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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Comparison of clinical outcomes in patients with localized or locally advanced urothelial carcinoma treated with neoadjuvant chemotherapy involving gemcitabine–cisplatin and high dose-intensity MVAC

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Abstract

Purpose To compare the efficacy and safety of high dose-intensity combination of methotrexate, vinblastine, adriamycin and cisplatin (HD MVAC) with gemcitabine plus cisplatin (GC) as a neoadjuvant chemotherapy (NAC) in muscle-invasive bladder cancer (MIBC) or locally advanced upper tract urothelial cancer (UTUC).

Patients and methods A retrospective analysis was conducted for patients with UC (cT2-4aN0-1M0) who received NAC from January 2011 and December 2017 at Asan Medical Center. Pathologic complete response (pCR), down-staging (< ypT2 and no N upstaging), disease-free survival (DFS), OS and safety were compared for each regimen.

Results Out of a total of 277 patients, 176 patients received GC and 41 patients received HD MVAC. With the exception of age (patients receiving HD MVAC were younger; $p = 0.002$), other baseline characteristics were well balanced between groups. pCR rates were 27.0% for GC and 22.6% for HD MVAC ($p = 0.62$), and down-staging rate was 50.8% for GC and 58.1% for HD MVAC ($p = 0.47$). There were no differences in OS (72.1% vs 73.1% for GC vs HD MVAC; $p = 0.58$) and DFS (54.9% vs 63.3% for GC vs HD MVAC; $p = 0.21$) at 3 years. HD MVAC with prophylactic G-CSF was associated with a higher incidence of febrile neutropenia ($p < 0.001$) than GC. The NAC regimen was not an independent prognostic factor for OS.

Conclusion Oncologic outcomes were not significantly different between the GC and HD MVAC when used as NAC in MIBC/UTUC.

Keywords Bladder cancer · Upper tract urothelial cancer · Neoadjuvant chemotherapy · High dose-intensity chemotherapy

Introduction

It is estimated that 550,000 new cases of bladder cancer occurred worldwide in 2018, with approximately one-third of patients presenting with the muscle-invasive form of the disease (MIBC). More than 20% of patients with non-muscle-invasive bladder cancer progress to MIBC, resulting in 200,000 deaths annually (Bray et al. 2018).

Neoadjuvant chemotherapy (NAC) in MIBC has been established as a standard treatment after SWOG prospective randomized trials demonstrated the efficacy of MVAC as NAC (Grossman et al. 2003). The subsequent meta-analysis of 11 trials encompassing 3005 patients supported the result that NAC led to an absolute improvement of 5-year overall survival (OS) by 5% and disease-free survival (DFS) by 9% (Advanced Bladder Cancer Meta-analysis Collaboration 2003). Despite

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a high level of evidence, NAC has not been used widely in clinical practice owing to concerns regarding treatment-related toxicity, over-treatment associated with limited accuracy of preoperative staging, and delay to surgery.

In advanced urothelial cancer (UC), the GC (gemcitabine and cisplatin) regimen is preferred to MVAC (methotrexate, vinblastine, adriamycin, and cisplatin) based on comparative efficacy with a better safety profile and tolerability (von der Maase et al. 2000). Besides, high-dose intensity (HD) MVAC with granulocyte colony-stimulating factor (G-CSF) support had statistically significant survival benefit and higher response rate, especially complete response, than MVAC, with comparable tolerance and fewer dose delays in metastatic UC (Sternberg et al. 2001, 2006).

Based on data in the metastatic setting, GC or HD MVAC is preferred to MVAC as NAC treatment in MIBC. Comparative data between GC and HD MVAC in a neoadjuvant setting are limited, and it has not been thoroughly assessed in randomized controlled trials. The National Comprehensive Cancer Network guideline recommends both GC and HD MVAC as preferred regimens without preference between them (National Comprehensive Cancer Network 2020). In comparison, the European Association of Urology and the American Urologic Association do not suggest specific regimens and refer to cisplatin-based chemotherapy (Alfred Witjes et al. 2017; Chang et al. 2017). A few retrospective studies recently compared the clinical outcomes of the HD MVAC regimen and the GC regimen when used as NAC in MIBC, which have shown somewhat contradictory results (Peyton et al. 2018; van de Putte et al. 2016; Zargar et al. 2018).

The evidence of NAC in upper tract urothelial cancer (UTUC) is scarce. The POUT study showed adjuvant platinum-based chemotherapy improved disease-free and metastasis-free survival in UTUC (Birtle et al. 2020). However, due to reduced kidney function after nephroureterectomy, the neoadjuvant setting may be preferred over adjuvant for chemotherapy administration in UTUC, especially for a clinical node-positive disease where the chance of overtreatment is minimal (Chakiryan et al. 2019), and retrospective studies have suggested survival benefit with NAC (Leow et al. 2014). Similar to bladder cancer, the data of comparative efficacy of NAC regimen in UTUC are lacking.

The aim of this study was therefore to compare the clinical outcomes of neoadjuvant GC with those of HD MVAC in patients with localized or locally advanced UC.

Patients and methods

Patients

Between January 2011 and December 2017, 290 consecutive patients with urothelial carcinoma who received neoadjuvant chemotherapy at Asan Medical Center, Seoul, Republic of Korea, were reviewed. Eleven patients who had distant metastasis (include M1a) or non-muscle-invasive bladder cancer were excluded. All remaining patients were histologically confirmed and documented to have stage cT2-4 N0 M0 or cTany N1 M0 cancer. Sixty-two patients who received NAC other than GC or HD MVAC were excluded. Overall, 217 patients were included in this analysis. The Institutional Review Board of Asan Medical Center approved this study.

Treatment and evaluation

GC chemotherapy was performed using the following schedule: gemcitabine 1000 mg/m^2 on Days 1 and 8 and cisplatin 70 mg/m^2 on Day 1, every 3 weeks. HD MVAC chemotherapy involved methotrexate 30 mg/m^2 on Day 1, vinblastine 3 mg/m^2 on Day 2, doxorubicin 30 mg/m^2 and cisplatin 70 mg/m^2 on Day 2, and G-CSF 300 μg/m^2 from Days 4–10 or long-acting G-CSF(pegfilgrastim) on Day 2, every 2 weeks. In both groups, patients without cN1 received four cycles of chemotherapy, whereas those with cN1 received six cycles if there was no evidence of disease progression and adverse events were tolerable.

Surgery was conducted only if all lesions were resectable, assessed by the urologic surgeon after NAC. Patients received partial or radical cystectomy, radical nephroureterectomy, or segmental ureterectomy, according to the lesions involved. No surgery was performed in case of clinical disease progression (cPD) to NAC. In the case of medically inoperable patients or refusal of surgery, concurrent chemoradiation or radiotherapy was recommended after NAC. Repeated CT scans were obtained immediately after neoadjuvant chemotherapy before surgery for cN0 disease, while we did additional CT scans after the 3rd cycle of NAC for patients with cN1 disease.

We defined the extent of resection as being macroscopically complete with a negative microscopic margin (R0), macroscopically complete with a positive microscopic margin (R1), or macroscopically incomplete (R2). We determined the pathological response based on cystectomy and pelvic lymph node dissection (PLND) for patients who underwent surgery. PLND was performed per a standardized template. We reviewed the rate of the patient's pathologic down-staging and pathologic complete response (pCR). Down-staging was defined as < ypT2 and no N upstaging at operation. pCR was defined as no evidence of residual tumor (ypT0N0). Toxicity during chemotherapy was classified in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 (National Cancer Institute 2010).

Statistical analysis

OS was defined as the duration of time from the start date of NAC to the date of death due to any cause. DFS was defined as the duration of time from the start date of neoadjuvant chemotherapy starting to the date of disease recurrence or death due to any cause, whichever occurred first. Survival rates and corresponding standard errors were estimated using the Kaplan–Meier method, and survival curves were compared using the log-rank test. Baseline characteristics, clinical response rates, pathologic down-staging rate, pCR between groups were compared using Pearson's chi-square test or Fisher's exact test for categorical variables and Student's *t*-test or Mann–Whitney *U* test for continuous variables, as appropriate. To identify clinical prognostic factors for OS and DFS, univariate and multivariate analyses were performed using Cox proportional hazard regression modeling. The key baseline characteristics and candidate prognostic factors, including age, sex, tumor histology, clinical stage, hydronephrosis at presentation, history of non-muscle-invasive bladder cancer, and neoadjuvant regimen were included in the univariate analysis. Variables exhibiting a potential association with survival ($p < 0.25$) in the univariate analysis and neoadjuvant regimen were included in the multivariate analysis. All analyses were computed using SPSS Statistics version 24 (IBM SPSS Inc. Armonk, NY, USA). All tests were two-sided, with p values of < 0.05 considered statistically significant.

Results

Patient characteristics

The baseline characteristics of patients in the GC ($n = 176$) and HD MVAC ($n = 41$) groups are presented in Table 1. The characteristics did not differ significantly between the two groups, with the exception of age: patients treated with HD MVAC were younger than those treated with GC ($p = 0.002$).

Neoadjuvant chemotherapy, administration, clinical response, and tolerability

The number of median chemotherapy cycles was 4 (IQR 3–4) for the GC group and 4 (IQR 3–5.5) for the HD MVAC group. All patients received at least two cycles of neoadjuvant chemotherapy. The percentage of patients who received fewer than 3 cycles of chemotherapy was 10.2% in the GC group and 2.4% in the HD MVAC group ($p = 0.135$). The clinical responses to NAC for both groups are listed in Supplement Table 1. There were no differences in clinical response rate between the groups: the cCR rate was 28.4% in the GC group and 17.1% in the HD MVAC group, and the cPD rate was 4.5% in GC group and 7.3% in HD MVAC group ($p = 0.337$). Grade 3 or worse hematologic adverse events that occurred are presented in Table 2. The incidence of CTCAE Grade 3/4 neutropenia was 46.6% in the GC group and 19.5% in the HD MVAC group; these values are significantly different ($p = 0.002$). Despite the higher incidence of Grade 3/4 neutropenia in the GC group, the HD MVAC with prophylactic G-CSF group was associated with a higher incidence of febrile neutropenia than GC (0.6% in the GC group vs. 12.2% in the HD MVAC group, $p < 0.001$). The incidences of severe anemia (5.7% in the GC group vs. 9.8% in the HD MVAC group, $p = 0.308$) and thrombocytopenia (10.2% in the GC group vs. 12.2% in the HD MVAC group, $p = 0.217$) were comparable between the two groups. Severe non-hematologic adverse events are detailed in Supplement 2.

Surgery and pathologic outcomes

Overall, 71% of patients underwent surgery after NAC. The proportion of patients who underwent surgery was not different between the two groups (69.3% in the GC group vs. 75.6% in the HD MVAC group, $p = 0.426$, Table 3).

The rate of incomplete resection was 9% ($n = 11$) in the GC group and 13% ($n = 4$) in the HD MVAC group. The down-staging rate was 50.8% in the GC group and 58.1% in the HD MVAC group ($p = 0.470$). The pCR rate was 27.0% in the GC group and 22.6% in the HD MVAC group ($p = 0.613$).

Survival outcomes

The survival outcome of patients with UC is shown by NAC regimen in Fig. 1. With a median follow-up duration of 37 months, there were no differences in OS and DFS between groups. The 3-year OS was 72.1% in the GC group and 73.1% in the HD MVAC group, the 5-year OS was 63.8% in the GC group and 67.9% in the HD MVAC group (HR = 1.21; 95% CI 0.60–2.43; $p = 0.588$), the 3-year DFS was 54.9% in the GC group and 63.2% in the HD MVAC group, and the 5-year DFS was 43.5% in the GC group and 63.2% in the HD MVAC group (HR = 1.42; 95% CI 0.81–2.49; $p = 0.211$).

Subgroup analysis

Our study consisted of patients with bladder cancer, upper tract urothelial cancer (UTUC), and both site involvement. We analyzed two groups of patients, bladder only subgroup and the UTUC subgroup (patients with upper tract lesions); the subgroups contained 180 and 37 patients, respectively.

The baseline characteristics of the bladder subgroup were not significantly difference, except in terms of age

Table 1 Baseline characteristics

Characteristics	Overall $N=217$	GC $N=176$	HD MVAC $N=41$	*p*-value
Age, years (median, range)		66 (29–84)	57 (42–77)	0.002
Male, (*n*, %)	179 (82.5)	145 (82.4)	34 (82.9)	0.935
TURBT histology, (*n*, %)				0.587
Pure UC	140 (64.5)	114 (64.8)	26 (63.4)	
Mixed UC[a]	71 (32.7)	58 (33.0)	13 (31.7)	
Pure variants[a]	6 (2.8)	4 (2.3)	2 (4.9)	
Stage (%)				
Bladder: TNM stage (*n*, %)				0.363
cT2/3N0	147 (75.7)	119 (75.8)	28 (75.7)	
cT4N0	17 (8.8)	16 (10.2)	1 (2.7)	
cT1-4aN1	30 (15.5)	22 (14.0)	8 (21.6)	
Upper tract UC[b]	37	32	5	0.204
cN0	22 (59.4)	21 (65.6)	1 (20.0)	
cN1	15 (40.5)	11 (34.4)	4 (80.0)	
Involved length, mm (median, range)		45 (15–207)	50 (35–75)	0.970
Involved thickness, mm (median, range)		20 (5–93)	42 (10–60)	0.700
Complete TURBT before NAC (*n*, %)				0.075
Yes	94 (43.3)	79 (44.9)	15 (36.6)	
No	44 (20.3)	39 (22.2)	5 (12.2)	
Unknown	79 (36.4)	58 (33.0)	21 (51.2)	
Hydronephrosis at presentation, (*n*, %)	63 (29.0)	46 (26.1)	17 (41.5)	0.052
Median chemotherapy cycle, (IQR)	4 (3–4)	4(3–4)	4 (3–5.5)	–
Laboratory tests (mean ± SD)				
Hb (g/dL)	13.07 ± 1.65	13.08 ± 1.67	13.00 ± 1.58	0.777
NLR	2.63 ± 1.71	2.65 ± 1.81	2.55 ± 1.23	0.738
GFR (mL/min/1.73 m^2)	81.52 ± 17.82	81.86 ± 16.96	79.99 ± 21.41	0.556
BUN (mg/dL)	16.39 ± 5.80	16.18 ± 4.57	17.33 ± 9.52	0.282
LDH (IU/L)	183.74 ± 38.14	182.67 ± 37.20	188.11 ± 42.04	0.445
CRP (mg/dL)	0.72 ± 1.40	0.76 ± 1.51	0.51 ± 0.71	0.353

TURBT Trans-urethral resection of bladder tumor, *UC* urothelial carcinoma, *NLR* neutrophil to lymphocyte ratio

[a]Includes squamous, micropapillary, adenocarcinoma, nested, sarcomatoid, neuroendocrine, and giant cell differentiation. Mixed UC was defined as urothelial carcinoma mixed with other cell types

[b]Clinical T stage of upper tract UC was not assessed owing to its inaccuracy by CT or MR. Instead, we measured lymph node metastasis and the involved ureter thickness and length instead

Table 2 Hematologic Adverse events of the GC and HD MVAC regimens

≥ Grade 3 hematologic AEs	Overall $N=217$	GC $N=176$	HD MVAC $N=41$	*p*-value
Any, *n* (%)	120 (55.3)	105 (59.6)	14 (34.1)	0.002
Anemia	14 (6.5)	10 (5.7)	4 (9.8)	0.308
Thrombocytopenia	23 (10.6)	18 (10.2)	5 (12.2)	0.217
Neutropenia	90 (41.5)	82 (46.6)	8 (19.5)	0.002
Febrile neutropenia	6 (2.8)	1 (0.6)	5 (12.2)	< 0.001

Other adverse events included mucositis, nausea/vomiting, diarrhea, hyperglycemia, azotemia, electrolyte imbalance, asthenia, thromboembolic event, pneumonia, and urinary tract infections (Supplement Table 2)

Table 3 Surgical and pathologic outcomes

Characteristics	Overall $N=217$	GC $N=176$	HD MVAC $N=41$	p-value
Surgery (n, %)	153 (70.5)	122 (69.3)	31 (75.6)	0.426
Residual tumor (n, %)				0.376
R0	138 (90.2)	111 (91.0)	27 (87.1)	
R1/R2	15 (9.8)	11 (9.0)	4 (12.9)	
Pathologic outcome (n, %)				0.681
ypT0	42 (27.5)	35 (28.7)	7 (22.6)	
ypTa	4 (2.6)	4 (3.3)	0 (0.0)	
ypTis	23 (15.0)	16 (13.1)	7 (22.6)	
ypT1	13 (8.5)	9 (7.4)	4 (12.9)	
ypT2	17 (11.1)	15 (12.3)	2 (6.5)	
ypT3	43 (28.1)	34 (27.9)	9 (29.0)	
ypT4	11 (7.2)	9 (7.4)	2 (6.5)	
				0.726
ypN0	105 (78.9)	83 (78.3)	22 (81.5)	
ypN1+	28 (18.3)	23 (18.9)	5 (16.1)	
Down-staging[a] (n, %)	80 (52.3)	62 (50.8)	18 (58.1)	0.471
Pathologic CR (ypT0N0) (n, %)	40 (26.1)	33 (27.0)	7 (22.6)	0.613

CR complete remission

[a]Downstaging was defined as < ypT2 and no *N* upstaging at surgery

(Supplement Table 3). Neither the clinical outcomes (Supplement Table 4) nor the pathologic outcomes differed significantly between the two regimens (Supplement Table 5). The down-staging rate of the bladder-involved subgroup was 55.3% for GC and 55.6% for HD MVAC ($p=0.983$), and the pCR rate was 31.9% for GC and 22.2% for HD MVAC ($p=0.510$). In the UTUC subgroup, there were no significant differences in pathologic outcomes (Supplement Table 6). But a numerically higher proportion of patients treated with HD MVAC achieved pCR (25% vs. 10.7%) and down-staging (75% vs. 35.7%).

Prognostic factors affecting survival outcomes

The univariate and multivariate analyses of the potential prognostic factors for DFS and OS are summarized in Table 4. In the univariate analysis, the TNM stage, hydronephrosis, anemia, and down-staging to NAC were statistically significant factors associated with OS. Among them, down-staging alone remained as significant factor affecting OS and DFS in multivariate analysis. NAC was not a statistically significant prognostic factor for neither OS nor DFS.

Discussion

Our study showed that the HD MVAC regimen when used as NAC did not show superiority in efficacy and safety in patients with MIBC/UTUC compared with the GC regimen. There were no statistically significant differences in

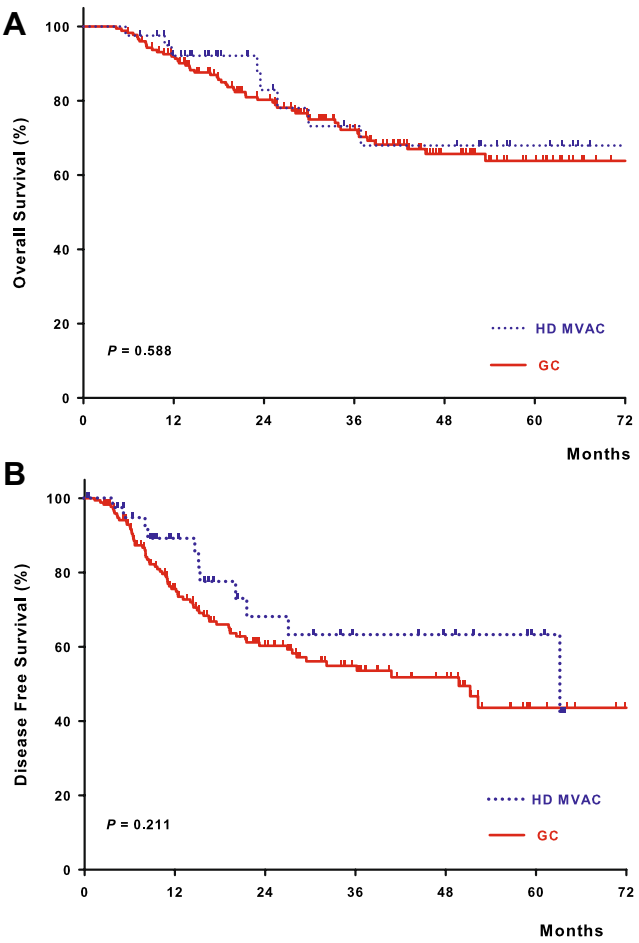

Fig. 1 Survival outcomes according to NAC regimen

Table 4 Univariate and multivariable analyses for overall survival and disease-free survival

Variable	Overall survival				Disease-free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age ≥ 65 (years, range)[a]	1.40 (0.83–2.37)	0.202			0.93 (0.59–1.44)	0.753		
Male[a]	0.61 (0.33–1.12)	0.117			0.60 (0.35–1.02)	0.062		
TURBT histology								
Pure UC	1				1			
Mixed UC	0.86 (0.48–1.55)	0.631			0.77 (0.47–1.27)	0.316		
Pure variants	1.30 (0.31–5.42)	0.712			1.23 (0.38–3.93)	0.728		
Stage[a]								
Bladder: TNM stage								
cT2N0	1				1			
cT3N0	1.25(0.58–2.68)	0.558			1.01 (0.55–1.86)	0.966		
cT4N0	2.12(0.86–5.21)	0.101			1.63 (0.73–3.60)	0.226		
cT1-4aN+	2.56(1.21–5.38)	0.013			1.64 (0.88–3.07)	0.115		
Upper tract UC								
cN0	1				1			
cN1+	1.62 (0.51–5.13)	0.413			2.15 (0.75–6.17)	0.152		
Hydronephrosis at presentation[a]	2.06 (1.21–3.51)	0.007			1.46 (0.91–2.34)	0.111		
History of NMI-bladder cancer	1.44 (0.72–2.85)	0.295			1.17 (0.61–2.21)	0.627		
History of NMI-bladder cancer, *n* (%)	1.44(0.72–2.85)	0.295						
Hb < 13 (g/dL)[a]	2.33(1.36–3.99)	0.002			1.33(0.85–2.08)	0.202		
GFR (ml/min)[a]								
≥ 60	1				1			
< 60 and ≥ 45	1.27(0.54–2.97)	0.576			0.73(0.31–1.68)	0.464		
< 45	4.98(0.68–36.5)	0.114			2.88(0.39–20.92)	0.294		
Neoadjuvant regimen[a]								
GP	1				1			
HD MVAC	0.81 (0.38–1.72)	0.589			0.66 (0.35–1.26)	0.214		
Iincomplete CTx[a] cycle (< 3)	1.43(0.81–2.54)	0.209			1.51(0.92–2.47)	0.102		
Down-staging[a]	0.16(0.07–0.36)	< 0.001	0.29 (0.12–0.68)	0.005	0.18(0.09–0.36)	< 0.001	0.29(0.13–0.62)	0.002
ypT0	1							
ypTa-Tis	2.93(0.65–13.11)	0.159			1.66(0.44–6.20)	0.448		
ypT1	2.03(0.33–12.20)	0.438			2.09(0.50–8.79)	0.312		
ypT2	6.59(1.70–25.54)	0.006			4.83(1.57–14.80)	0.006		
ypT3	8.36(2.47–28.30)	0.001			6.40(2.43–16.80)	< 0.001		
ypT4	15.38(3.96–59.67)	< 0.001			10.20(3.31–31.37)	< 0.001		
ypN+	3.20(1.71–5.98)	< 0.001			3.06(1.73–5.40)	< 0.001		

[a]Included in multivariate analysis

pCR, down-staging rate, OS, and DFS between groups. The proportion of patients who were not operated on owing to clinical progression or a deteriorated condition associated with adverse events was comparable between groups. Even though prophylactic G-CSF was given to all patients receiving HD MVAC, febrile neutropenia occurred more frequently in patients treated with HD MVAC group.

There are five published studies that compared GC and HD MVAC regimens used as NAC for bladder cancer (Table 5). Three of the studies were retrospective observational analyses, and two were prospective randomized studies (Flaig et al. 2019; Peyton et al. 2018; Pfister et al. 2021; van de Putte et al. 2016; Zargar et al. 2018). However, one is a randomized phase II trial with a primary endpoint of

Table 5 Studies comparing GC and HD MVAC in NAC

Study	Design	Arm	No. of patients	Endpoints	Inclusion criteria	Baseline characteristics		Follow-up duration (median)	Efficacy			Safety	
						Age (median)	Stage		pCR	Down-staging (pPR) (%)	Survival	Any Grade ≥3	FN
van de Putte et al	Retrospective Single center	HD MVAC	80	pCR, Toxicity	cT3-4aN0-1 including M1a nodes (15%)	57	cT3/4:68.8%, cN+:76.3%, cM1a:17.5%	NR	28.8%	37.6	NR	31.6%	7.6%
		GC	51			63	cT3/4:78.4%, cN+:50.9%, cM1a:13.7%		31.4%	43.2		43.6%	0%
Zargar et al	Retrospective Multicenter	HD MVAC	100	pCR, pPR, OS, CSS	cT3-4aN0M0	61	cT4a:30%	1.8 years	28.0%	41.0	Median OS: 7 years	NR	NR
		GC	219			67	cT4a:24.7%	1.2 years	14.6%	30.1	Median OS: 4.2 years		
Peyton et al	Retrospective Single center	HD MVAC	46	pPR, OS	>cT2NxMx	61.5	cT3/4:21.7%	11 months	41.3%	52.5	2-Year OS:73.3%	31%	NR
		GC	204			66	cT3/4:27.6%	15 months	24.5%	41.3	2-Year OS:62%	NR	NR
Flaig et al	Prospective	HD MVAC	85	COXEN score, OS, pT0 rate, tolerability	cT2-4aN0M0	64.8	cT3/4a:13.0%	NR	32%	56	NR	NR	NR
		GC	82			64.4	cT3/4a:8.0%	NR	35%	50			
Pfister et al	Prospective	HD MVAC	218	PFS at 3 years, toxicity, RR, OS, and TTP	cT2-T4aN0M0	63	cT3/4a:9.6%	NR	42%	63	NR	52%[a]	6.5%
		GC	219			63	cT3/4a:5.5%		36%	49		55%[a]	2.4%
Our study	Retrospective Single center	HD MVAC	41	pCR, pPR(down-staging), OS, DFS	cT2-4aN0M0 or cTanyN1M0	58.9	cT3/4a:27.0%, cN+:21.6%	25.0 months	22.6%	58.1	3-Year OS:73.1% 3-Yearr DFS:63.2%	34.1%[a]	12.2%
		GC	176			64.4	cT3/4a:37.6%, cN+:14.0%	41.0 months	27.0%	50.8	3-Year OS:72.1% 3-Year DFS:54.9%	59.6%[a]	0.6%

pCR pathologic complete remission, *pPR* pathologic partial response, *OS* overall survival, *DFS* disease-free survival, *NR* not reported, progression-free survival, *TTP* time to progression; pCR was defined as ypT0N0, and down-staging (pPR) was defined as less than ypT2N0 and no N upstaging, *FN* febrile neutropenia

[a]Any hematologic adverse event grade 3 or higher

regimen-specific COXEN score (Flaig et al. 2019). The other is a multicenter randomized phase III trial but only reported secondary endpoints of pathology response and toxicity (Pfister et al. 2021). In contrast to our study, Peyton et al. and Zargar et al. showed that the HD MVAC regimen led to higher pCR and longer OS than the GC regimen (Peyton et al. 2018; Zargar et al. 2018). Similar to our analysis, Van de Putte et al. showed no differences in pCR rates between GC and HD MVAC (van de Putte et al. 2016). In the SWOG S1314 trial (COXEN Trial), even though the comparison of the efficacy between the two regimens was not the primary objective, both regimen showed no difference in pCR and pPR (< pT2) between the two regimens (Flaig et al. 2019). In the GETUG/AFU V05 VESPER trial, although the primary endpoint was not reported, there was no difference in pCR between regimens, while more patients in the HD MVAC arm achieved pPR ($p = 0.07$) (Pfister et al. 2021). The results of our analysis were mostly consistent with those of the latter three studies. Given the fact that the proportions of patients with incomplete NAC cycles (< 3) and those who did not undergo surgery were higher in the GC group in the current study, no statistical difference in pCR rate and OS suggests that it would be difficult to achieve better clinical outcome with just change of regimen from GC to HD MVAC.

The pCR rate in the HD MVAC group was 27.0% and 22.7% for the GC group in the current study. Peyton et al., the SWOG S1314 (COXEN) study, and the VESPER study showed a higher pCR rate than others (Flaig et al. 2019; Peyton et al. 2018; Pfister et al. 2021). The reason for this is probably higher proportions of patients with cT2 disease in these studies, 68.7%, 87%, and 90.3%, respectively. The pCR rate in the HD MVAC group in the current study was comparable with that reported by Choueiri et al., which enrolled patients with similar baseline clinical characteristics with the current study (Choueiri et al. 2014).

Although Grade 3 or higher neutropenia was more frequent in the GC group, the incidence of febrile neutropenia was significantly higher in the HD MVAC group, which were in line with the study reported by Van de Putte et al., and the VESPER trial (van de Putte et al. 2016). The majority of neutropenia encountered in the GC group was found on laboratory exam on day 8. It did not lead to clinically significant neutropenic fever if dose reduction or dose delay of gemcitabine is adequately employed. Besides, grade 3 or worse mucositis developed only in patients in the HD MVAC group, which is in line with higher grade 3 or worse gastrointestinal toxicities in the HD MVAC arm in the VESPER trial. From the perspective of adverse events, the GC regimen seems better and more tolerable.

The present study has several limitations. As anticipated from retrospective study design, selection bias may have occurred. Indeed, there was a statistically significant difference in the age between the HD MVAC and GC groups. The inclusion of patients with UTUC may have influenced the results of the analysis. However, in subgroup analysis involving only patients with MIBC, there were no significant differences in clinical and pathological outcomes. The difference in cohort size between the two groups and the small sample size in total may also have reduced the statistical power to assess the benefit of HD MVAC. A possible underestimation of toxicity may also have occurred because of different sampling points. Also, patients' co-morbidity and performance status data were not captured and may act as a confounding factor for the statistical analysis.

The ongoing clinical trial results, the GETUG/AFU V05 VESPER trial, are eagerly needed to draw a firm conclusion on the benefit of HD MVAC over GC in terms of survival. However, as the VESPER trial compares six cycles of HD MVAC with four cycles of GC, a new question on an adequate number of NAC would be incurred.

Conclusion

Our findings did not show the superiority of the neoadjuvant HD MVAC regimen to the GC regimen in terms of efficacy and safety in patients with localized or locally advanced urothelial cancer.

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Author contributions Dr. YJ Lee and JL Lee 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. Concept and design: YJ Lee, JL Lee. Acquisition, analysis, or interpretation of data: YJ Lee, JL Lee, YS Kim, BS Hong, YM Cho, JL Lee. Drafting of the manuscript: YJ Lee, JL Lee. Critical revision of the manuscript for important intellectual content: YJ Lee, JL Lee, YS Kim, BS Hong, YM Cho, JL Lee. Statistical analysis: YJ Lee, JL Lee. Administrative, technical, or material support: YJ Lee, JL Lee, YS Kim, BS Hong, YM Cho, JL Lee. Data analysis: YJ Lee, JL Lee.

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Declarations

Conflict of interest The authors declare that there are no relevant conflict of interests.

Consent for publication All authors consent to publish this study in J Cancer Res Clin Oncol.

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