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Preoperative Chemotherapy with Dose-Dense Methotrexate, Vinblastine, Doxorubicin and Cisplatin for Muscle-Invasive Urothelial Carcinoma of the Bladder

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Abstract

Background: Neoadjuvant cisplatin-based chemotherapy for Muscle-Invasive Bladder Cancer (MIBC) is supported by level 1 evidence, however the optimal chemotherapy regimen remains to be determined.

Objective: We report a five-year retrospective experience with preoperative Dose-Dense Methotrexate, Vinblastine, Doxorubicin and Cisplatin (DD-MVAC) in patients with node-negative and node-positive MIBC, with a focus on the importance of the number of chemotherapy cycles.

Methods: Patients were treated between 2011 and 2015 with preoperative DD-MVAC for node-negative or node-positive MIBC. The primary efficacy endpoint was Pathological Complete Response (pCR) on cystectomy specimens. Secondary endpoints included overall survival, relapse-free-survival and safety.

Results: Sixty-nine patients were treated with DD-MVAC, among which 14 were initially node-positive. The median number of chemotherapy cycles was 5. Fifty-five patients underwent cystectomy, of which 52% achieved pCR. Patients who received more than 4 chemotherapy cycles achieved pCR more often although this was not statistically significant (59% versus 33%, p =0.069). There were non-significant trends toward better overall survival and relapse-free survival in patients who received more than 4 chemotherapy cycles. The cumulative incidence of grade 3-4 adverse events was 62%, mainly due to hematological toxicity. Febrile neutropenia occurred in 10% of patients. No toxic death occurred.

Conclusions: DD-MVAC is an effective preoperative chemotherapy regimen for MIBC, albeit responsible for frequent but manageable hematological toxicity. Pursuing chemotherapy up to 6 cycles may result in better pathological response and better survival, although this call for confirmation by larger trials.

Keywords: Bladder cancer; Neoadjuvant therapy; Cancer chemotherapy agents; Cystectomy

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Introduction

Neoadjuvant Chemotherapy (NAC) has been shown to improve survival in Muscle-Invasive Bladder Cancer (MIBC) [1,2]. However the reputed toxicity of the classic Methotrexate, Vinblastine, Doxorubicin and Cisplatin (MVAC) regimen, as well as concerns about the feasibility of radical cystectomy after chemotherapy, resulted in slow implementation of NAC in routine practice. Since classic MVAC has been supplanted in the metastatic setting by less toxic regimens, namely Gemcitabine-Cisplatin (GC) and dose-dense MVAC (DD-MVAC), efforts are being made to evaluate these regimens in the preoperative setting [3,4].

The overall benefit from NAC in MIBC is associated with the low relapse rates in patients who achieve Pathological Complete Response (pCR) after chemotherapy [5-7]. Thus the efficacy of

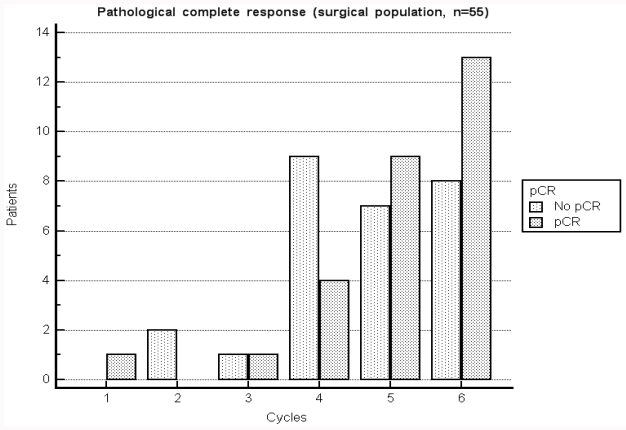

Figure 1: Pathological complete response according to the number of chemotherapy cycles in patients who underwent radical cystectomy (N =55).

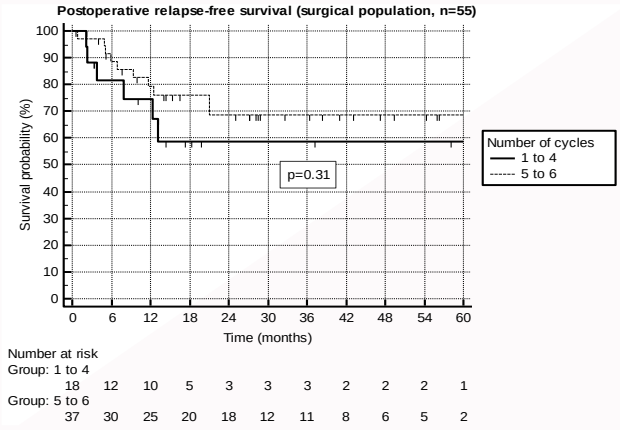

Figure 2: Outcome according to the number of chemotherapy cycles in surgical patients (N =55).
Figure 2A: Postoperative relapse-free survival.

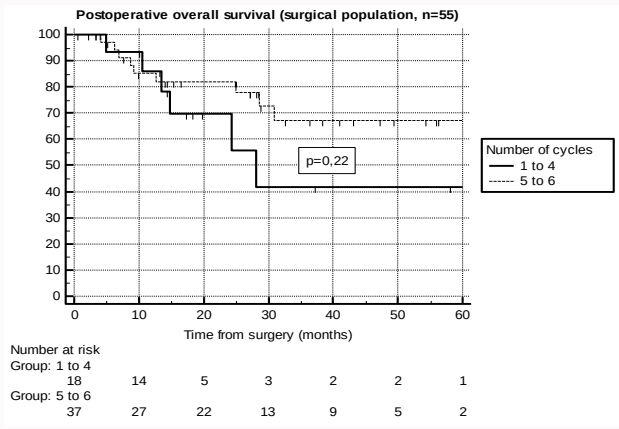

Figure 2B: Overall survival.

preoperative MVAC, DD-MVAC or GC has been evaluated through histological outcomes with no direct prospective comparison of survival to this day [8-14]. Dose-dense MVAC (3 to 4 cycles) is the most dose-intense regimen commonly used in the management of urothelial carcinoma, delivering twice the dose of cisplatin and doxorubicin as classic MVAC in an equivalent amount of time. Because this may result in higher pCR rates, DD-MVAC has been the preferred preoperative chemotherapy regimen for urothelial carcinoma patients at our institution since 2011. Here we present our 5-year experience with preoperative DD-MVAC in patients with MIBC with a special focus on the impact of the number of chemotherapy cycles on efficacy and toxicity.

Patients and Methods

Patients and data retrieval

We searched our database for patients treated at our institution with preoperative DD-MVAC starting on January 1st, 2011. Patients must have had undergone at least one cycle of chemotherapy and finished chemotherapy for long enough to allow for surgery as of October 30th, 2015. Patients with non-muscle-infiltrating disease (pT1) were excluded unless the tumor was located in a bladder diverticulum. Patients with node-positive (cTxN1-3M0) disease were included. Patients with inoperable metastatic disease were excluded, as well as patients with non-bladder-located urothelial carcinoma or non-urothelial bladder cancer. Patients enrolled in a prospective trial at the time of chemotherapy were excluded. All data was retrieved from medical reports at our institution or referring centers where curative surgery might have been performed. Follow-up was last updated on December19th, 2016.

Treatment plan

The same chemotherapy regimen of methotrexate (30 mg/m² on day 1), Vinblastine (3 mg/m² on day 2), doxorubicin (30 mg/m² on day 2) and cisplatin (70 mg/m² on day 2) repeated every 14 days was used for all patients in an inpatient setting. Granulocyte-Colony Stimulating Factor (G-CSF) support was typically administered 48 hours after chemotherapy in the outpatient setting. Dose reductions were at the discretion of the treating physician. The planned number of cycles before surgery was 6 regardless of lymph node status, although chemotherapy could be discontinued prematurely at the discretion of the treating physician in case of excessive toxicity or disease progression. CT-scan reassessment of disease extension was typically performed after 4 cycles. After chemotherapy patients were referred to their urologist for radical cystectomy and lymphadenectomy, unless metastatic progression occurred. Pelvic radiotherapy could be proposed to patients who declined radical surgery and presented an adequate response to chemotherapy as evaluated by Transurethral Resection (TUR). Postoperative follow-up was performed by either the oncologist at our institution or the treating urologist, or both.

Safety assessment

Clinical toxicities and significant laboratory values were prospectively documented at the beginning of each chemotherapy cycle. Toxicities were retrospectively graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) based on individual medical reports. Reasons for changes in the planned chemotherapy were documented.

Efficacy assessment

The primary efficacy endpoint was the rate of Pathological Complete Response (pCR), defined as the absence of residual disease on cystectomy specimens after preoperative chemotherapy (ypT0N0) in the subset of patients who underwent curative-intent surgery. Associations between pCR status and initial cTNM stage, the number of chemotherapy cycles received and the macroscopic completeness of initial TUR were evaluated in univariate analysis using Pearson's Chi-squared test. Pathological Down staging (pDS), defined as the

Table 1: Patient characteristics.

	All patients		According to surgery				According to chemotherapy			
			Cystectomy		No cystectomy		1-4 cycles		5-6 cycles	
Total	69	100%	55	100%	14	100%	23	100%	46	100%
Sex (N;%)										
Male	56	81%	44	80%	12	86%	17	74%	39	85%
Female	13	19%	11	20%	2	14%	6	26%	7	15%
Age (years)										
Median	65		64		66		66		64	
Range	38-84		38-84		52-84		46-84		38-84	
Smoking history (N;%)										
Never-smoker	11	16%	8	15%	3	21%	5	22%	6	13%
Once-smoker	30	43%	26	47%	4	29%	8	35%	22	48%
Active smoker	28	41%	21	38%	7	50%	10	43%	18	39%
Histology (N;%)										
Squamous differenciation	13	19%	11	20%	2	14%	6	26%	7	15%
Glandular differenciation	3	4%	3	5%	0	0%	0	0%	3	7%
Micropapillary	4	6%	4	7%	0	0%	2	9%	2	4%
Histoprognostic factors (N;%)										
Carcinoma *in situ*	14	20%	12	22%	2	14%	4	17%	10	22%
Lymhovascular invasion	14	20%	12	22%	2	14%	5	22%	9	20%
Clinical TN stage (N;%)										
cT1-2N0	45	65%	36	65%	9	64%	15	65%	30	65%
cT3N0	8	12%	6	11%	2	14%	3	13%	5	11%
cT4N0	2	3%	2	4%	0	0%	2	9%	0	0%
cTxN1	9	13%	7	13%	2	14%	2	9%	7	15%
cTxN2-3	5	7%	4	7%	1	7%	1	4%	4	9%
All node-positive	14	20%	11	20%	3	21%	3	13%	11	24%
Urinary tract distension	25	36%	19	35%	6	43%	7	30%	18	39%
Completeness of initial transurethral resection (N;%)										
Complete	22	32%	18	33%	4	29%	9	39%	12	26%
Incomplete	16	23%	14	25%	2	14%	6	26%	11	24%
Data missing	31	45%	23	42%	8	57%	8	35%	23	50%
Initial performance status (N;%)										
0	47	68%	35	64%	8	57%	14	61%	29	63%
1	26	38%	19	35%	5	36%	8	35%	16	35%
2	2	3%	1	2%	1	7%	1	4%	1	2%
Number of chemotherapy cycles (N;%)										
1	1	1%	1	2%	0	0%	1	25%	-	-
2	3	4%	2	4%	1	7%	3	75%	-	-
3	2	3%	2	4%	0	0%	2	11%	-	-
4	17	25%	13	24%	4	29%	17	89%	-	-
5	22	32%	16	29%	6	43%	-	-	22	48%
6	24	35%	21	38%	3	21%	-	-	24	52%
Curative-intent surgery (N;%)										
Yes	55	80%	55	100%	-	-	18	78%	37	80%
No	14	20%	-	-	14	100%	5	22%	9	20%
Delay to cystectomy (days)										
Median	28		28		-		32		25	
Range	8-439		8-439		-		31-439		8-131	

absence of muscle-infiltrating tumor on cystectomy specimens (ypT0-1N0), was analyzed in the same way as pCR. Overall Survival (OS) was defined for all patients as the time from the first cycle of chemotherapy to death from any cause. Post-operative OS and post-operative Relapse-Free Survival (RFS) were defined for patients who underwent cystectomy as the time from surgery to death from any cause and as the time from surgery to death from any cause or disease recurrence, respectively. The Kaplan-Meier method was used to describe survival results and the log-rank test was used to compare survival results between subgroups of patients characterized by number of chemotherapy cycles received (1-4 or 5-6) and pCR status in surgical patients. Patients were censored at the time of last follow-up in all survival analyses. Follow-up was last updated on December 19th, 2016.

Results

Patients

Seventy-seven patients were eligible for this study, among which 8 were excluded because they were enrolled in a prospective trial. Baseline characteristics of the 69 remaining patients are listed in Table 1. Median follow-up from the start of chemotherapy was 19.8 months (range: 2.8 to 69.3). Median postoperative follow-up for patients who underwent surgery was 19.7 months (range: 0.4 to 66.6).

Chemotherapy

A total 335 chemotherapy cycles were delivered to 69 patients. The median number of cycles per patient was 5 (range 1 to 6) with a median duration of chemotherapy of 74 days. Overall, 53 patients (77%) required dose reduction and/or premature discontinuation of chemotherapy. Chemotherapy was prematurely discontinued because of excessive toxicity in 40 patients (58%) and for other reasons (including patient's choice) in 4 patients. For one patient the reason for discontinuation of chemotherapy was not available.

Safety

Incidence of the most frequent adverse events is reported in Table 2. Overall, 62% of patients experienced grade 3-4 toxicity, most of it hematological toxicity. Seven patients (10%) developed febrile neutropenia or sepsis. No treatment-related death occurred. The most frequent reasons for premature discontinuation of chemotherapy were poor renal tolerance (13 patients), poor hematological tolerance (14), infection (8), digestive complications and/or stomatitis (8) and fatigue (7).

Surgery

Fifty-five patients (80%) were treated with radical cystectomy. Median time between the beginning of chemotherapy and surgery was 105 days (range 45 to 504). Median time between the end of the last chemotherapy cycle and surgery was 28 days (range 8 to 439). Three patients did not underwent cystectomy because of disease progression (objectivized by CT-scan after 4 cycles of chemotherapy in 2 patients and during surgery after 5 cycles in one patient with peritoneal carcinomatosis). One patient was diagnosed with aggressive lymphoma and another with amyotrophic lateral sclerosis shortly after discontinuation of chemotherapy; both did not undergo surgery. Two patients were lost to follow-up after chemotherapy, for which the reasons for not performing surgery are unknown. The most frequent reason for not performing cystectomy was patient's choice. Among seven patients who declined surgery, four underwent pelvic radiotherapy and three did not receive local treatment.

Table 2: Toxicity of preoperative dose-dense MVAC (N =69).

	All grades		Grade 3-4	
	(N;%)		(N;%)	
Hematological toxicity				
Neutropenia	31	45%	23	33%
Thrombopenia	55	14%	14	20%
Anemia	67	97%	20	29%
Infectious adverse events				
Febrile neutropenia	7	10%	7	10%
Mucous and digestive adverse events				
Stomatitis	35	51%	8	12%
Nausea and vomiting	58	84%	12	17%
Diarrhoea	21	30%	2	3%
Neurosensory adverse events				
Peripheral neuropathy	11	16%	0	0%
Loss of hearing	6	9%	0	0%

Efficacy

Among 55 patients who underwent cystectomy, 28 achieved pCR (51%) and 31 achieved pDS (56%). Pathological response rates according to initial cTNM status, completeness of initial TUR and number of chemotherapy cycles are shown in Table 3. Pathological response seemed to increase with the number of chemotherapy cycles (Figure 1). pCR rates in patients who received 3 to 4 cycles and patients who received 5 to 6 cycles were 33% and 59%, respectively (p =0.088 in univariate analysis using Pearson' Chi-squared test). Postoperative RFS and OS showed non-significant trends toward better survival in patients who underwent 5-6 chemotherapy cycles (Figure 2).

Discussion

The standard NAC regimen for MIBC is 3 cycles of classic MVAC, which yields a 5% absolute survival benefit at 5 years [1]. Extrapolating from the metastatic setting, where DD-MVAC with G-CSF support has been proven as effective as and better tolerated than classic MVAC, DD-MVAC is being imported in the preoperative setting [4]. In previous retrospective or prospective studies, DD-MVAC yielded pCR rates of 28% to 43% (Table 4) [9,11-15]. Our findings confirm that DD-MVAC is an effective preoperative chemotherapy regimen for MIBC, associated in our study with a 51% pCR rate in 55 operated patients. pCR status was associated with significantly improved survival (data not shown), in agreement with the admitted place of pCR as a surrogate marker for survival in MIBC patients [7]. Of note, no patient was denied surgery because of chemotherapy-related adverse events.

An advocated advantage of DD-MVAC over classic MVAC is the short two-week interval between cycles, allowing for faster administration, thus minimizing delay to surgery. In a retrospective analysis of 241 consecutive bladder cancer patients who received classic (52 patients) or DD-MVAC (189 patients), similar pathological response and survival rates were observed with greaterhematological toxicity in the classic MVAC group [14], therefore suggesting that chemosensitivity of bladder tumor cells does not seem to be related to the dose intensity of cytotoxic drugs. Beyond dose intensity, the total doses of cytotoxic drugs could impact the antitumor effect. Indeed we observed that pursuing DD-MVAC beyond 4 cycles, thus delivering up to twice the dose of cisplatin and doxorubicin in the same amount

Table 3: Pathological response with preoperative DD- MVAC (N=55).

	Patients (N)	pCR (N)	pCR (%)	pDS (N)	pDS (%)
All surgical patients	55	28	51%	31	56%
Initial TNM staging					
cT1-2N0	36	18	50%	20	56%
cT3N0	6	4	67%	4	67%
cT4N0	2	0	0%	1	50%
cTxN1	7	4	57%	4	57%
cTxN2-3	4	2	50%	2	50%
All node-positive	11	6	54%	6	54%
Completeness of initial transurethral bladder resection (N;%)					
Complete	18	13	72%	14	78%
Incomplete	14	5	36%	6	43%
Data missing	23	10	43%	11	48%
Number of chemotherapy cycles received					
01-Apr	18	6	33%	8	44%
05-Jun	37	22	59%	23	62%

pCR: Pathological Complete Response; pDS: Pathological Down Staging

Table 4: Reports from the literature of preoperative dose-dense MVAC for muscle-invasive bladder cancer.

Author	Study type	Year	Number of patients	cN+ (%)	Number of cycles	Cystectomy (% patients)	Adverse events (% Grade 3-4)	% FN	pCR rate
Blick [11]	Retrospective	2012	80	15%	3 or 4	75%	26%*	0%	43%
Choueiri [12]	Prospective	2014	36	43%	4	97%	10%	0%	28%
Plimack [13]	Prospective	2014	44	7%	3	98%	12%	2%	38%
McConkey [15] **	Retrospective	2015	44	0%	4	98%	-	-	39%
Van de Putte [9]	Retrospective	2015	80	76%***	4	96%	32%	8%	29%
Pouessel [14]	Retrospective	2016	189	21%	04-Jun	88%	-	7%	35%
Present study	Retrospective	2016	69	20%	6	80%	62%	10%	51%

*Only 42% of data available.
**Study of DD-MVAC + bevacizumab in cN0 patients with higher-risk features.
***T2N0 included only if lymphovascular invasion.
cN+: Clinically Node-Positive Patients At Baseline; FN: Febrile Neutropenia; pCR: Pathological Complete Response

of time as compared to classic MVAC, resulted in a higher proportion of patients achieving pCR, with better RFS and OS, although this did not reach statistical significance, possibly because of the small number included in this study. This observation was not explained by baseline characteristics of patients since they were generally well balanced between the two subgroups (≤ 4 versus >4 cycles). However patients who received ≤ 4 cycles had slightly more frequent squamous differentiation as well as complete initial TUR but lower clinically positives nodes.

Eleven of 14 (79%) node-positive patients underwent cystectomy after chemotherapy (4 cycles: 2 patients, 5: 5 patients, 6: 4 patients). Interestingly pCR rates were similar in the operated patients with initially node-positive (54%) and node negative disease (50%). Although caution should be warranted because of the small number of node-positive patients, this may support an aggressive management of node-positive tumors with preoperative chemotherapy and surgery.

We report a higher frequency of grade 3-4 toxicity (62%) than in previous reports of preoperative DD-MVAC, mainly due to hematological toxicity. When only considering adverse events occurring before initiation of the fifth cycle this figure remained high (51%), so we believe that pursuing chemotherapy after 4 cycles in the majority of our patients is not the cause of this unexpectedly high toxicity rate. Red blood cell transfusion was necessary in 51% of the patients, platelet transfusion in 16%. Febrile neutropenia occurred in 10% of patients, a figure consistent with the findings of the retrospective study by van de Putte et al (8%) but higher than in the prospective studies by Plimack et al and Choueiri et al which possibly included more selected patients. Results from the retrospective study by Blick et al are to be taken with caution since safety data was available for less than half the patients. The incidence of grade 3-4 adverse events was 60% in cT1-2N0 patients and 67% in non-cT1-2N0 patients. Febrile neutropenia rates were 9% and 10%, respectively. The proportion of patients who received >4 chemotherapy cycles was 67% in both subgroups. Thus, it does not seem that patients with worse prognosis according to cTNM status were more likely to cease chemotherapy prematurely because of excessive toxicity.

Our results are to be mitigated by the incomplete data regarding the completeness of initial TUR, which may confuse the interpretation of pathological response to chemotherapy [7]: patients with initial complete TUR did achieve pCR twice more often than patients in whom it was deemed incomplete (72% vs 36%, p =0.039). Other limitations include the short median follow-up and the retrospective design.

Conclusion

Our findings confirm the efficacy of preoperative DD-MVAC for MIBC and hint at a greater benefit of pursuing chemotherapy beyond 4 cycles. Although no definitive conclusions can be drawn, we believe attention should be paid to this particular factor in future reports of preoperative chemotherapy for MIBC. A multicenter, phase III study is ongoing in France in patients with cT2-cT4 N0 disease and normal renal function, comparing 6 cycles of DD-MVAC and 4 cycles of GC with progression-free survival as primary endpoint.

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