The effect of cisplatin-based neoadjuvant chemotherapy on the renal function of patients undergoing radical cystectomy

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ABSTRACT

INTRODUCTION: Cisplatin-based neoadjuvant chemotherapy (NAC) is the standard of care for patients with muscle-invasive bladder cancer (MIBC) undergoing radical cystectomy (RC). Cisplatin, however, can induce renal toxicity. Furthermore, RC is an independent risk factor for renal injury, with decreases in estimated glomerular filtration rate (eGFR) of up to 6 mL/min/1.73 m^2 reported at one year postoperatively. Our objective was to evaluate the effect of cisplatin-based NAC and RC on the renal function of patients undergoing both.

METHODS: We analyzed a multicenter database of patients with MIBC, all of whom received cisplatin-based NAC prior to RC. eGFR values were collected at time points T1 (before NAC), T2 (after NAC but before RC), and T3 (one year post-RC). eGFR and proportion of patients with eGFR <60 ml/min/1.73m^2 (chronic kidney disease [CKD] stage ≥3) were compared between these time points. As all patients in this dataset had received NAC, we identified a retrospective cohort of patients from one institution who had undergone RC during the same time period without NAC for context.

RESULTS: We identified 234 patients with available renal function data. From T1 to T3, there was a mean decline in eGFR of 17% (13 mL/min/1.73 m^2) in the NAC cohort and an increase in proportion of patients with stage ≥3 CKD from 27% to 50%. The parallel cohort of patients who did not receive NAC was comprised of 236 patients. The mean baseline eGFR in this cohort was lower than in the NAC cohort (66 vs. 75 mL/min/1.73 m^2). The mean eGFR decline in this non-NAC cohort from T1 to T3 was 6% (4 mL/min/1.73 m^2), and the proportion of those with stage ≥3 CKD increased from 37% to 51%.

CONCLUSIONS: Administration of NAC prior to RC was associated with a 17% decline in eGFR and a nearly doubled incidence of stage ≥3 CKD at one year after RC. Patients who underwent RC without NAC had a higher rate of stage ≥3 CKD at baseline but appeared to have less renal function loss at one year.

INTRODUCTION

In the setting of resectable muscle-invasive bladder cancer (MIBC), cisplatin-based neoadjuvant chemotherapy (NAC) prior to radical cystectomy (RC) is the gold standard treatment.[1] In a seminal paper by Grossman et al, neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) was associated with a trend towards improved survival (OS) compared to RC alone,[2] which has been confirmed as a 5–6% five-year survival benefit with cisplatin-based NAC in the BA06 30894 trial and several meta-analyses.[3-5] Contemporarily,

gemcitabine-cisplatin (GC) has been adopted by many based on better tolerability and similar OS compared to conventional MVAC in the metastatic setting.[6] Recently, however, the phase 3 VESPER trial reported a progression-free and OS advantage for dose-dense MVAC (ddMVAC) in comparison to GC.[7] The VESPER trial data present a compelling argument for the use of ddMVAC as the preferred choice for NAC in patients who can tolerate it, while GC remains an acceptable option.

Despite strong evidence to support the use of NAC, its adoption has been slow. Studies have demonstrated that fewer than 30% of U.S. and Canadian patients undergoing RC for MIBC receive NAC.[8-11] Although the reasons for this are multifactorial, baseline chronic kidney disease (CKD) is a common barrier to administration of cisplatin-based NAC.[9,12] Cisplatin is a recognized and well-studied nephrotoxin with deleterious effects proportional to both cumulative dose and peak plasma concentration.[13-17] Renal injury secondary to cisplatin treatment may occur in as many as 30% of patients receiving it, despite prophylactic strategies such as pre-treatment hydration.[13,14] The risk is assumed to be greater in patients with pre-existing renal disease, hence the relative contraindication to administration of cisplatin in patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.[1] While carboplatin is less nephrotoxic and sometimes substituted for cisplatin in patients with advanced disease and decreased renal function, it is believed to render inferior oncologic outcomes.[18] Major guideline groups recommend proceeding directly to RC in patients who are not eligible for cisplatin NAC, while trimodal therapy and clinical trials are relevant options in selected patients.[1,19]

Independent of cisplatin, RC has been associated with a small but significant long-term decline in renal function.[20-27] While the oncologic effects of NAC and RC have been well-studied, there is a relative paucity of data on the renal impact of combining these two potentially nephrotoxic treatments. The aim of this study was to quantify the impact of combined NAC and RC on patients' renal function. We also analyzed the change in renal function of a separate cohort of patients from one institution who underwent RC without NAC. Although a formal comparison was not performed, this data was provided for context.

METHODS

Patients

Anonymized data was collected for patients who underwent RC with cisplatin-based NAC between January 1991 and November 2015. The data was drawn from a multicenter, collaborative database shared by 19 institutions in North America and Europe. Renal function was analyzed at three separate time points: before initiation of NAC (T1), after completion of NAC but before RC (T2), and at one year post-RC (T3). For illustrative purposes, we also described a separate single-center cohort of patients who underwent RC without NAC at one institution (the non-NAC cohort). These patients had eGFR collected pre-treatment (T1) and at one year post-RC (T3).

Patients without an eGFR or creatinine listed at any one of these time points were excluded. If a patient was missing an eGFR value but a creatinine was available, eGFR was calculated using the CKD-Epi formula. Of these, entries that were missing data on any of the variables in the CKD-Epi equation (age, sex, ethnicity, creatinine) were excluded due to inability to calculate eGFR. Patients who received non-cisplatin NAC (e.g., carboplatin regimens) were excluded. The primary endpoint was mean eGFR at the three time points. The proportion of patients with CKD stage ≥3 (i.e., eGFR <60 mL/min/1.73 m^2) at each time point was a secondary endpoint.

Statistical analysis

The T-test was used within each cohort to compare mean eGFR across the time points and Fisher's exact test was used to compare proportion of patients with stage 3 or greater CKD. The non-NAC cohort was analyzed for illustrative purposes, but statistical testing was not performed between the NAC and non-NAC cohorts due to the differences in nature of the populations.

Logistic regression was used to assess a relationship between a decline in eGFR from T1 to T3 and several clinical risk factors in patients in the NAC cohort. These variables included age, baseline eGFR, presence of preoperative hydronephrosis, administration of three or more cycles of NAC, and presence of a continent (vs. incontinent) urinary diversion. All statistical analysis was performed using SPSS version 25.0 (IBM, 2017).

RESULTS

Based on available records, we identified 578 patients who received NAC and who had valid eGFR data at time point T1 (before NAC). Of these, 234 had sufficient data at T2 (after NAC, before RC) and T3 (one year post-RC) and were included in the analysis. In the non-NAC cohort, 236 patients had sufficient data at the T1 and T3 time points and were included. Demographic data for the NAC and non-NAC cohorts

are outlined in Table 1. Of note, over 50% of patients who received NAC also received a continent urinary diversion, compared to 24% of those who did not receive NAC. Approximately 35% of NAC and 24% of non-NAC patients had pre-treatment hydronephrosis.

In the NAC cohort, mean pre-treatment (T1) baseline eGFR was 75 mL/min/1.73 m^2 (Table 1). The pre-treatment eGFR was below 60 mL/min/1.73 m^2 in 27% of patients. There was a statistically significant decline by 8 mL/min/1.73 cm^2 in mean eGFR from baseline (T1) to post-NAC/pre-RC (T2; p<0.01). There was a further statistically significant decline by 5 mL/min/1.73 m^2 from T2 to one year post-RC (T3; p<0.01). Overall, those who received NAC followed by RC experienced an approximately 17% eGFR decline (13 mL/min/1.73 m^2, p<0.01) between baseline and one year post-RC (Table 2). The proportional degree of decline was similar between patients with baseline GFR below and above 60 mL/min/1.73 m^2 (15% vs. 18%, p=0.3). There was a significant increase in the proportion of patients classified as stage ≥3 CKD from baseline (27% at T1) to post-NAC/pre-RC (59% at T2, p<0.01), but no subsequent change from post-NAC/pre-RC (59% at T2) to one year post-RC (50% at T3, p=0.051) (Table 3).

In the separate non-NAC cohort, the mean pre-treatment baseline (T1) eGFR was 66 mL/min/1.73 m^2 (Table 1). Mean eGFR in the non-NAC cohort declined by 6% (4 mL/min/1.73 m^2, p<0.01) from pre-treatment (T1) to one year post-RC (T3). The proportional degree of decline was similar between patients with baseline GFR below and above 60 mL/min/1.73 m^2 (3% vs. 8%, p=0.1) (Table 2). The proportion of patients with stage ≥3 CKD also increased in the non-NAC group from 36.8% at baseline (T1) to 50.9% at one year (T3) (p<0.05) (Table 3). Inter-cohort statistical testing was not performed due to the different characteristics of the two group; however, the NAC cohort appeared to have a higher baseline eGFR and experienced a greater absolute and relative eGFR decline throughout the study period (Figure 1). At baseline, there appeared to be a greater proportion of patients with stage ≥3 CKD in the non-NAC cohort, although at one year post-RC, the prevalence in both groups was approximately 50%.

Analysis within the NAC cohort revealed that patients who received three or more cycles of NAC experienced a similar degree of renal function decline at one year as those who received fewer than three (14% vs. 23%, p=0.3). Similarly, the degree of renal injury at one year was similar in those who received a continent vs. incontinent diversion (16% vs. 13%, p=0.4). Patients with preop-

Table 1. Baseline patient characteristics for NAC and non-NAC patient groups

	NAC	Non-NAC
Total patients, n	228	236
Mean age at RC (SD)	63.1 (11.0)	68.7 (10.7)
Male, n (%)	178 (78.1)	191 (80.9)
Race, n (%)		
Caucasian	180 (78.9)	Data not available
Black	24 (10.5)	Data not available
Asian	8 (3.5)	Data not available
Hispanic	6 (2.6)	Data not available
Data not available	12 (5.2)	Data not available
Histology at TURBT, n (%)		
Urothelial	217 (95.2)	218 (91.6)
Non-urothelial	2 (0.8)	18 (7.6)
Data not available	9 (3.9)	0 (0)
cT stage, n (%)		
cT0	1 (0.4)	0 (0)
Ta/Tis	0 (0)	33 (14.0)
cT1	14 (6.1)	74 (31.4)
cT2	129 (56.6)	82 (34.7)
cT3	63 (27.6)	32 (13.6)
cT4	20 (8.8)	10 (4.2)
Data not available	1 (0.4)	4 (1.7)
pT stage, n (%)		
pT0	51 (22.4)	32 (13.6)
pTis/pTa	35 (15.3)	57 (24.1)
pT1	17 (7.5)	28 (11.9)
pT2	53 (23.2)	31 (13.1)
pT3	50 (21.9)	55 (23.3)
pT4	22 (9.6)	29 (12.3)
Data not available	0 (0)	4 (1.7)
Diversion type, n (%)		
Continent	129 (56.6)	57 (24.2)
Incontinent	73 (32.0)	167 (70.8)
Data not available	26 (11.4)	12 (5.0)

ddMVAC: dose-dense methotraxate, vinblastine, doxorubicin, and cyclophosphamide; GC; gemcitabine plus cisplatin; NAC: neoadjuvant chemotherapy; RC: radical cystectomy; SD: standard deviation; TURBT: transurethral resection of bladder tumor.

Table 1 (cont'd). Baseline patient characteristics for NAC and non-NAC patient groups

	NAC	Non-NAC
Pre-treatment hydronephrosis, n (%)		
Present	80 (35.1)	56 (23.7)
Absent	146 (64.0)	173 (73.3)
Data not available	2 (0.9)	7 (3.0)
Mean number of NAC cycles, (SD)	3.5 (0.9)	N/A
NAC regimen, n (%)		
GC	139 (59)	N/A
MVAC	23 (10)	N/A
ddMVAC	62 (26)	N/A
Data not available	10 (4)	N/A
Clinical response to NAC (%)		
Partial response	35 (15.0)	N/A
Complete response	53 (22.6)	N/A
No response	46 (19.7)	N/A
Progression	4 (1.7)	N/A
Data not available	96 (41.0)	N/A

ddMVAC: dose-dense methotraxate, vinblastine, doxorubicin, and cyclophosphamide; GC; gemcitabine plus cisplatin; NAC: neoadjuvant chemotherapy; RC: radical cystectomy; SD: standard deviation; TURBT: transurethral resection of bladder tumor.

Table 2. Mean glomerular filtration rate at three time points

	Glomerular filtration rate (mL/min/1.73 cm^2)	
	NAC	Non-NAC
No. patients	234	236
T1: Pre-treatment (95% CI)	75 (72–77)	66 (64–69)
T2: Post-NAC, pre-RC (95% CI)	67 (64–70)	N/A
T3: 1 year post-RC (95% CI)	62 (59–65)	62 (59–66)
Overall change (%)	-17	-6

CI: confidence interval; NAC: neoadjuvant chemotherapy; RC: radical cystectomy.

erative hydronephrosis displayed a non-significant trend towards lesser renal function decline than those without (10% vs. 18%, p=0.09), perhaps as a result of relief of obstruction from therapy. There was no evidence of a difference in renal function decline between patients who received GC vs. ddMVAC (18% vs. 15%, p=0.4).

Table 3. Proportion of patients with stage 3 or greater chronic kidney disease at study time points

	% with GFR <60 mL/min/1.73 cm^2	
	NAC	Non-NAC
T1: Pre-treatment	27	37
T2: Post-NAC, pre-RC	59	N/A
T3: 1-year post-RC	50	51

GFR: glomerular filtration rate; NAC: neoadjuvant chemotherapy; RC: radical cystectomy.

These findings are supported by multivariable logistic regression analysis, which was performed to identify associations between GFR and several patient variables. Among the variables examined, there was no correlation with patient age, presence of preoperative hydronephrosis, administration of three or more cycles of NAC, use of GC vs. ddMVAC, or continent vs. incontinent urinary diversion; however, a lower baseline eGFR was associated with a decline in eGFR from T1 to T3 (odds ratio 1.4 per 10-point decrease in baseline eGFR, 95% confidence interval 1.2–1.7).

DISCUSSION

We identified a significant 17% decline in eGFR from the start of treatment to one year postoperative in patients with MIBC who received NAC and RC. The clinical relevance of this finding is reflected by the increase in proportion of patients with stage ≥3 CKD (eGFR <60 mL/min/1.73 m^2) from 27% to 50%. We selected this renal function threshold as an indicator of clinically significant dysfunction that may lead to symptoms, other sequelae, and the need for dose adjustment of medications.

For context, there was only a 6% eGFR decline in a fully separate group that did not receive NAC. While the patients who received NAC began treatment with a higher mean eGFR, by one year post-RC, both cohorts had numerically similar eGFRs. Similarly, although the final proportion of patients with stage ≥3 CKD in the non-NAC group was similar to that of the NAC group (51% vs. 50%), the starting percentage was higher in the non-NAC group (36.8% vs. 27.0%). This comparison suggests that NAC may negatively impact renal function in patients with MIBC undergoing RC. The excess reduction in eGFR appeared to occur in the immediate aftermath of NAC administration, as both cohorts were at similar eGFR levels immediately prior to RC and subsequently experienced a modest eGFR decline of similar magnitude after RC. This suggests that

most of the renal injury occurred as a result of NAC as opposed to RC.

Logistic regression analysis identified baseline eGFR as the only factor correlated to a decline in eGFR at one year after RC. This corresponds to the known phenomenon of increased susceptibility to renal injury associated with pre-existing CKD that exists in general and specifically in relation to cisplatin.[13-16] The other covariates examined, including age, hydronephrosis, number of NAC cycles received, and type of urinary diversion, did not show an association.

Several groups have examined the effects of RC with or without perioperative chemotherapy (Table 4). In these retrospective trials, rates of NAC use ranged from 10–36%, while adjuvant chemotherapy was administered at a lower frequency. All studies identified a downward trend in renal function after RC, although they often differed in the metrics examined. Across several studies, the mean eGFR decline one year post-RC ranged from 2–10 mL/min/1.73 m^2, with perioperative chemotherapy usage rates varying from 11–41%.[20-27] In a study of 1631 patients where only 12% received perioperative chemotherapy, the mean eGFR decline at one year was 5 mL/min/1.73 m^2.[22] In a separate study by Chandrasekar et al,[24] the mean eGFR decline of 175 patients who underwent RC without NAC was 1.6 mL/min/1.73 m^2 one year after surgery, whereas it was 19.1 mL/min/1.73 m^2 in the 66 who received cisplatin NAC. These results parallel the 4 mL/min/1.73 m^2 and 13 mL/min/1.73 m^2 declines in eGFR found in our non-NAC and NAC cohorts, respectively. While few studies stratified their analysis of eGFR change by chemotherapy administration, the use of perioperative chemotherapy was frequently examined in multivariable analyses. These revealed an inconsistent relationship with decline in eGFR,[20-27] with the majority not finding a significant relationship (Table 4). This is perhaps unsurprising given the difficulty of adjusting for the multitude of interconnected confounding factors that may affect renal function in patients undergoing RC.

Limitations

The present study is useful in that unlike much of the existing literature, it specifically examines the trend in renal function in a pure cohort of patients who received NAC and underwent RC. This allows for insight beyond what is provided by multivariable analysis alone. To our knowledge, this study represents the largest cohort of NAC patients analyzed in this way; however, the lack of a proper control cohort of patients who did not receive

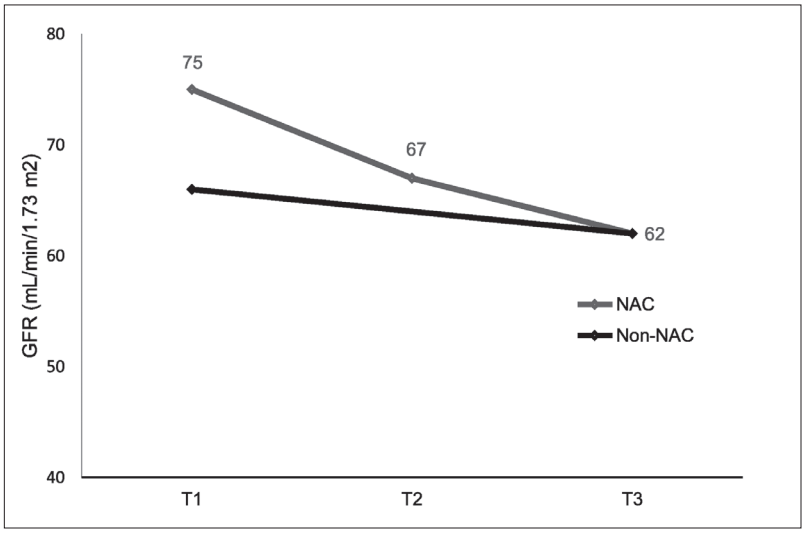

Figure 1. Change in mean glomerular filtration rate (GFR) over study time points. NAC: neoadjuvant chemotherapy.

NAC prior to RC is a definite limitation. Although we offer a similar cohort of patients who underwent RC without NAC for illustrative purposes, statistical comparison between the two groups was not possible, and as such, we were unable to draw direct conclusions about the effect of NAC on renal function.

We acknowledge several other limitations.

Firstly, we relied on the assumption that the measured eGFR and creatinine values available to us rep-

Table 4. Studies of renal function in patients undergoing RC

Study	n	Perioperative chemotherapy (%)	Change in eGFR (mL/min/1.73 m^2 unless otherwise specified)	Chemotherapy associated with declining eGFR
Gershman et al[21]	1383	11	40% with >10 unit decline at 1 year	No
Eisenberg et al[20]	1631	12	-5 at 1 year	No
Rouanne et al[22]	226	Neoadjuvant – 10 Adjuvant – 18	-2 at 1 year	No
Chandrasekar et al[24]	241	Neoadjuvant – 27	NAC: -19.1 at 1 year Non-NAC: -1.2 at 1 year	Yes – in cisplatin subgroup only
Schmidt et al[25]	3360	Neoadjuvant – 21 Adjuvant – 13	-2/year	Neoadjuvant – No Adjuvant – Yes
Ahmadi et al[26]	508	Neoadjuvant – 23 Adjuvant – 12	43% with ≥10 unit decline at 3.7 years	Yes
Lone et al[27]	644		-10 at 1 year	No
Makino et al[23]	91	41	-6.2 at 1 year	No

eGFR: estimated glomerular filtration rate; NAC: neoadjuvant chemotherapy; RC: radical cystectomy.

resented steady-state measurements. Unfortunately, these measures are known to be prone to intra-patient fluctuation, as well as inter-patient variation due to differences in physiology and laboratory techniques. We aimed to mitigate this variation with a large sample size.

We were also unable to determine whether subjects had medical conditions, such as diabetes or hypertension, which can impact renal function, or whether they were exposed to nephrotoxins, such as intravenous contrast or non-steroidal anti-inflammatory drugs. We did not have access to data on use of adjuvant chemotherapy or postoperative events, such as ureteric stricture, pyelonephritis, recurrence, or commencement of dialysis, all of which could impact our results.

Further, we acknowledge that a retrospective analysis such as this, with many missing variables, is at high risk of selection and confounding biases. It is conceivable that patients with impaired renal function are more likely to have laboratory data available at all time points, so that we may be systematically biased towards detection of renal impairment after treatment.

Finally, another limitation of our study was the lack of sufficient data beyond one year of followup, which hindered our ability to describe the long-term effects of bladder cancer treatment on renal function and potential subsequent effects that might have clinical significance. As the prognosis of bladder cancer improves, these long-term data will become increasingly important for gauging the effects of therapy. As different treatment alternatives emerge that may not have nephrotoxic potential, it is conceivable that the impact on long-term renal function could influence treatment selection.

It is important to note that while patients receiving cisplatin NAC and RC appeared to experience greater renal function decline than those received RC only, the clinical significance of this is not clear. Given the definitive and significant OS advantage conferred by NAC, we strongly believe that the benefits of this treatment outweigh the potential risks in patients fit enough to receive it.

CONCLUSIONS

We examined a cohort of patients who underwent NAC and RC alongside a separate cohort of patients who underwent RC only. While both groups ended with similar renal function measures one year post-RC, patients undergoing NAC appeared to have better starting renal function and experienced a greater degree of decline, possibly attributable to NAC. Despite its inherent limitations, this study is one of few to provide a detailed quantification of the effect of cisplatin-based NAC on renal function in patients with bladder cancer. Future studies will hopefully continue to assess the long-term impact of cisplatin-based NAC in patients with bladder cancer, allowing us to better implement this important therapy in an often-complex patient population.

COMPETING INTERESTS: The authors do not report any competing personal or financial interests related to this work.

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