Master of Medicine

Comparing clinical outcomes between patients with urothelial carcinoma who treated neoadjuvant chemotherapy by Gemcitabine-Cisplatin and dose-dense MVAC

요로상피세포암종 환자에서 수술전 보조항암화학요법으로 Gemcitabine-Cisplatin 치료와 dose-dense MVAC 을 시행받은 환자의 치료성적 비교분석

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Comparing clinical outcomes between patients with urothelial carcinoma who treated neoadjuvant chemotherapy by Gemcitabine-Cisplatin and dose-dense MVAC

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Abstract

Background

Prospective randomized trials demonstrated efficacy of MVAC (Methotrexate, Vinblastine, Doxorubicin, Cisplatin) neoadjuvant chemotherapy (NAC) in muscle invasive bladder cancer (MIBC). In metastatic setting urothelial cell carcinoma (UCC), clinical trials showed no difference in oncologic outcomes between Gemcitabine-Cisplatin (GC) and MVAC, and another prospective trial proved dose-dense (dd) MVAC had significantly better overall survival (OS) and response rate then MVAC. Comparative data between GC and ddMVAC are limited in neoadjuvant setting.

Methods

A retrospective analysis of patients with urothelial carcinoma (cT2-4aN0-1M0) who received NAC from January 2011 and December 2017 in Asan Medical Center was conducted. Patients who received GC were compared to patients received ddMVAC in terms of outcomes including downstaging (<ypT2 and no N upstaging), pathologic complete response (pCR, ypT0N0), disease-free survival (DFS), and overall survival (OS) and tolerability.

Results

In a total of 277 patients, 176 patients received NAC with GC and 41 patients with dose-dense MVAC. The median chemotherapy cycle is 4 (IQR 3-4) cycles for GC group, 4 (IQR 3-5.5) cycles for dose-dense MVAC group. With an exception of age; GC group is associated with younger age (p=0.002), other baseline characteristics are well balanced between groups. Downstaging rate are 50.8% in GC group, 58.1% in dose-dense MVAC group (p=0.47). The rates of achieving ypT0 (28.7% vs 22.6%, p=0.68), ypN0 (78.3% vs 81.5%, p=0.39). There were no differences in overall survival (OS) at 3 year (72.2% vs 73.2%, p=0.58), disease-free survival (DFS) at 3 years (54.9% vs 63.3%, p=0.21) according to chemotherapy regimens. ddMVAC with prophylactic G-CSF are associated with higher incidence of febrile neutropenia (p=0.004) than GC. NAC regimen is not independent prognostic factor for OS on multivariable analysis.

Conclusions

GC regimen had no significant difference in oncologic outcomes compare to ddMVAC as NAC in UCC.

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Introduction

Bladder cancer is estimated that 550,000 new cases will occur in worldwide in 2018, with approximately one third of patients presenting with muscle invasive disease (MIBC). More than 20% of patients with non-muscle invasive disease also progress to MIBC, resulting in 200,000 deaths with MIBC annually [1]

In muscle-invasive urothelial bladder cancer, Clinical trials demonstrate the efficacy of platinum-based combination chemotherapy including MVAC (Methotrexate, Vinblastine, Doxorubicin, Cisplatin), Gemcitabine-Cisplatin (GC). [2, 3, 4] Neoadjuvant chemotherapy in MIBC has been established as a standard treatment after SWOG prospective randomized trials had demonstrated efficacy of MVAC neoadjuvant chemotherapy (NAC).[2,3] Subsequent meta-analysis of 11 trials with 3,005 patients supported the result that NAC had show absolute improvement of 5-year overall survival (OS) by 5% and disease free survival (DFS) by 9%.[3]

Despite high level of evidence, NAC is not widely used in clinical practice with concern for treatment related toxicity and delay of surgery. Furthermore, even if treated with NAC, GC regimen is increasingly used than MVAC despite lack of comparative data.[5,6] Multicenter prospective phase II trial proved ddMVAC had significantly better overall survival and response rate then MVAC with comparable tolerance in metastatic setting MIBC,[7,8,9] another clinical trials demonstrated no difference in oncologic outcomes between Gemcitabine-Cisplatin (GC) and MVAC in metastatic setting.[10]

However, comparative data between GC and ddMVAC are limited in neoadjuvant setting. Although this has not been proven in randomized phase III trials in neoadjuvant setting bladder cancer, the guidelines of the National Comprehensive Cancer Network, European Association of Urology suggest that GC is recommended as a reasonable alternative to ddMVAC in guidelines.[11,12,13] Recently, the clinical outcomes of ddMVAC regimen direct comparing for GC regimen as neoadjuvant chemotherapy in locally advanced MIBC have been reported in few retrospective studies, but most of these studies lack a randomization or conducted by single institution, limiting the level of evidence. [14,15,16]

The aim of this study was to compare the clinical outcomes of patients who received neoadjuvant GC chemotherapy (GC group) with received ddMVAC chemotherapy (ddMVAC group) in patients with

muscle invasive urothelial bladder cancer.

Methods

Patients

Between January 2011 and December 2017, 290 patients with urothelial carcinoma who received neoadjuvant chemotherapy in Asan medical center, Seoul, Republic of Korea were reviewed.
All patients are histologically documented 'cT2-4 N0 M0' or 'cT1-4a N1 M0' stage, and 11 with distant metastasis (include M1a) or non-muscle invasive bladder cancer excluded. 1 patient who have T1 disease with positive lymph nodes (N1) are included to muscle-invasive urothelial carcinoma and received neoadjuvant chemotherapy. 62 patients who received neoadjuvant chemotherapy except GC or ddMVAC were excluded, and a total of 217 patients were thus included in this analysis. The Institutional Review Board of Asan Medical Center approved this study.

Treatment and evaluation

Patients who received standard dose of GC chemotherapy were classified as the GC group, and patients who were treated with ddMVAC regimen were classified as ddMVAC group. GC chemotherapy was performed on a schedule of Gemcitabine 1000 mg/m2 on day 1,8 and Cisplatin 70 mg/m^2 on day 1, every 3 weeks, and ddMVAC chemotherapy consisted of Methotrexate 30mg/m^2 on day 1, Vinblastine 3mg/m^2 on day 2, Doxorubicin 30mg/m^2 on day 2, and Cisplatin 70mg/m^2 on day 2 with G-CSF 300ug/m^2 from day 4-10, every 2 weeks. In both group, patients without clinical metastatic nodes received 4 cycles of chemotherapy , while those with clinically metastatic nodes received 6 cycles.
The surgery was conducted only if all lesions were resectable by department of urology, after the end of neoadjuvant chemotherapy. Patient received partial or radical cystectomy, radical nephrouretectomy or uretectomy according to their involved lesion. No surgery was performed for clinically progression of disease (cPD) after NAC. In case of medically inoperable patients or refusal to surgery, concurrent chemoradiation or close surveillance of recurrence was conducted after completing neoadjuvant

chemotherapy. CT scans were performed at least once between finish neoadjuvant chemotherapy and operation.

After neoadjuvant chemotherapy followed by operation, we reviewed patients' downstaging rate and pathologic complete response (pCR). Downstaging rate defined as <ypT2 & no N upstaging at operation. Pathologic CR defined as no evidence of residual tumor (ypT0N0).

The extent of resection was defined as macroscopically complete with a negative microscopic margin (R0), macroscopically complete with a positive microscopic margin (R1), or macroscopically incomplete (R2). For all patients, pathological response was determined based on cystectomy and pelvic lymph node dissection (PLND). PLND was performed according to a standardized template. Postoperative complications were classified according to the Accordion Severity Grading System of Surgical Complications[17]

Toxicity

Toxicity was classified according to the Common Terminology Criteria for Adverse Events (CTCAE).[18]

Statistical analysis

Overall survival (OS) was defined as the duration of time from neoadjuvant chemotherapy starting date to the date of death from any cause. Disease free survival (DFS) was defined as the duration of time from neoadjuvant chemotherapy starting date to the date of disease recur, or death from 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 of the groups were compared using Pearson's chi-square test or Fisher's exact test for categorical variables and Student's T-test for continuous variable, as appropriate. Clinical response rates, pathologic outcomes and tolerability of the groups were compared using Pearson's chi-square test or Fisher's exact test, as appropriate.

To identify clinical prognostic factors for OS and DFS, univariate and multivariate analyses were performed using Cox proportional hazard regression modeling. Key baseline characteristics and

candidate prognostic factors including age, sex, tumor histology, clinical stage, hydronephrosis at presentation, history of non-muscle invasive bladder cancer, neoadjuvant regimen (GP vs. ddMVAC) were included in the univariate analysis.

In the multivariate analysis, variables exhibiting a potential association with survival ($P < 0.25$) in the univariate analysis, along with age, sex, TNM stage, Hydronephrosis at presentation, and neoadjuvant regimen were included.

All analysis were performed using IBM SPSS Statistics version 24. All tests were two-sided, with P< 0.05 considered statistically significant.

Results

Patient characteristics

The baseline characteristics of urothelial cell carcinoma patients in the GC (n= 176) and ddMVAC (n= 41) groups are presented in Table 1. With an exception of age, the baseline characteristics did not differ significantly between the two groups; patients treated with ddMVAC were younger than those treated with GC (64 ±10 vs. 59±9, p=0.002).

Table 1. Baseline characteristics

Characteristics	Overall n=217, 100%	GC n=176, 81.1%	ddMVAC n=41, 18.9%	p-value¶
Age at diagnosis, years (range)		64 ±10	59±9	0.002†
Male, (%)	179(82.5)	145(82.4)	34(82.9)	0.935
TURBT Histology, (%)				0.587§
Pure UCC	140(64.5)	114(64.8)	26(63.4)	
Mixed UCC*	71(32.7)	58(33.0)	13(31.7)	
Pure Variants*	6(2.8)	4(2.3)	2(4.9)	
Stage, (%)				

Bladder : TNM Stage				0.363
cT2N0	95(48.9)	76(48.4)	19(51.4)	
cT3N0	52(26.8)	43(27.4)	9(24.3)	
cT4N0	17(8.8)	16(10.2)	1(2.7)	
cT1-4aN1+	30(15.5)	22(14.0)	8(21.6)	
Upper tract UCC**	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 ureter length (range)	55.17±36.27	55.26 ± 38.59	54.60 ± 17.27	0.97†
Involved ureter thickness (range)	30.24±24.22	29.63 ± 24.75	34.20 ± 22.58	0.70†
Complete TURBT at diagnosis				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, (%)	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				
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/1.73m$^{2)}$	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	183.74±38.14	182.67±37.20	188.11±42.04	0.445†
CRP	0.72±1.40	0.76±1.51	0.51±0.71	0.353†

Abbreviations: TURBT, Trans-urethral resection of bladder tumor; UCC, Urothelial cell carcinoma; NLR, Neutrophil to lymphocyte ratio *Includes squamous, micropapillary, adenocarcinoma, nested, sarcomatoid, neuroendocrine, giant cell differentiation. Mixed UCC defined as urothelial carcinoma mixed with other cell type; **Clinical T stage of upper tract UCC was not assessed due to its inaccuracy by CT or MR. We measured lymph node metastasis and involved ureter thickness and length instead. †Compared with T-test; ¶Compared with Chi-square test. §Compared with Fisher's exact test;

Neoadjuvant chemotherapy, administration, clinical response and tolerability

The median chemotherapy cycle is 4 (IQR 3-4) cycles for GC group, 4 (IQR 3-5.5) cycles for dd MVAC

group. All patients received at least two cycles of neoadjuvant chemotherapy. The percentage of patients who received less than 3 cycles of chemotherapy were 10.2% in GC group, and 2.4% in ddMVAC group (p=0.135). Table 2 lists clinical responses to NAC in two groups. There was no difference in clinical response rates between groups; cCR rate was 28.4 % in GC group and 17.1 % in ddMVAC group while cPD rates was 4.5% in GC group and 7.3% in ddMVAC group (p=0.337). Table 3 shows severe adverse events in two groups. Incidence rate of CTACE grade 3-4 neutropenia was 46.6% in GC group, and 19.5 % in ddMVAC group (p=0.002). Despite of higher incidence of grade 3,4 neutropenia in GC group, ddMVAC with prophylactic G-CSF group are associated with higher incidence of febrile neutropenia than GC (0.6% in GC group vs. 12.2 % in ddMVAC group, p<0.001). The incidence of severe anemia (5.7% in GC group vs. 9.8 % in ddMVAC group, p=0.308) and thrombocytopenia (10.2 % in GC group vs. 12.2% in ddMVAC group, p=0.217) was comparable between two groups. Severe non-hematologic adverse event was detailed in Table S1.

Table 2. Clinical response rates by regimen

	Overall N-217, 100%	**GemCis N=176, 81.1%**	**ddMVAC N=41, 18.9%**	**p-value***
Clinical Response evaluation				0.337
CR	57(26.3)	50(28.4)	7(17.1)	
NonPD	138(63.6)	110(62.5)	28(62.1)	
PD	11(5.1)	8(4.5)	3(7.3)	
Not evaluable	11(5.1)	8(4.5)	3(7.3)	
incomplete CTx cycle (<3)	19(8.8)	18(10.2)	1(2.4)	0.135

*Compared with Fisher's exact test

Table 3. Tolerability of GC vs ddMVAC regimen

Severe adverse events (>Grade 3)	**Overall n=217, 100%**	**GC n=176, 81.1%**	**ddMVAC n=41, 18.9%**	**P-Value†**
Any severe adverse events	120 (55.3)	105(59.6)	14(34.1)	0.002
Hematologic, (%)				

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 include mucositis, nausea/vomiting, diarrhea, hyperglycemia, azotemia, electrolyte imbalance, asthenia, thromboembolic event, pneumonia, urinary tract infections. †Compared with Chi-square test; ‡Compared with Fisher's exact test.

Sugery and pathologic outcomes

71% of patients underwent surgery after NAC. Proportion of patients who underwent surgery did not differ between two groups (69.3% in GC group vs. 75.6% in ddMVAC group, p=0.426, Table 4). Incomplete resection rate was 9% (n=11) in GC group and 13% (n=4) in ddMVAC group. Downstaging rate are 50.8% in GC group, 58.1% in dose-dense MVAC group (p=0.470). Pathologic CR (pCR) rate are 27.0% in GC group, and 22.6% in dose-dense MVAC group (p=0.613).

Table 4. Surgical and pathologic outcomes

Characteristics	**Overall n=217, 100%**	**GC n=176, 81.1%**	**ddMVAC n=41, 18.9%**	**p-value†**
Operation	153(70.5)	122(69.3)	31(75.6)	0.426
Residual tumor				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				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)	

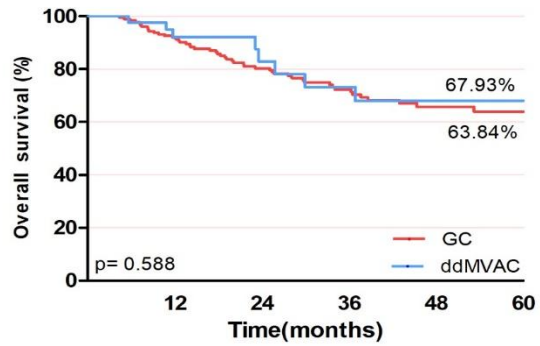
ypT4	11(7.2)	9(7.4)	2(6.5)	
				0.726
ypN0	105(78.9)	83(78.3)	22(81.5)	
ypN1+	28(18.3)	23(18.9)	5(16.1)	
Downstaging*	80(52.3)	62(50.8)	18(58.1)	0.471
Pathologic CR (ypT0N0)	40(26.1)	33(27.0)	7(22.6)	0.613

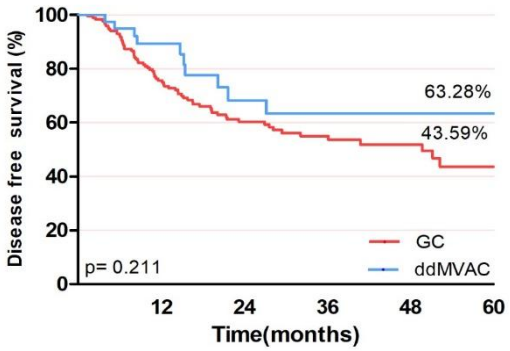
Abbreviations: CR,Complete remission; PD,Progression of disease; * Downstaging defined as <ypT2 & no N upstaging at operation.†Compared with Chi-square test;

Survival outcomes

Figure 1 shows survival outcome of UCC patients according to neoadjuvant chemotherapy regimen. With a median follow-up duration of XX months there was no difference in overall survival and disease free survival between groups. 3 year overall survival was 72.1% in GC group and 73.1% in ddMVAC group, 5 year overall survival was 63.8% in GC group and 67.9% in ddMVAC group (HR=1.21; 95% CI, 0.60 to 2.43; p=0.588), 3 year disease free survival was 54.9% in GC group and 63.2% in ddMVAC group, 5 year disease free survival was 43.5 % in GC group and 63.2 % in ddMVAC group (HR=1.42;95% CI, 0.81 to 2.49; p=0.211).

Figure 1. Survival outcomes according to NAC regimens





NAC regimen	3yr OS (%)	5yr OS (%)	p-value*	3yr DFS (%)	5yr DFS (%)	p-value*
			0.588			0.211
GC	72.1 %	63.8 %		54.9%	43.5 %	
ddMVAC	73.1 %	67.9 %		63.2%	63.2 %	

Abbreviations: OS,Overall survival; DFS,Disease free survival * Compared with Kaplan-Meier survival analysis

Univariate and multivariate analysis of survival outcomes in all patients

Table 5 summarizes the results of the univariate and multivariate analyses of the potential prognostic factors for DFS and OS. In the univariate analysis, TNM stage and presence of hydronephrosis was statistically significant factors associated with OS and strong tendency to be associated with DFS. Neither univariate analysis nor multivariate analysis showed associated of NAC regimen of either OS or DFS.

Table 5. Univariate and multivariable analysis for overall survival and disease free survival

Variable	Overall survival				Disease free survival			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
	HR (95% CI)	p-value†	HR (95% CI)	p-value†	HR (95% CI)	p-value†	HR (95% CI)	p-value†
Age ≥ 65	1.40(0.83-2.37)	0.202			0.93(0.59-1.44)	0.753		
Male	0.61(0.33-1.12)	0.117			0.60(0.35-1.02)	0.062		
TURBT Histology								
Pure UCC	1				1			
Mixed UCC	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								
Bladder : TNM Stage								
cT2N0	1	0.127			1			
cT3N0	1.33(0.70-2.52)	0.376			1.01(0.552-1.86)	0.966		
cT4N0	2.01(0.91-4.47)	0.083			1.63(0.73-3.60)	0.226		
cT1-4aN+	2.11(1.05-4.21)	0.034			1.64(0.88-3.07)	0.115		
Upper tract UCC								
cN0	1				1			
cN1+	1.62(0.51-5.13)	0.413			2.15(0.75-6.17)	0.152		
Hydronephrosis at presentation	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		
Neoadjuvant regimen								
GP	1				1			
ddMVAC	0.81(0.38-1.72)	0.589			0.66(0.35-1.26)	0.214		

Discussion

In our retrospective analysis, ddMVAC regimen failed to show superiority in efficacy and safety in muscle-invasive bladder cancer patient compare to GC regimen. Both group did not show any statistical difference in pCR, downstaging rate, and in OS and DFS. Toxicity profiles were comparable between groups, but even though prophylactic G-CSF was given to all patients with ddMVAC, febrile neutropenia developed in 12.2% of patients. The proportion of patients who were not operated on due to clinical progression or deteriorated condition associated with adverse events were comparable between groups.

This result is a contradictory of several studies that have been published to date. In our best knowledge, there are only four published study with direct comparison of GC and ddMVAC regimen as neoadjuvant chemotherapy in bladder cancer (Table 6).[14,15,16,19] Three of the studies were retrospective observational analysis and one study was a prospective trial, but the comparison of the two therapies was not the primary goal. In contrast to our study, Peyton et al.[16] and Zargar et al.[15] showed ddMVAC regimen lead more favorable results than GC. And Van de putte et al.[14] reported single center, retrospective analysis that there was no difference in pCR and toxicity rates, in line with our analysis. In the SWOG S1314 trial (COXEN Trial),[19] the comparison of the two regimens was not the primary objective, but the only prospective study published so far shows that there is no difference between pCR (pT0) and PR (<pT2) between the two groups. Our analysis is consistent with this prospective trial.

Compared with the previous studies, our study showed a similar number of patients enrolled in the study. (van de putte, plague, peyton). 15% of overall patients enrolled in our study had clinically metastatic lymph node (cN+) while analysis of Fleig et al. and Zargar et al. included only patients with clinically lymph node negative disease (cN0).

Peyton et al. and SWOG S1314 (COXEN) reported a higher proportion of patients achieving pCR, which is superior to other previous studies and our present study. The reason for this is that the proportion of patients with cT2 in these studies was 68.7% and 87%, respectively, and significantly higher than other studies and our patients. pCR rate of ddMVAC group was comparable to analysis of Choueiri et al. which was similar baseline clinical staging to our study. [20]

Although overall experience with perioperative chemotherapy in non-urothelial carcinoma is limited, several studies reported that neoadjuvant chemotherapy may have benefit in patients with variant histologies.[21] However, non-urothelial carcinoma showed more aggressive natural histology, and it is well known that pT0 rate at operation after NAC is lower than pure urothelial carcinoma.[22] The proportion of non-pure UCC included in our study is considered to be slightly higher than worldwide prevalence. Given this, the higher proportion of mixed histology and pure variants was one of the reasons for the lower pCR rate in our study than previous reported studies.

The reason of relatively lower pCR rate than the downstaging rate in comparison with the previous studies is considered to be that higher proportion of patients with clinical N+ disease. In particular, while not statistically significant, ddMVAC group had more N + disease than GC group. This is warranted by that the ddMVAC group showed a slightly higher downstaging rate than GC group, although the pCR rate was slightly lower.

Of the 4 direct comparison studies, the analysis of Van de putte et al. is the only study that reported the toxicity profile of both two regimens. Our study confirmed that incidence rate of febrile neutropenia was significantly higher in the ddMVAC group than GC group, but that of grade 3 or higher toxicity was higher in the GC group, which in line with previous study. Compared with analysis of Van de putte, which reported 0% of FN incidence rate and 43.6% of any severe toxicities in GC group, our study was higher with 0.6% of FN incidence rate and 59.6% of any severe toxicities in GC group. The reason for the higher incidence rate of grade 3,4 adverse event including neutropenia in the GC group is possibly due to that GC group had more elderly patients than ddMVAC group.

Our present study has several limitations. As anticipated for any retrospective study, selection bias may have existed for both groups. Indeed, there were significant differences in baseline characteristics between the ddMVAC and GC groups regarding age. Although the physician has tried to apply the strict and identical criteria to patients to apply both regimens, GC group may have included a part of patients who are expected not stand intense treatment and have more treatment-related toxicity.

Although no statistical significance, the proportion of patients with incomplete NAC cycles (<3) was higher in the GC group, The fact that proportion of patients with incomplete NAC cycle (<3) and with

of those who did not undergo surgery due to symptomatic adverse event and intolerability was higher in the GC group despite the proportion of patients with clinical PD after completing NAC were comparable in both group may support this discrepancy. In previous retrospective studies also had age discrepancy between two groups, which is on account of retrospective observation design.

Difference in cohort size between two groups may have lowering our statistical power. The possible underestimation of toxicity may also occur. Patients' co-morbidity and performance status data were not captured and may act as a confounding factor for statistical analysis. In contrast to the previously published study which Asian was less than 5% of the race among study enrolled patients, our study enrolled almost all of patients with Asian patients and it may slightly differ to international real-world result, require attention to interpretation.

Conclusion

In conclusion, our findings failed to show superiority of neoadjuvant ddMVAC regimen in efficacy, safety and oncologic outcomes compare to GC regimen in patient with locally advanced bladder cancer, suggesting GC regimen as a reasonable alternative option of ddMVAC. Further prospective comparative trial needed for more definitive conclusion.

Table S1. Severe non-hematologic toxicities according to neoadjuvant chemotherapy regimens

Adverse event (Gd>3)	GC (n=176)	ddMVAC (n=41)
General weakness	1	1
Mucositis		2
Fatigue	4	
Epistaxis	1	
Dizziness	1	
asthenia 3	4	
Urinary incon 3	1	
Hematuria	4	1
Hyperglycemia	7	
Nausea/vomitng	9	4
Elevated LFT	2	
Azotemia	8	3
Renal infarction	1	
Urinary tract infection	4	
Upper respiratory infection	5	
Acute peripheral ischemia	1	
Constipation	1	
Diarrhea	1	
Bacteremia	1	2
Hearing impairment	2	
Hypocalcemia	2	
Hyponatremia	1	
Hypokalemia	2	
Hyperkalemia		1
Thromboembolic event	1	
Tinnitus	2	
Septic pneumonia	1	1
Total	67 (38.1%)	15 (36.6%)

study	Year	Design	Arm	Patients	Objective	Inclusion criteria	Baseline characteristics			Median follow up period	Efficacy		Survival outcomes	Safety		comments
							Median Age	Stage	other		pCR rate	Down-staging (pPR)	OS or DFS	Any Grade >3	FN	
van de Putte et al.	2016	Retrospective Single center	ddMVAC	80	pCR, Toxicity	cT3-4aN0-1 including M1a nodes(15%)	57	cT3/4 :68.8% cN+ :76.3% cM1a :17.5%	higher N stage**	NR	28.8%	37.6%	NR	31.6%	7.6%	pCR, Ppr, Toxicities :ddMVAC ~ GC
			GC	51			63	cT3/4 :78.4% cN+ :50.9% cM1a :13.7%	had higher ACCI**		31.4%	43.2%		43.6%	0%	
Zargar et al.	2017	Retrospective Multicenter	ddMVAC	100	pCR, pPR, OS, CSS	cT3-4aN0M0	61	cT4a :30%	higher variant histology (9%)	1.8year	28%	41%	Median OS: 7years	NR	NR	pCR, OS ddMVAC>GC
			GC	219			67	cT4a :24.7%		1.2year	14.6%	30.1%	Median OS: 4.2years			
Peyton et al.	2018	Retrospective Single center	ddMVAC	46	pPR, OS	>cT2NxMx who received NAC	61.5	cT3/4 :21.7%		11mo	41.3%	52.5%	2Year OS :73.3 mo	31%	NR	pCR, OS ddMVAC>GC
			GC	204			66	cT3/4 :27.6%		15mo	24.5%	41.3%	2Year OS :62 mo	NR	NR	
Flaig et al.	2019	prospective	ddMVAC	85	regimen-specific COXEN score, OS, pT0 rate, tolerability	cT2-4aN0M0	64.8	cT3/4a :13.0%		NR	32%	56%	NR	NR	NR	pCR,pPR rate: ddMVAC~GC
			GC	82			64.4	cT3/4a :8.0%		NR	35%	50%				
Our study		Retrospective Single center	ddMVAC	41	pCR,down-staging,, OS, DFS	cT2-4aN0M0 or cT1-4aN1M0	58.9	cT3/4a :27.0% cN+: 21.6%	higher N stage**	25.0mo	22.6%	58.1%	3Yr OS: 73.1% 3Yr DFS: 63.2%	34.1% ***	12.2%	pCR, pPR,OS,DFS ddMVAC~GC
			GC	176			64.4	cT3/4a :37.6% cN+: 14.0%		41.0mo (Total 40.9mo)	27.0%	50.8%	3Yr OS: 72.1% 3Yr DFS: 54.9%	59.6%	0.6%	

Table S2. Abbreviations: pCR,pathologic Complete Remission;pPR,pathologic partial response;PaR,Pathologic Response;OS,Overall survival;DFS,Disease free survival ;NR,Not Reported;ACCI,Age-adjusted Charson Cormobidity Index *pCR was defined as ypT0N0, pPR(denote Downstaging, PaR) was defined as less than ypT2N0 and no N upstaging **Statistically insignificant *** Any > grade 3 hematologic adverse event

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