplatin over carboplatin in everyday clinical practice.

2. Patients and methods

2.1. Cohort

For this retrospective cohort study, patients diagnosed with primary mUCB between 2016 and 2019 were identified from the Netherlands Cancer Registry (NCR). This nationwide population-based registry, held by the Netherlands Comprehensive Cancer Organisation, includes data on all cancer diagnoses for residents of the Netherlands since 1989. We included any patient who received at least one cycle of first-line chemotherapy with a cisplatin- or carboplatin-based regimen. Patients with metachronous metastases were not included. The Privacy Review Board of the NCR approved the study (ref. K19.163) and waived the need for written informed consent.

2.2. Clinical data and outcomes

The NCR contains data about patient and tumour characteristics, disease stage, and initial treatment. Data managers at the NCR supplemented these data with information retrieved from electronic health records, including body mass index, comorbidities, performance status, laboratory test results obtained within 30 d before starting systemic treatment, treatment details (eg, number of cycles and dose adjustments), and oncologic follow-up. Clinical data follow-up was completed by July 2020.

If performance status was documented as the Karnofsky performance score (KPS), it was converted to Eastern Cooperative Oncology Group (ECOG) score, as follows: KPS 100 = ECOG 0; KPS 80–90 = ECOG 1; KPS 60–70 = ECOG 2; KPS 40–50 = ECOG 3; and KPS 10–30 = ECOG 4 [9]. We used the age-adjusted Charlson Comorbidity Index (aCCI), excluding the presence of mUCB itself (ie, the morbidity of interest), and categorised patients as those with aCCI 1, 2, 3, and $\geq$4. Renal function was categorised as 0–39 (cisplatin ineligible), 40–59 (eligible for split-dose cisplatin), and 60–79 or $\geq$80 ml/min (cisplatin eligible).

The primary outcome was OS, defined as the time from receiving a diagnosis of mUCB to death. Information on vital status was obtained through linkage with the Personal Records Database, which includes records of emigration and death for all inhabitants of the Netherlands. Patients were censored on the date of last linkage (January 31, 2021) if they had emigrated or were still alive. We collected at least 2 yr of follow-up data for all patients.

2.3. Statistical analyses

The chemotherapy groups were compared descriptively by frequencies or medians with interquartile ranges (IQRs), as appropriate. Descriptive unadjusted survival times were estimated with the Kaplan-Meier method and 95% confidence intervals (CIs). We compared unadjusted and adjusted survival curves by calculating the restricted mean survival time (RMST) of each curve to time horizons of 6, 12, 18, and 24 mo, before calculating the differences in RMST between chemotherapy groups to estimate the survival benefit of cisplatin-based regimens over carboplatin-based regimens. RMST represents the area under the survival curve, provides an absolute measure of survival time at a specified time horizon (tau), and is a clinically interpretable summary measure of time-to-event outcomes [10].

To adjust for differences in patient and disease characteristics between the chemotherapy groups, an inverse probability weighting (IPW) approach based on a propensity score was used [11–13]. The propensity score [14], or the probability of undergoing cisplatin as opposed to carboplatin conditional on relevant covariates, was calculated based on a logistic regression model with cisplatin-based chemotherapy as the dependent variable and age, sex, aCCI, renal function, performance status, haemoglobin level, presence of visceral metastasis,

Table 1 – Treatment characteristics of patients with metastatic urothelial carcinoma of the bladder treated with first-line cisplatin- or carboplatin-based chemotherapy

	Chemotherapy				Total	
	Carboplatin		Cisplatin			
	N	%	*N*	%	*N*	%
Total	189	53	170	47	359	100
Number of cycles administered						
1	27	14	27	16	54	15
2	18	10	19	11	37	10
3	31	16	18	11	49	14
4	20	11	19	11	39	11
5	18	10	15	9	33	9
6	67	35	62	36	129	36
>6	1	1	1	1	2	1
Unknown	7	4	9	5	16	4
Reduced dose						
No	141	75	132	78	273	76
Yes	48	25	38	22	86	24
Second-line treatment						
None	117	62	86	51	203	57
Cisplatin-based chemotherapy	7	4	3	2	10	3
Other chemotherapy	10	5	26	15	36	10
Immunotherapy	55	29	55	32	110	31

presence of bone metastasis, presence of only distant lymph node metastases, and number of Bajorin risk factors [15]. Weights were assigned to each patient based on the inverse of the propensity score (IPW). In this way, patients who were more likely to undergo one treatment based on their covariates but received the other treatment were assigned more weight. The covariate balance between chemotherapy groups after IPW was checked by calculating standardised differences. Higher standardised differences indicate a stronger association between the treatment and the covariate, and standardised differences below <0.1 indicate a negligible association and are therefore considered optimal for balance after IPW [16]. Kaplan-Meier curves were then adjusted for the IPW to account for baseline differences between both chemotherapy groups.

A propensity score approach was chosen over regular covariate adjustment to attenuate confounding by indication in the observational setting, while limiting the risks of overfitting and model misspecification [17]. We used IPW instead of other propensity score methods (eg, propensity score matching, stratification, or adjustment) because it is more appropriate for the estimation of the average treatment effect, which is the estimate that fitted our objectives [18] and seemed to perform best in our setting (ie, survival outcomes with considerable overlap in propensity score) [19]. RMST was used to compare survival curves for its clinical interpretability, unlike other summary statistics such as hazard ratios, which are a relative measure, or risk ratios at a single time point, which ignore curve shapes. RMST estimates also do not require assuming proportional hazards and are easily compared between studies if the same time horizon is chosen.

Analyses were performed in *R* version 4.0.3 (packages *stats*, *survminer*, *survMisc*, *RISCA*, and function *akm_rmst*), and full analysis code is available online (Github.com/AnkeRichters).

3. Results

3.1. Cohort

Between 2016 and 2019, a total of 1041 patients were diagnosed with primary mUCB in the Netherlands, of whom 365 (35%) received first-line chemotherapy. The other 676 mUCB patients received immunotherapy (39; 4%), radical or partial cystectomy (five; 0.5%), radiotherapy to the bladder (68; 7%), radiotherapy or surgery of metastatic sites (61; 6%), or only local or no cancer-directed treatment (503; 48%). Among the 365 patients treated with chemotherapy, six did not receive cisplatin or carboplatin and were excluded from further analyses. The remaining 359 patients were included for further analysis and divided into cisplatin and carboplatin groups comprising 170 (47%) and 189 (53%) patients, respectively (Table 1).

The most common regimens included gemcitabine in both groups, accounting for 95% in the cisplatin group and 99% in the carboplatin group. Other patients in the cisplatin group received (dose-dense) methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). A majority (56%) of patients in each group received four to six cycles of chemotherapy, with dose reductions required in 22–25% of cases (Table 1). Most patients (57%) did not receive second-line systemic therapy, with second-line therapy being more common in the cisplatin group (49%) than in the carboplatin group (38%). Immunotherapy was the most frequently used second-line therapy.

3.2. Propensity model

The median age of patients was 67 (IQR 59–73) yr, 72% were male, and median aCCI was 3 (IQR 2–4). Visceral metastases were present in 49%, and 36% only had metastases in distant lymph nodes. The cisplatin group differed from the carboplatin group on most prognostic factors, including age, gender, aCCI, performance, renal function, haemoglobin level, metastatic location, and number of Bajorin risk factors (Table 2). The probability of receiving cisplatin, conditional on these factors (ie, propensity score), is shown by the chemotherapy group in Figure 1. Propensity scores overlapped between the two chemotherapy groups across the

Table 2 – Patient and disease characteristics of patients with metastatic urothelial carcinoma of the bladder treated with first-line cisplatin- or carboplatin-based chemotherapy

	Chemotherapy				Total		Standardised difference	
	Carboplatin		Cisplatin				Before IPW	After IPW
	N	%	*N*	%	*N*	%		
Age at diagnosis (yr)							0.699	0.096
Median (IQR)	70 (64–75)		65 (57–70)		67 (59–73)			
<50	5	3	17	10	22	6		
50–59	26	14	44	26	70	19		
60–69	56	30	66	39	122	34		
70–79	85	45	43	25	128	36		
≥80	17	9	–	–	17	5		
Gender							0.128	0.065
Male	142	75	118	69	260	72		
Female	47	25	52	31	99	28		
Age-adjusted CCI							0.942	0.015
Median (IQR)	3 (2–5)		2 (2–3)		3 (2–4)			
1	11	6	39	23	50	14		
2	37	20	59	35	96	27		
3	49	26	51	30	100	28		
≥4	92	49	21	12	113	31		
ECOG performance status							0.286	0.052
0	65	34	79	46	144	40		
1	51	27	45	26	96	27		
≥2	10	5	8	5	18	5		
Unknown	63	33	38	22	101	28		
eGFR (ml/min)							0.819	0.082
0–39	35	19	1	1	36	10		
40–59	53	28	25	15	78	22		
60–79	52	28	69	41	121	34		
≥80	40	21	66	39	106	30		
Unknown	9	5	9	5	18	5		
Visceral metastasis	98	52	79	46	177	49	0.108	0.016
Liver metastasis	26	14	24	14	50	14	0.010	0.066
Bone metastasis	56	30	47	28	103	29	0.044	0.005
Distant LN metastases only	63	33	66	39	129	36	0.115	0.041
Haemoglobin (g/l) [a]							0.076	0.032
<100	53	28	45	27	98	26		
≥100	127	67	119	70	246	18		
Unknown	9	5	6	4	15	4		
Bajorin risk factors							0.324	0.084
0	61	32	65	38	126	35		
1	57	30	64	38	121	34		
2	8	4	3	2	11	3		
PS unknown, no visceral metastasis	28	15	21	12	49	14		
PS unknown, visceral metastasis	35	19	17	10	52	14		

CCI = Charlson Comorbidity Index; ECOG = Eastern Cooperative Oncology Group; eGFR = estimated glomerular filtration rate; IPW = inverse probability weighting; IQR = interquartile range; LN = lymph node; PS = performance status.
[a] Haemoglobin level of 100 g/l is equivalent to 6.21 mmol/l.

entire range. Standardised differences in the distribution of prognostic factors between the two groups before and after IPW are shown in Table 2. After applying IPW, these decreased to <0.1, indicating sufficient covariate balance.

3.3. *Overall survival*

The median OS (mOS) periods for the cisplatin and carboplatin groups were 13.1 (95% CI: 12.2–16.8) and 11.5 (10.3–13.5) mo, respectively. After IPW adjustment, the mOS periods were 16.7 (12.5–not estimated) and 12.3 (10.7–14.5) mo, respectively (Fig. 2). The respective RMSTs at 6, 12, 18, and 24 mo were 5.5, 9.6, 12.4, and 14.5 mo in the cisplatin group compared with 5.5, 9.3, 11.5, and 12.8 mo in the carboplatin group (Table 3). The adjusted RMST differences between the two chemotherapy groups at 6, 12, 18, and 24 mo ranged from −0.1 to 2.0 mo and were not statistically significantly different from 0 mo (Fig. 3 and Table 3).

4. Discussion

We found the mOS differences of cisplatin over carboplatin for patients with primary mUCB to be small to negligible, with unadjusted mOS of 13.1 and 11.5 mo, respectively. IPW-adjusted differences in RMST between the cisplatin and carboplatin groups were <2 mo and were not statistically significant for time horizons up to 24 mo. These findings

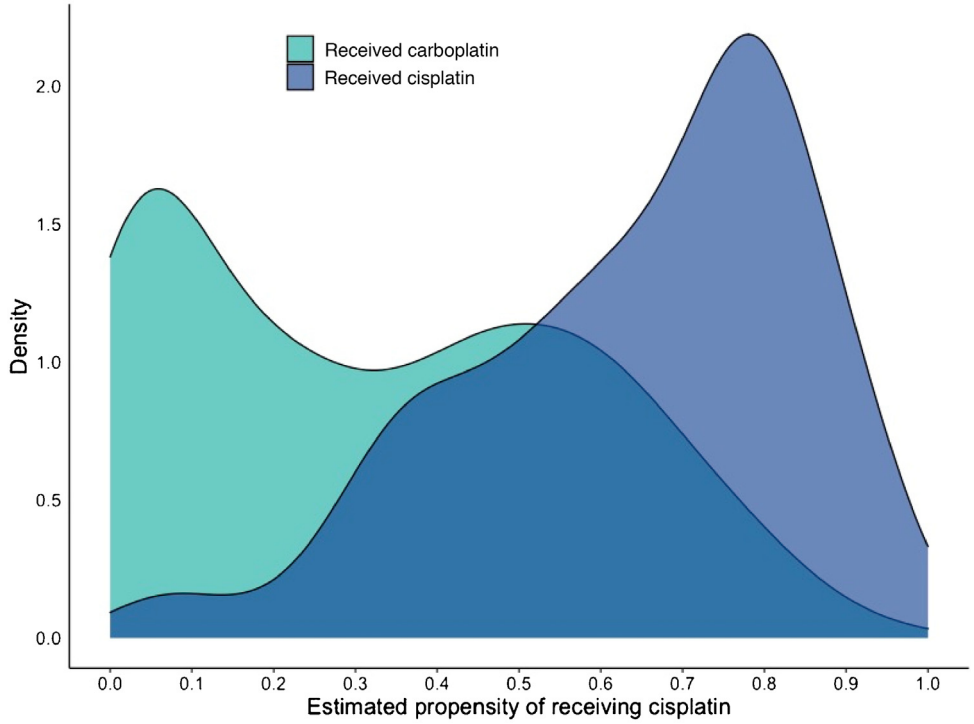

Fig. 1 – Distribution of probability of receiving cisplatin-based chemotherapy per chemotherapy group. This density plot shows smoothed distribution of propensity scores by chemotherapy group. Propensity was calculated as the probability of receiving cisplatin-based chemotherapy, conditional on the available prognostic factors.

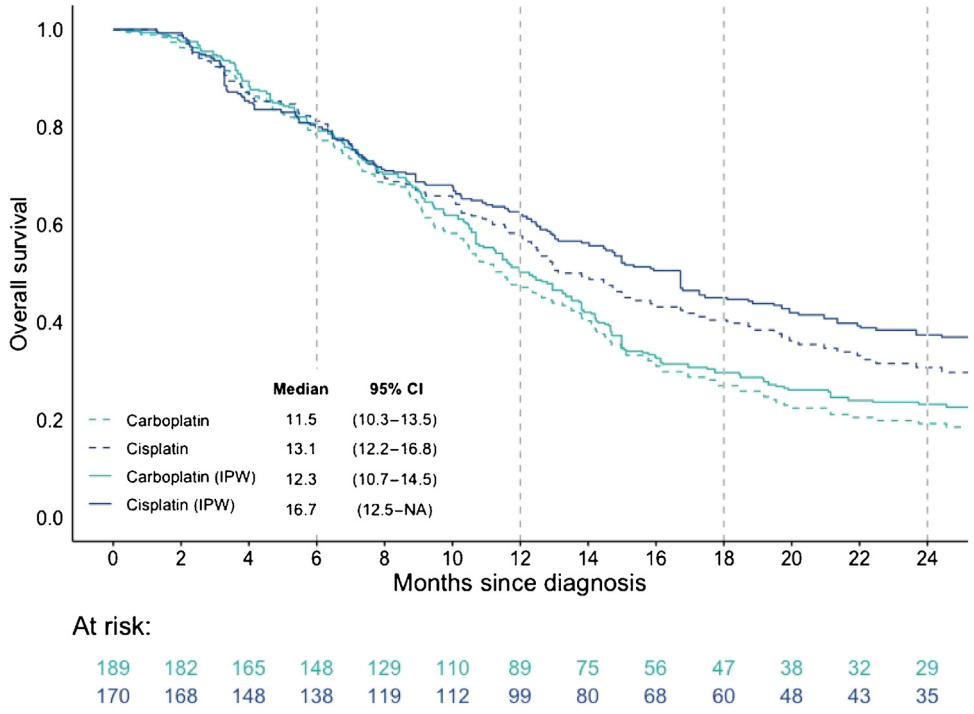

Fig. 2 – Kaplan-Meier curves, unadjusted and adjusted for inverse probability of treatment weight. Dashed lines show Kaplan-Meier estimated survival curves for patients with mUCB by chemotherapy group. The "at risk" table shows the number of patients at risk in each group per time point. Solid lines show the inverse probability weighted (IPW) Kaplan-Meier estimated survival curves. IPW was calculated based on age, sex, age-adjusted Charlson Comorbidity Index, renal function, performance status, haemoglobin level, and metastasis (liver, bone, any visceral, and distant lymph node metastasis only). CI = confidence interval; mUCB = metastatic urothelial carcinoma of the bladder; NA = not available.

Table 3 – Restricted mean survival times and differences of patients with metastatic urothelial carcinoma of the bladder treated with first-line cisplatin- or carboplatin-based chemotherapy

Tau	Observed RMST		RMST difference (95% CI)	
	Cisplatin	Carboplatin	Unadjusted	Adjusted for IPW
6 mo	5.53	5.50	0.03 (−0.21; 0.27)	−0.07 (−0.42; 0.28)
12 mo	9.61	9.29	0.32 (−0.38; 1.03)	0.16 (−0.92; 1.24)
18 mo	12.42	11.45	0.97 (−0.20; 2.14)	1.05 (−0.80; 2.91)
24 mo	14.52	12.78	1.74 (0.14; 3.33)	1.97 (−0.69; 4.63)

CI = confidence interval; IPW = inverse probability weighting; RMST = restricted mean survival time.
The RMST differences are calculated as $RMST_{cisplatin} - RMST_{carboplatin}$.

indicate that the OS benefit of cisplatin over carboplatin is small to nonexistent in a contemporary clinical cohort of patients with mUCB.

In the only randomised study comparing OS for cisplatin- and carboplatin-based therapy, Dreicer et al [4] reported slightly longer survival than in our study, showing mOS of 15.4 mo for MVAC and 13.8 mo for carboplatin-paclitaxel. Von der Maase et al [7] also reported slightly longer mOS when comparing two cisplatin-containing regimens, MVAC (15.4 mo) and gemcitabine-cisplatin (14.0 mo), although a third of their population had only locally advanced disease without distant metastasis. Finally, the EORTC study 30986 by De Santis et al [8] reported lower mOS estimates than in our study when comparing two carboplatin-containing regimens, methotrexate-carboplatin-vinblastine (8.1 mo) and gemcitabine-carboplatin (9.3 mo). However, they included only cisplatin-ineligible patients, resulting in a population with less favourable distributions of performance status, renal function, and Bajorin risk factors than in our cohort.

More recently, several randomised studies have compared OS data for first-line treatment with checkpoint inhibitors and chemotherapy. In the IMvigor-130 study (2020), comparing first-line atezolizumab and platinum-based chemotherapy (2:1 carboplatin to cisplatin), the overall mOS was 13.4 mo for the chemotherapy arm [20]. This estimate was higher than ours, despite prognostic factors such as metastatic sites being less favourably distributed. In the DANUBE study (2020), which compared durvalumab and platinum-based chemotherapy, the mOS was 12.1 mo in the chemotherapy arm [21]. When compared with our population, the DANUBE study had considerably more patients with metastatic sites other than distant lymph nodes, but also more favourable distributions of performance status and Bajorin risk factors. Lastly, the KEYNOTE-361 study compared pembrolizumab and chemotherapy in a population similar to ours, reporting mOS of 14.3 mo for chemotherapy (45% cisplatin, 55% carboplatin) and 12.3 mo for carboplatin alone [22]. None of these studies included only patients with urothelial carcinoma

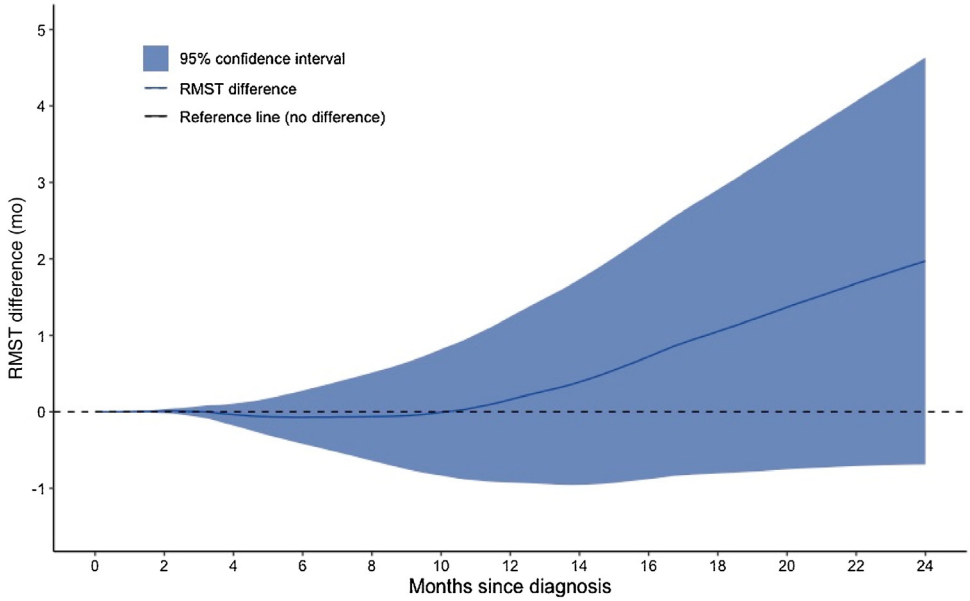

Fig. 3 – Restricted mean survival time differences of patients with metastatic urothelial carcinoma of the bladder treated with first-line cisplatin- or carboplatin-based chemotherapy. The RMST differences are calculated as follows: $RMST_{cisplatin} - RMST_{carboplatin}$. Differences >0 indicate a survival benefit of patients treated with cisplatin-based chemotherapy; differences <0 indicate a survival benefit of patients treated with carboplatin-based chemotherapy. RMST = restricted mean survival time.

of the bladder, even though this accounted for most cases. In general, reported mOS data after cisplatin- or carboplatin-based chemotherapy show some variation across studies, but the overall tendency is for trial-reported OS after chemotherapy to be slightly higher than the mOS in our cohort. This is expected due to the patient selection for trials.

Poor performance status and poor renal function (glomerular filtration rate [GFR] ≤60 ml/min) affect prognosis in mUCB and are the major contraindications for cisplatin [23]. In chemotherapy-treated patients, Bajorin risk factors are used most often for prognosis (Karnofsky performance status <80% and the presence of visceral metastasis) [15]. Other relevant factors reported in literature include performance status, GFR of 30–60 ml/min, presence of lymph node metastasis only, and haemoglobin level [8,15,24–28]. In the current study, we considered age, sex, aCCI, renal function, performance status, haemoglobin level, presence of visceral metastasis, presence of bone metastasis, presence of liver metastasis, and having only distant lymph node metastases to be prognostic factors after first-line chemotherapy. The propensity to receive cisplatin as opposed to carboplatin overlapped between both chemotherapy groups across the complete range of propensity scores. This indicates that there was variety in treatment choice within combinations of incorporated prognostic factors, even at the more extreme ranges of propensity. Reasons for this may include the need for hospital admission with cisplatin-based treatment, perceived survival benefits, or perceived frailty, beyond the factors measured. The large overlap in the probability of receiving cisplatin resulted in adequate balancing for all factors after IPW, indicating a low risk of residual bias in the adjusted analyses.

The main limitations of this study concern data completeness and proper specification of the propensity model. Data were derived from electronic health records, which meant that relevant factors were missing in some patients (eg, performance status). This was addressed by using a missing indicator category in the analyses. The applied RMST approach offered important benefits over commonly used summaries of survival curves (eg, mOS), including its direct clinical interpretability, lack of reliance on model assumptions (ie, a model-free approach), and descriptive comparability with other cohorts that have different follow-up times. Survival curves in this study were adjusted by IPW, which relied on the proper specification of the propensity model. Although the final analysis may be biased if factors that influenced the allocation to cisplatin or carboplatin were omitted, we think that all relevant factors were included and properly accounted for, as indicated by the standardised differences between groups after IPW.

With cisplatin- and carboplatin-based chemotherapy regimens being the main treatment options for mUCB patients, even with immunotherapy options available, and with existing randomised studies being suboptimal and outdated, a new randomised study into this comparison is warranted. Cisplatin-based chemotherapy may still exert survival benefit when assessing longer follow-up times. In the current study, both the cisplatin and the carboplatin group seemed to approach a plateau phase in the survival curve after 24 mo, with the plateau being somewhat higher in the cisplatin group. With time frames longer than 24 mo, a higher plateau could be translated into a significant RMST benefit, although this could not be assessed in the current study. Sufficiently long follow-up would therefore be important for a future randomised study.

5. Conclusions

In conclusion, our findings in a contemporary cohort of patients with mUCB show that first-line cisplatin-based chemotherapy offers only a limited and nonsignificant OS benefit when compared with carboplatin-based chemotherapy. We think that this should be appraised in the context that cisplatin-based regimens have been associated with substantially more toxicity than carboplatin-based regimens in earlier studies.

***Author contributions*:** Anke Richters had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Richters, Boormans, van der Heijden, van der Heijden, Meijer, Mehra, Kiemeney, Aben.
Acquisition of data: Richters.
Analysis and interpretation of data: Richters, Aben.
Drafting of the manuscript: Richters.
Critical revision of the manuscript for important intellectual content: Boormans, van der Heijden, van der Heijden, Meijer, Mehra, Kiemeney, Aben.
Statistical analysis: Richters.
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