Original Study

Evidence or Prejudice? Critical Re-Analysis of Randomized Controlled Trials Comparing Overall Survival After Cisplatin Versus Carboplatin-Based Regimens in Advanced Urothelial Carcinoma

Anke Richters,[1,2] Lambertus A.L.M. Kiemeney,[2] Niven Mehra,[3] Hans M. Westgeest,[4] Alison Birtle,[5] Richard T. Bryan,[6] Katja K.H. Aben[1,2]

Abstract

Guidelines recommend cisplatin over carboplatin for treatment of advanced urothelial carcinoma since 2008. This recommendation is based on (a meta-analysis of) two small RCTs, one with a questionable censoring approach. Secondary analysis of individual patient data from these RCTs did not demonstrate overall survival benefit from cisplatin over carboplatin. Considering lower toxicity and larger population eligibility for carboplatin, guideline recommendations should be reconsidered.

Introduction: For many years EAU guidelines have recommended the use of cisplatin-based regimens over carboplatin for treatment of advanced urothelial cell carcinoma (UCC) in eligible patients. The claim of an overall survival (OS) benefit is based on (a meta-analysis of) 2 RCTs totalling 190 patients, of which one study has methodological flaws. These studies warrant secondary analysis to substantiate the evidence for an OS benefit of cisplatin- versus carboplatin-based regimens. **Patients and Methods:** Individual patient data (IPD) were reconstructed from the 2 RCTs, assessing OS in both treatment arms. IPD of both studies were then jointly reanalysed to assess an OS estimate with Kaplan-Meier methods, with, and without an alternative censoring scenario to assess the impact of the original biased censoring approach. Kaplan-Meier curves were compared by calculating restricted mean survival time (RMST) differences. **Results:** In each study individually, and in both studies combined, the survival benefit of cisplatin versus carboplatin was less than 1 month and not significant in a follow-up window of 12 months. This was also the case when an alternative censoring scenario was applied. **Conclusion:** Careful scrutiny of the data on which guidelines base the recommendation of cisplatin-based chemotherapy for the treatment of advanced UCC does not uphold the finding that cisplatin leads to an OS benefit when compared to carboplatin. This conclusion, combined with higher toxicity in cisplatin-based regimens warrants a reconsideration of this guideline recommendation.

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Introduction

Platinum-based chemotherapy has been the long-established standard of care for treatment of advanced and metastatic urothelial carcinoma, which can be categorized into cisplatin-based, and carboplatin-based combination regimens. In 2004, a phase III RCT was published on the efficacy of cisplatin-based chemotherapy versus carboplatin-based chemotherapy for the treatment of advanced/metastatic urothelial cancer.[1] In 2007, a phase II trial also comparing cisplatin and carboplatin regimens was published, including an overall survival (OS) analysis.[2] The phase III trial did not report a difference in OS, but was terminated prematurely because of low patient accrual, and was therefore underpowered. The phase II trial intended to compare safety profiles and so did

[1]Department of Research and Development, The Netherlands Comprehensive Cancer Organization, Utrecht, The Netherlands
[2]Department for Health Evidence, Radboud university medical center, Nijmegen, The Netherlands
[3]Department of Medical Oncology, Radboud university medical center, Nijmegen, The Netherlands
[4]Department of Medical Oncology, Amphia Hospital, Breda, The Netherlands
[5]Lancashire Teaching Hospitals NHS Foundation Trust, Preston, England, United Kingdom, University of Manchester & University of Central Lancashire.
[6]Bladder Cancer Research Centre, Institute of Cancer & Genomic Sciences, University of Birmingham, Birmingham, United Kingdom

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Address for correspondence: Anke Richters, PhD, Department of Research and Development, The Netherlands Comprehensive Cancer Organization, PO Box 19079, Utrecht 3501 DB, The Netherlands
E-mail contact: a.richters@iknl.nl

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not set out to formally test a difference in OS; it was also halted prematurely due to low accrual. These 2 trials were summarized in a 2012 meta-analysis on the comparison of the 2 regimens, along with 2 other randomized studies that did not report on OS.[3,4] The meta-analysis reported a non–significant pooled relative risk of 0.775 (95% CI 0.56-1.07) for surviving up to 12 months for cisplatin compared to carboplatin, using data from the 2004 phase III, and the 2007 phase II studies.[5] Despite reporting this pooled relative risk estimate for OS, the meta-analysis did not state any conclusions for OS; instead, it focused on a higher likelihood of objective response with cisplatin (particularly complete response), and did not report on safety profiles.

With objective response considered to be an intermediate endpoint, many clinicians and patients alike would argue that within the context of advanced urothelial carcinoma, a disease with an overall poor prognosis, only improved OS or improved quality of life are relevant.[6] The 1-year OS from cisplatin-based regimens and carboplatin-based regimes in this setting have been estimated at approximately 60% and 41%, respectively, but with considerable differences in baseline prognosis.[7,8] Despite the lack of demonstrated OS benefit, EAU guidelines have been recommending cisplatin-based treatment since 2008, possibly based on more favourable response rates. More recent versions refer to the meta-analysis of Galsky et al. for this recommendation. The EAU guidelines are also supported by ESMO.[9] Meanwhile, data from the same studies indicate toxicity profiles of cisplatin to be worse than those of carboplatin,[1] with considerable nephrotoxicity, ototoxicity, and haematological toxicity associated with cisplatin.

We observed that 3 considerations warranted the secondary analysis of the 2 studies with OS data to improve the evidence-base for this guideline recommendation. Firstly, the emphasis on objective response rate is in our opinion not justified because the response rate analysis may be flawed: the 4 studies included in the meta-analysis had varying proportions (up to 27%) of randomized patients that were omitted from the response rate analysis. This is at odds with RECIST guidelines, which emphasize that all eligible patients should be included in the denominator including those who are non–evaluable.[10] This observation, together with considerably divergent response rates across the 4 studies, casts doubt on the validity of the conclusion. Secondly, intermediate endpoints are only relevant if the endpoints that they are considered to be associated with are unavailable; overall survival data for this comparison are available. However, the only phase III study designed to directly answer the question of survival benefit was stopped prematurely and is underpowered to demonstrate a survival benefit by itself; as the authors stated, *"despite the important limitations in interpreting a Phase III trial that is significantly underpowered, relevant information can be gleaned from this prospective experience."*[1] Additionally, the meta-analysis summarizes the 2 studies with OS data by calculating a relative risk for overall mortality at 12 months, even though this measure is not the most informative summary of the available data. For example, one can hypothesize a trial population with a 12-month survival proportion of 20% in both arms, but with the survival curves diverging until the 12-month point - such differences represent clinically relevant survival times, and are obscured by only looking at a single timepoint. A joint analysis of both studies' individual patient data would utilize all scarce OS data. The final consideration, is the censoring approach used in the OS analysis of the 2007 phase II study - both study arms consisted of 55 patients, of whom 25 patients dropped out prematurely, primarily as a result of adverse events.[2] This explains the unusually high censoring rate early in the follow-up that can be observed in the survival curves. This violates the important assumption of uninformative censoring for Kaplan-Meier analysis, biasing the estimates derived from it.[11]

We aimed to address these considerations by performing a secondary analysis of the phase III and phase II studies to re-evaluate the evidence supporting the preference of cisplatin over carboplatin-based chemotherapy for the treatment of advanced urothelial carcinoma.

Methods

Data Extraction From Published Trials

Two randomized clinical trials comparing cisplatin-based chemotherapy and carboplatin-based chemotherapy for the systemic treatment of advanced urothelial carcinoma in which OS data are included have been published. With the full data sets unavailable, individual patient data (IPD) were derived by digitizing the published Kaplan-Meier curves of OS from each of these 2 studies.[12] In studies with small patient populations such as these, the Kaplan-Meier curves are a direct graphical representation of IPD on survival times, allowing extraction of each endpoint, and corresponding time directly from the graph. The plots based on the extracted IPD were reconstructed and compared to the original for accuracy.

Censoring Approach

Censoring in survival analysis should be uninformative, meaning that patients who are censored are assumed to have the same survival prospects as non–censored patients,[11] ie patients who are censored are no more or less likely to experience the event at a certain time than those who remain under follow-up.[13]

The censoring approach used by Dogliotti et al. was ambiguously described, as they reported that 25 out of 55 patients in each arm discontinued the study early, quoting adverse events as the primary reason. Meanwhile, the article reported all 110 patients evaluable for OS, yet showed many censoring events in the OS graph, all of them in the first year. This suggests that patients were censored on discontinuation of the treatment. Additionally, Dogliotti et al. reported median OS times per treatment arm that do not correspond with the displayed OS curves.

Because we cannot observe the actual survival times of the censored patients, we introduced an alternative scenario that we considered to be more realistic. Based on a retrospective analysis of 198 cisplatin or carboplatin-treated patients,[14] we estimated the median survival after discontinuation of chemotherapy to be 6 months. For the censored patients from the phase II study, IPD were adjusted to include this alternative scenario, ie all patients that were censored were assumed to die 6 months after the censoring date. As a sensitivity analysis, a second scenario using survival time distributions from Dreicer et al. was considered of which results are shown in the supplementary file.

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Table 1 Restricted Mean Survival Times of the Phase III and Phase II RCT Comparing Cisplatin and Carboplatin

Study	RMST up to 6 mo			RMST up to 12 mo		
	Cis.	Carbo.	$Diff_{cis\text{-}carbo}$ (95% CI)	Cis.	Carbo.	$Diff_{cis\text{-}carbo}$ (95% CI)
Dreicer	5.62	5.45	0.17 (-0.32, 0.66)	9.81	9.10	0.71 (-0.77, 2.19)
Dogliotti	5.65	5.62	0.03 (-0.38, 0.45)	10.15	9.27	0.87 (-0.52, 2.27)
Dreicer + Dogliotti	5.63	5.54	0.09 (-0.23, 0.41)	10.02	9.26	0.76 (-0.24, 1.76)
Dreicer + Dogliotti (alt. cens.)	5.65	5.57	0.08 (-0.23, 0.38)	9.92	9.29	0.63 (-0.27, 1.54)

RMST = restricted mean survival times; Cis. = cisplatin-based chemotherapy; Carbo. = carboplatin-based chemotherapy; Diff = difference in restricted mean survival time; CI = confidence interval; alt. cens. = alternative censoring scenario.

Overall Survival Comparison

IPD of both trials were merged and jointly analysed by constructing Kaplan-Meier survival curves to estimate an OS benefit, based both on the original IPD, and based on IPD with the adjustment for informative censoring.

To compare cisplatin-treated patients to carboplatin-treated patients, restricted mean survival time (RMST) differences were calculated. While various alternative summaries of survival curves are possible and common (eg median survival time, proportion survival at fixed timepoint, hazard ratios), RMST was chosen for the following reasons: RMST represents the area under the survival curve and takes into account all available survival times (in contrast to comparing survival proportions at one time-point or comparing durations of median survival), does not require assuming proportional hazards, and does not rely on model specification assumptions, as is necessary for calculating hazard ratios. Additionally, RMST has a clinically meaningful interpretation on the absolute scale (unlike hazard ratios)[15] with the RMST being interpreted as the mean survival time between randomization and a prespecified time horizon,[16] and the RMST difference as the average gain in survival time due to one treatment versus the other during the specified time horizon.[17]

Results

The 2 studies combined included 190 patients, of whom 96 were randomized to receive cisplatin and 94 to carboplatin (Figure 1). Both studies included chemotherapy-naïve advanced urothelial carcinoma patients, mostly males (> 75%), with ECOG 0-2, and adequate renal function. Median age was between 64 and 67 years.

The presented OS curves were reconstructed (Figures. 2A and 2B). In the study of Dogliotti et al., the majority of censoring took place in the first 12 months, with the overall censored proportion being considerably higher than that of Dreicer et al. Survival curves were also constructed for the data of Dogliotti et al. with the alternative censoring scenario (Figure 2C). Figure 2D shows these plots combined for direct comparison on a constant follow-up time axis.

Data from both studies combined are shown in Figure 2E (original data) and Figure 2F (alternative censoring scenario). From Figures 2E and 2F, RMSTs were calculated up until 6 and 12 months, which are shown in Table 1. Both with and without alternative censoring, the RMST difference between cisplatin and carboplatin arms at 6 and 12 months was less than 1 month and not statistically significant.

Discussion

This secondary analysis of published results from a phase II and a phase III trial on the efficacy of cisplatin-based chemotherapy versus carboplatin-based chemotherapy for the treatment of advanced urothelial carcinoma shows no significant OS benefit for cisplatin-based regimens. It also highlights a censoring pattern in one of the studies that results in potentially severely biased estimates. This seems to have not been accounted for in the meta-analysis that forms the basis for those guidelines recommending cisplatin over carboplatin.

In the meta-analysis referred to by the EAU guidelines, the OS benefit was summarized as the relative risk of being alive at 12 months after treatment with cisplatin compared to treatment with carboplatin.[5] The relative risk was calculated to be 0.775 (95%CI 0.56-1.07). Although not statistically significant, it seems this estimate together with a higher response rate and, in particular, a higher rate of complete response among cisplatin-treated patients is interpreted as beneficial. However, intermediate endpoints such as response rates carry no direct clinical relevance to patients, and should only be used if correlated with a relevant outcome (such as OS or quality of life) if that relevant outcome itself is unavailable. The meta-analysis by Galsky et al. defends this use of response rate by referring to the correlation with OS in another study. However, given that OS is available in both studies, and does not show a benefit (as demonstrated in the meta-analysis by Galsky et al. with the pooled relative risk and the reanalysis in the current study), a higher response rate is irrelevant.[6]

In this secondary analysis, survival curves were constructed with adapted data to mitigate the censoring approach as employed by Dogliotti et al. If patients are censored on discontinuation of treatment due to severe adverse events, it is likely that at least some of these patients have shorter survival times than those who were not censored because they did not have severe adverse events. Such informative censoring will introduce bias, not only in estimates per arm,[18] but also in comparison between arms if censoring frequency, and/or censoring times in arms are imbalanced.[13] Although they refrain from direct comparison of the survival curves (eg with a Log-Rank test), the curves themselves are prone to bias due to their censoring approach. This is problematic as these potentially biased

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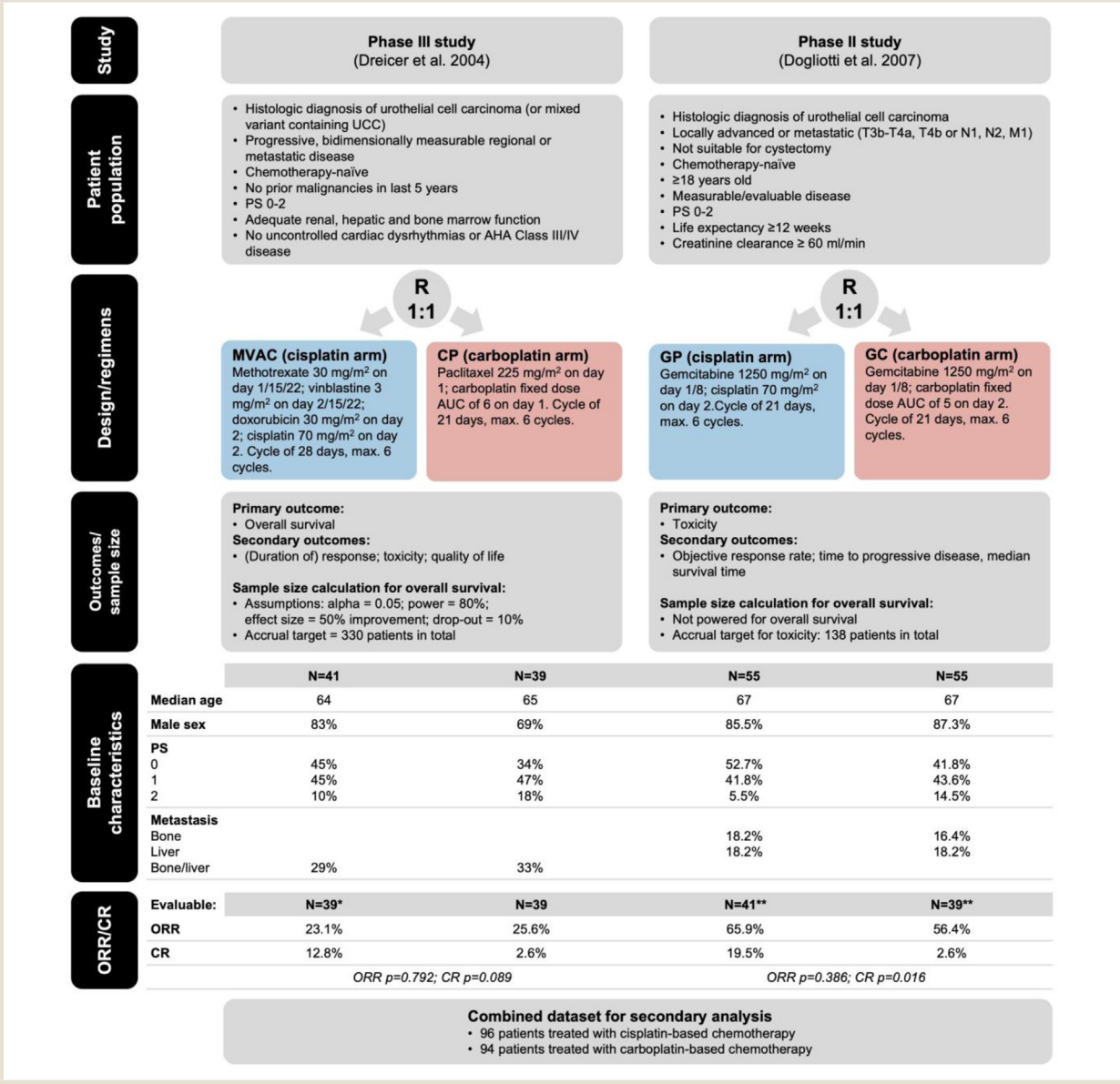
Figure 1 Overview of characteristics of included randomized studies. MVAC = methotrexate, vinblastine, doxorubicin and cisplatin; CP = carboplatin and paclitaxel; GP = gemcitabine and cisplatin; GC = gemcitabine and carboplatin; ORR = objective response rate; CR = complete response. * Non–evaluable due to withdrawal before treatment started (n = 1) and loss to follow-up (n = 1). ** Non–evaluable due to discontinuation of treatment prior (n = 7) to completing 1 cycle and unaddressable, non–medical reasons (n = 23).



OS data are incorporated in the meta-analysis. Therefore, an alternative censoring scenario was used that we considered more realistic in an attempt to circumvent violating the Kaplan-Meier assumption of non–informative censoring. It showed that the alternative scenario led to considerably different curves, which was also the case in a sensitivity analysis with a second scenario. We emphasize that other scenarios are possible as well, including a scenario where censoring in the 2 arms is informative to a different extent in each arm. For instance, one could argue that for some patients who have to discontinue cisplatin treatment due to toxicity, it may be possible to cross over to carboplatin, whereas the reverse is much less likely. It should be kept in mind that while carboplatin is usually reserved in clinical practice for patient's ineligible to undergo cisplatin, the specific trials only included cisplatin-eligible patients. Differential cross-over could thus affect survival after discontinuation of first line of chemotherapy differently in both arms, but this cannot be assessed with the available data because no post-protocol treatments were reported in either study.

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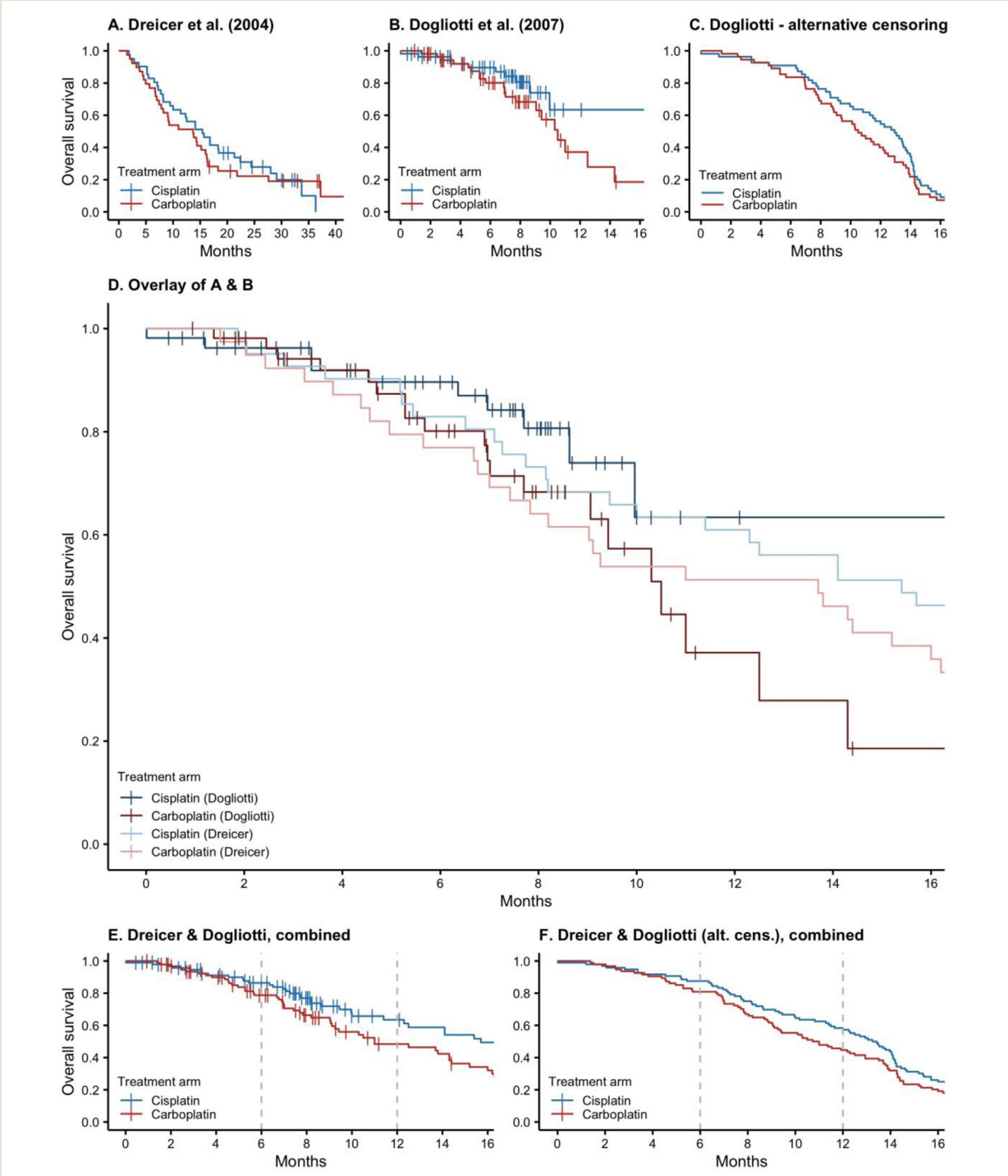
Figure 2 Kaplan-Meier curves for overall survival based on reconstructed data from Dreicer et al. and Dogliotti et al.



The fact that both studies were prematurely discontinued due to accrual difficulties is an important incentive to jointly analyse the 2 studies to increase statistical power. Combining IPD from both studies is, however, hindered by 2 analytical choices in each of the articles. Firstly, the 2007 phase II publication defined survival as time from commencing therapy, even though this is not considered a valid approach nor best practice for intention to treat analyses[19] as it may lead to immortal time bias if patients experience the endpoint between randomization and therapy commencement. The phase III trial indeed calculated OS as time from randomization, as

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is common. The second analytical choice was the biased censoring approach applied in the phase II trial but not in the phase III trial.

These choices are reversible, and in our opinion, there are better approaches to reject or consolidate the evidence supporting the preference of cisplatin-based chemotherapy over carboplatin. Ideally, we would re-analyse the data of the study by Dogliotti et al. with possibly available (or retrospectively collected) survival data for censored subjects in the study, while also using time from randomization instead of time from onset of therapy. Alternatively, the informative censoring could be tackled more accurately than our approach by using an inverse probability of censoring based on covariates,[20] for which re-analysis of the data including all available covariates is necessary. To do so, we have contacted multiple authors to request data access but have not received responses.

Until these analyses can be performed, it should be considered that the OS analysis as performed in the 2012 meta-analysis was prone to bias[5]; notwithstanding, neither the findings from the meta-analysis, nor this secondary analysis of the original IPD, nor our adapted IPD indicate a survival benefit of cisplatin over carboplatin. While the meta-analysis cites the objective response rate as an important indication of the superiority of cisplatin-based chemotherapy over carboplatin-based chemotherapy, it is disputed that response rates correlate well with OS both across cancer types, and in urothelial cancer specifically.[21] Unjustified focus on surrogate endpoints, such as response rate, when OS data are or could easily become available, has previously led to the use of more toxic regimens that do not improve survival (eg bevacizumab for breast cancer). Therefore, in the context of available OS data not demonstrating an OS benefit of cisplatin-based regimens in this setting, the data on response rate should be considered with extreme caution. Toxicity profiles of both regimens are well-described and are favourable for carboplatin-based regimens.[1] Balanced clinical decision-making should incorporate best-available knowledge on both potential benefits and harms, as well as the consideration that many more patients would be eligible for carboplatin than for cisplatin-based regimens.

These findings also have implications for many ongoing and anticipated studies of systemic treatments for advanced urothelial carcinoma - selection based on eligibility for cisplatin is common and carboplatin-containing regimens are often considered as inferior control arms. For instance, if checkpoint inhibitors (pembrolizumab, avelumab) or antibody-drug conjugates (eg enfortumab-vedotin) develop more prominent roles in earlier treatment, considerations regarding nephropathy (that may preclude patients from receiving later line cisplatin) are no longer fundamental if carboplatin provides similar OS results.

Conclusion

Careful scrutiny of the data on which guidelines base the recommendation of cisplatin-based chemotherapy for the treatment of advanced urothelial carcinoma does not uphold the finding that cisplatin yields a survival benefit when compared to carboplatin. This conclusion, combined with the more significant toxicity from cisplatin-based regimens, warrants serious reconsideration of guideline recommendations until sufficient, high-quality study data are available for analysis.

Clinical Practice Points

What is Already Known About This Subject?. Cisplatin-based combination regimens are considered the preferred option for treatment of metastatic urothelial cancer (mUC), with carboplatin-based chemotherapy considered suboptimal. EAU guidelines cite an overall survival benefit associated with cisplatin, based on 2 randomized clinical trials, and a meta-analysis on both. Both randomized trials comparing overall survival between cisplatin and carboplatin-treated patients were seriously underpowered and one has methodological flaws.

What are the New Findings?

Re-analysis of individual patient data from both allowed for pooling of trial populations, including a corrective scenario for informative censoring in one study. In each study individually, and in both studies combined, the survival benefit of cisplatin versus carboplatin was less than 1 month, and not significant in a follow-up window of 12 months. This was also the case when an alternative censoring scenario was applied.

How Might it Impact on Clinical Practice in the Foreseeable Future?

The findings from this study, combined with higher toxicity in cisplatin-based regimens, warrant a reconsideration of this guideline recommendation.

Disclosure

Conception and design: Richters; data curation: Richters; formal analysis: Richters; interpretation of data: Richters, Kiemeney, Mehra, Westgeest, Birtle, Bryan, Aben; writing – original draft: Richters; writing – review & editing: Kiemeney, Mehra, Westgeest, Birtle, Bryan, Aben; supervision: Aben, Kiemeney. HMW reports consultancy fees from Astellas and Roche, and travel expenses from Ipsen and Astellas. NM reports consulting fees from Astellas Pharma, Bristol-Myers Squibb, Genzyme, Janssen-Cilag, MSD Oncology, and Roche; funding or clinical trial and laboratory research support to his institution from Astellas Pharma, Janssen-Cilag, Pfizer, Roche/Genentech, and Sanofi; and accommodation and expenses from Astellas Pharma, Bristol-Myers Squibb, MSD Oncology, and Roche. AB reports participation in advisory boards and educational meeting support for Janssen, Astellas, Sanof Genzyme, Bayer, and Roche. RTB reports contribution to advisory boards for Olympus Medical Systems and Janssen, UroGen Pharma, and QED Therapeutics. All remaining authors have declared no conflicts of interest.

Supplementary file: Second alternative censoring scenario

Data Sharing Statement

Full analysis code is available on Github.com/AnkeRichters.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2021.12.017.

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