

Chemotherapy for muscle-invasive bladder cancer: impact of cisplatin delivery on renal function and local control rate in the randomized phase III VESPER (GETUG-AFU V05) trial

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Abstract

A deep analysis of data from a randomized trial of perioperative chemotherapy in muscle-invasive bladder cancer shows that a minimum number of 4 cycles is required to optimize the chances of pathological complete response at cystectomy. Increasing the number beyond 4 cycles does not lead to a clinically significant deterioration in renal function without obvious gain on pathological complete response.

Background: Cisplatin-based combination chemotherapy before surgery is the standard of care for muscle-invasive bladder cancer. However, the optimal chemotherapy modalities have not been precisely defined to date.

Patients and Methods: In the VESPER trial, patients received after randomization either gemcitabine and cisplatin (GC, 4 cycles) or methotrexate, vinblastine, doxorubicin and cisplatin (dose dense [dd]-MVAC, 6 cycles). Creatinine clearance (CrCl) was calculated before each cycle according to the Cockcroft and Gault formula. Definition criteria for local control after neoadjuvant chemotherapy included pathological complete response (ypT0N0), pathological downstaging (<ypT2N0) and organ-confined disease (<ypT3N0) at cystectomy. Baseline and treatment characteristics were studied in multivariate logistic models to determine their potential role for each type of pathological responses.

Results: A total of 2,128 cycles of chemotherapy were delivered, including 2,120 (99.6%) with cisplatin. Full doses of cisplatin were given in 1866 (88%) cycles. Twenty-three (4.7%) patients had to stop chemotherapy (12 GC, 11 dd-MVAC) because of renal failure. No difference in CrCl median values was observed between the two regimens during the first four cycles. A mild decrease occurred thereafter in patients treated with two additional cycles of dd-MVAC. A minimum total dose of 270 mg/m² for cisplatin was mandatory to optimize pathological complete responses.

Conclusion: At least 4 cycles of cisplatin-based chemotherapy should be delivered before cystectomy. Increasing the number of cycles beyond 4 cycles does not lead to a clinically significant deterioration in renal function but without obvious gain on local control.

Key words: Muscle-invasive bladder cancer, cisplatin-based chemotherapy, neoadjuvant treatment, pathological complete response

Introduction

Primary surgical management of muscle-invasive bladder cancer (MIBC) with radical cystectomy and extended pelvic lymph node dissection can usually cure 50% of patients. Neoadjuvant cisplatin-based combination chemotherapy (NAC) before surgery has demonstrated a survival benefit based on level 1 evidence, with regimens including cisplatin, methotrexate, vinblastine with (MVAC) or without (CMV) doxorubicin.¹⁻³ However due to significant toxicities, alternative combinations such as dose dense MVAC (dd-MVAC) and gemcitabine-cisplatin (GC) have been proposed over the last two decades. Although different retrospective studies suggested better outcomes with dd-MVAC,^{4,5} no prospective randomized trial comparing the respective impact on survival of dd-MVAC and GC had been reported so far. In the phase III VESPER trial recently conducted by The French Genitourinary Tumor Group (GETUG), patients received either regimen after randomization. More severe asthenia, gastrointestinal side effects and anemia along with a higher control rate were observed in the dd-MVAC arm.⁶ In the present report, the authors focused on renal function during chemotherapy and investigated the role of cisplatin delivery (total dose, dose intensity) on local control rate.

Patients and Methods

Patients and chemotherapy protocol

As previously described, 500 MIBC patients were included in the VESPER trial from February 2013 to March 2018 in 28 French participating centres after informed signed consent (Clinical trial registry: clinicaltrials.gov - NCT 018 12369).⁶ Key inclusion criteria were histologically confirmed muscle-invasive urothelial carcinoma and disease defined by a cT2, cT3 or cT4a N0 (lymph node \leq 10 mm on CT scan) M0 staging for patients receiving NAC or pT3 or pT4 or pN+ regardless of pT stage and M0 for patients receiving adjuvant chemotherapy.

Patients received after randomization either gemcitabine 1250 mg/m² on day 1 and day 8 and cisplatin 70 mg/m² on day 1 every 3 weeks for a total of 4 cycles (GC regimen) or 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 with G-CSF from day 3 to day 9, every 2 weeks for a total of 6 cycles (dd-MVAC regimen). In both arms, creatinine clearance (CrCl) was calculated before each cycle according to the Cockcroft and Gault (CG) formula: $CrCl = (140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female}) / (72 \times \text{serum creatinine})$. A CrCl of 50 mL/min or more was required to enter the trial and start chemotherapy with full standard doses. The following adaptations were done in subsequent cycles for cisplatin according to CrCl: \geq 60 mL/min, 70 mg/m²; between 50 and 59 mL/min, 50 mg/m²; between 40 and 49 mL/min: 40 mg/m²; $<$ 40 mL/min: end of treatment. Regarding neutropenic fever or other grade \geq 3 toxicities, a 15% dose reduction was done for all drugs in both arms. In the absence of toxicity recovery within 14 days, or in case of grade 4 toxicity despite a dose reduction of 15%, chemotherapy was stopped.

Renal impairment during chemotherapy was defined by the threshold of a CrCl requiring cisplatin dose reduction, i.e. $<$ 60 mL/min. The following criteria were used for efficacy on

bladder cancer: pathological complete response (pCR or ypT0N0 stage), pathological downstaging (<ypT2N0 stage) and organ-confined disease (<ypT3N0 stage) at cystectomy.

Statistical methods

The diagram shown in Figure 1 issues the sample sizes for the analyses of the two endpoints discussed in the present study, i.e. renal impairment-free survival and pathological responses. As regards descriptive results, qualitative data were reported as frequency and percentage, quantitative data as either means and standard deviation or as median and 95% range depending on the normal distribution assessment of the variable. Renal impairment-free survival was computed throughout chemotherapy with an event defined as a CrCl < 60 mL/min and a time of origin at D1 of the first cycle of chemotherapy. Patients with a clearance of creatinine < 60 mL/min at the baseline were excluded from this analysis. First, survival was computed by subgroups with Kaplan-Meier method. Curves are presented with 95% confidence interval adjusted with a Locally Weighted Regression and Smoothing Scatterplots (LOWESS) method. Then, covariates joint effects were analyzed in a Cox proportional hazard model with covariates backward selection on Akaike information criterion. Probabilities of complete response, pathological downstaging and organ-confined disease after NAC were analyzed on multivariate logistic models with covariates stepwise selection on Akaike information criterion. Considering the strong correlation between chemotherapy arm and the planned dose of cisplatin, an interaction term was introduced into these models, which made it possible to describe the effect of the dose of cisplatin in each arm. All statistical analysis were performed with R statistical software v3.6.2 (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients' characteristics

Baseline characteristics of the 493 patients retained in the intent-to-treat analysis are reported in Table 1. Median age was 63 years (range, 33-80). According to body mass index (BMI), 40% and 19% of patients were classified as overweight or obese, respectively. Most patients were smokers or former smokers, 38% of patients had hypertension and 6.9% a history of coronary heart disease. Median CrCl was 87 mL/min (range, 51-152). Ten percent of patients had a calculated CrCl below 60 mL/min. Most patients received chemotherapy in the neoadjuvant setting (89% of cases). Characteristics were generally well balanced between the two arms, although the percentage of patients with diabetes was higher in the GC arm ($p=0.026$).

Cisplatin delivery

A total of 2,128 cycles of chemotherapy were delivered during the study, including 2,120 (99.6%) with cisplatin (Table 2). Thirty-one patients did not received cytotoxic doses according to their real body surface area (BSA) value since local investigators capped BSA at 2 m² in 25 patients, 2.1 m² in 1 patient and 2.2 m² in 5 patients. Full doses of cisplatin were given in 1866 (88%) cycles and 23 (4.7%) patients had to stop chemotherapy (12 GC and 11 dd-MVAC) because of renal failure. Five of them (22%) had a CrCl less than 60 mL/min at the onset of chemotherapy. In the GC arm, the median number of cycles was 4 regardless of the setting (neoadjuvant or adjuvant). However, the median total dose of cisplatin was significantly lower in patients who received adjuvant chemotherapy ($p=0.002$). In the dd-MVAC arm, the median numbers of cycles were 6 and 5 in the neoadjuvant and adjuvant setting, respectively, without any significant difference regarding the median total dose and dose intensity of cisplatin.

Changes in creatinine clearance during treatment

Figure 1 underlines serial changes in CrCl during chemotherapy in the whole population and according to treatment arms and baseline CrCl values. No difference in CrCl median values was observed between the two regimens during the first four cycles. A mild decrease occurred thereafter in patients treated with two additional cycles of dd-MVAC. Renal impairment-free survival curves are shown in Figure 2. Among baseline characteristics, age ≥ 60 , BMI < 20 and CrCl between 60 and 90 retained significant prognostic value for the occurrence of renal impairment during chemotherapy (Table 3).

Impact of cisplatin delivery on pathological responses

Among 437 patients who received NAC, 397 of them (91%) underwent cystectomy. Pathological complete response, pathological downstaging and organ-confined disease status were observed in 155 (39%), 224 (56%) and 278 (70%) patients, respectively. Baseline and treatment delivery characteristics were studied in multivariate logistic models to determine their potential role for each type of pathological responses (Table 4). Obese patients had a higher rate of complete pathological response. As previously reported, treatment arm had a significant, independent prognostic value with better efficacy of dd-MVAC regarding pathological downstaging and organ-confined disease status. No evidence for an additional effect of dose intensity on disease control was observed. In the GC arm, patients who received 4 cycles clearly achieved better outcomes as compared to patients who received 3 cycles or less for all types of pathological responses. In the dd-MVAC arm, increasing the number of cycles beyond four did not appear to provide statistically higher local control rates.

Discussion

Cisplatin has emerged as a major cytotoxic agent in urothelial tract tumors in the late 70s.⁷ As single agent, cisplatin was initially reported to produce response rates as high as 40%, but prospective randomized trials failed to confirm these results and complete responses were rarely observed. Although essentially palliative for patients with metastatic disease, the benefit of chemotherapy on response rates and overall survival was subsequently reported through the development of cisplatin-based combination regimens such as MVAC or CMV.^{8,9} Then their use in the perioperative setting led to establish NAC and radical cystectomy as current standard of care for MIBC.¹⁻³

Given the potential for renal toxicity with cisplatin-based chemotherapy, adequate renal function is a prerequisite, with a common eligibility threshold of measured or calculated CrCl of ≥ 60 mL/min in clinical trials or medical oncologist community surveys.¹⁰ However, no formal consensus has been established and robust data did not exist to support a specific renal function threshold and an optimal methodology to assess eligibility for as well as dose adaptations of cisplatin throughout therapy in MIBC. Regarding cisplatin eligibility, many contradictory results have been reported according to methods used for CrCl evaluation. In a retrospective study including 116 patients, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was more likely to deem a patient eligible for cisplatin compared with the CG formula, especially beyond 70 years of age.¹¹ Another study found no difference between CDK-EPI equation, CG formula and the Modified Diet in Renal Disease (MDRD) equation, except for the subset of patients age > 80 in whom the CDK-EPI equation identified a much smaller proportion of cisplatin-eligible patients.¹² Finally, in a third, retrospective study including 208 patients who received MVAC for advanced bladder cancer, concordance between calculated and measured CrCl was low, especially in those older than

65 years. The ability to complete at least 3 cycles of MVAC was related to a measured CrCl more than 60 mL/min, but not to a calculated CrCl more than 60 mL/min.¹³

In the VESPER trial, the CG formula was used both for cisplatin eligibility (with 50 mL/min as threshold) and cisplatin dose adjustments throughout chemotherapy cycles. The present report confirms the relevance of this approach. Indeed, full doses of cisplatin were given in the majority of scheduled cycles (88%) and only 23 patients (4.7%) had to stop treatment because of renal failure. Moreover, 50 patients (10%) were included with a measured CrCl below 60 mL/min and only 10% of them had to stop chemotherapy because of renal failure. A trend towards poorer cisplatin delivery was observed in the adjuvant setting, with a lower median total dose of cisplatin in the GC arm and a reduced median number of cycles in the dd-MVAC arm. However, the number of patients who were treated in the adjuvant setting remains too small to draw firm conclusions. As the optimal number of cycles in the perioperative setting is still unknown, it is important to emphasize that increasing the number of cycles to six in the dd-MVAC arm did not lead to a clinically significant deterioration in renal function. Without major surprise, older age (≥ 70 years), low BMI (< 20 kg/m²) and baseline CrCl < 90 mL/min were identified as independent prognostic variable for occurrence of renal impairment and therefore cisplatin dose modifications during chemotherapy.

In patients who are treated with NAC, achieving pCR in the bladder and lymph nodes at surgery has been shown to be a strong surrogate for survival outcomes.^{1,14-16} It has been also suggested that pathologic downstaging was associated with improved survival.^{17,18} In the VESPER trial, we observed no significant difference in the complete pathologic response rate between the two arms but higher pathologic downstaging and higher organ-confined disease rates in the dd-MVAC arm.⁶ Our prospective randomized data offered the possibility to refine the potential relationship between patients' baseline characteristics, cisplatin delivery and

pathologic responses. BMI \geq 25 kg/m² and a minimum number of cycles of 4 cycles of chemotherapy were identified as independent prognostic variables regarding pCR at surgery. The influence of BMI for patients treated with NAC for MIBC was recently studied in a retrospective, single institution experience.¹⁹ Toxicity and efficacy of NAC were compared between obese patients receiving chemotherapy based on capping at a body-surface area of 2.2 m² and healthy weight patients. Obese patients were individually paired with normal BMI patients sharing similar clinical and biological characteristics. The pCR rate was similar in both groups. In the VESPER trial, 31 (6.3%) patients did not receive optimal cytotoxic doses since BSA was capped by local investigators. Therefore, a lower pCR rate related to a potential drug underdosing could have been expected in obese patients. The opposite observation might be related to sarcopenic obesity. However, sarcopenia has previously been linked to renal impairment and prognosis after NAC,^{20,21} but not to pathological response.^{20,22} Moreover, we did not observe a higher myelosuppression suggesting greater exposure due to weight-based dose calculation in obese patients.

The optimal number of NAC cycles remains undefined. A survival benefit for 3 cycles of MVAC or CMV is supported by level 1 evidence.¹⁻³ Alternative combinations with 3 to 4 cycles of dd-MVAC were reported in 2 phase II trials.²³⁻²⁴ The pCR rates (26% and 38% after 4 and 3 cycles, respectively) were roughly similar to that observed in the VESPER trial (42%). Our data strongly argue for a lesser chance of obtaining a pCR when less than 4 cycles of GC or dd-MVAC are delivered. However, increasing the number of cycles beyond four did not appear to provide statistically higher local control rates.

In conclusion, prospective data from the VESPER trial provide answers as to the optimal number of cisplatin-based chemotherapy cycles in the neoadjuvant setting for patients with MIBC. A minimum number of 4 cycles is required to optimize the chances of getting a pCR at

cystectomy after NAC. Increasing the number to 6 cycles does not lead to a clinically significant deterioration in renal function but the benefit on patients' survival remains to be proven.

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Disclosure

Authors have declared no conflicts of interest.

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Table 1 – Baseline patients' characteristics

Variable	GC (N=245)	dd-MVAC (N=248)	Total (N=493)
Age, years, No (%)			
<60	75 (31)	82 (33)	157 (32)
60-69	119 (49)	124 (50)	243 (49)
≥70	51 (21)	42 (17)	93 (19)
<i>Mean (standard deviation)</i>	63 (7.6)	62.6 (7.9)	62.8 (7.7)
Sex, No (%)			
Male	206 (84)	202 (81)	408 (83)
Female	39 (16)	46 (19)	85 (17)
Body mass index, kg/m², No (%)			
<18.5	3 (1.2)	9 (3.6)	12 (2.4)
18.5-<25	95 (39)	95 (38)	190 (39)
25-<30	100 (41)	99 (40)	199 (40)
≥30	47 (19)	45 (18)	92 (19)
<i>Mean (standard deviation)</i>	26.6 (4.7)	26.0 (4.4)	26.3 (4.5)
Body surface area (m²)			
<i>Mean (standard deviation)</i>	1.9 (0.2)	1.9 (0.2)	1.9 (0.2)
Medical history, No (%)			
Tobacco	198 (84)	197 (81)	395 (80)
Hypertension	100 (41)	89 (36)	189 (38)
Coronary artery disease	13 (5.3)	19 (7.7)	32 (6.5)
Diabetes	14 (5.7)	4 (2)	18 (4)
Performance status, No (%)			
0	171 (70)	165 (67)	336 (68)
1	72 (29)	82 (33)	154 (31)
Unknown	2 (0.8)	1 (0.4)	3 (0.6)
Hemoglobin (g/dL)			
<i>Median (95% range)</i>	14.1 (10.7-16.5)	14.0 (11.0-16.5)	14.0 (10.8-16.5)
Alkaline phosphatases (UI/L)			
<i>Median (95% range)</i>	73 (46-138)	73 (42-148)	73 (45-146)
Total bilirubin (mg/L)			
<i>Median (95% range)</i>	4.4 (1.8-11.0)	4.7 (2.0-11.0)	4.7 (1.8-11)
Serum creatinine (mg/L)			
<i>Median (95% range)</i>	9 (6-14)	9 (5-14)	9 (5-14)
Creatinine clearance, mL/min, No (%)			
50-59	27 (11)	23 (9.3)	50 (10)
60-89	113 (46)	107 (43)	220 (45)
≥90	105 (43)	118 (48)	223 (45)
<i>Median (95% range)</i>	86 (52-157)	88.5 (51-147)	87 (51-152)

Table 2 – Cisplatin delivery

	Neoadjuvant chemotherapy		Adjuvant chemotherapy	
	GC (N=219)	dd-MVAC (N=218)	GC (N=26)	dd-MVAC N=(30)
Number of cycles <i>Median (range)</i>	4 (1-4)	6 (0-6)	4 (1-4)	5 (1-6)
Total	803	1093	92	140
Total with cisplatin	803	1087	91	139
Total with full doses of cisplatin (%)	745 (93)	926 (85)	73 (80)	122 (88)
Total dose (mg) <i>Median (95% range)</i>	522 (134-608)	700 (132-895)	454 (125-579)	675 (131-843)
Dose intensity (mg/m²/week) <i>Median (95% range)</i>	22.9 (16.9-24.1)	31.8 (20.5-35.7)	21.9 (14.6-23.8)	33.8 (21.5-35.2)
Relative dose intensity	98%	91%	94%	97%

Table 3 – Cox proportional hazard model for renal impairment during chemotherapy

Baseline characteristics	Hazard ratio (95% CI)	p value
Age (years)		
< 60	-	
60-69	2.37 (1.21-4.64)	0.012
≥ 70	4.85 (2.27-10.4)	< 0.001
Body mass index (kg/m²)		
< 20	3.20 (1.43-7.15)	0.005
20-<25	-	
25-<30	0.82 (0.48-1.41)	0.5
≥ 30	0.70 (0.35-1.42)	0.3
Coronary artery disease		
No	-	
Yes	1.82 (0.86-3.86)	0.12
Creatinine clearance (mL/min)		
≥ 90	-	
60-89	2.93 (1.69-5.10)	< 0.001
Chemotherapy arm		
GC	-	
dd-MVAC	1.20 (0.75-1.93)	0.5

Covariates tobacco, timing of chemotherapy (adjuvant or neoadjuvant), sex, lymph nodes involvement, diabetes, high blood pressure and OMS status were excluded in this order from the final model with the backward selection. Chemotherapy arm was forced in the selection.

Table 4 – Logistic model for pathological responses at cystectomy

	N	Complete pathological response		Pathological downstaging		Organ-confined disease	
		<i>Odd ratio (95% CI) p value</i>		<i>Odd ratio (95% CI) p value</i>		<i>Odd ratio (95% CI) p value</i>	
<u>Body mass index (kg/m²)</u>							
< 20	23	0.83 (0.30-2.29)	0.7	0.41 (0.16-1.10)	0.078		
20-<25	126	-		-			
25-<30	164	1.90 (1.16-3.12)	0.011	1.67 (1.03-2.73)	0.038		
≥ 30	84	1.83 (1.02-3.29)	0.043	1.29 (0.72-2.30)	0.4		
<u>Creatinine clearance at baseline (mL/min)</u>							
≥90	187					-	
60-89	174					0.64 (0.39-1.04)	0.069
50-59	36					0.28 (0.13-0.60)	0.001
<u>High blood pressure</u>							
No	237					-	
Yes	160					0.65 (0.40-1.03)	0.065
<u>Coronary artery disease</u>							
No	369			-			
Yes	28			2.05 (0.83-5.02)	0.12		
<u>Chemotherapy arm</u>							
GC	198	-		-		-	
dd-MVAC	199	1.40 (0.77-2.56)	0.3	2.06 (1.08-3.93)	0.029	2.46 (1.10-5.52)	0.028
<u>Cisplatin dose-intensity (mg/m²/week)</u>							
≥ 30	218	-		-		-	
25-30	46	1.04 (0.50-2.18)	0.9	0.71 (0.33-1.51)	0.4	0.75 (0.31-1.79)	0.5
< 25	132	1.06 (0.37-3.02)	0.9	0.84 (0.30-2.39)	0.7	0.75 (0.22-2.60)	0.7
<u>Total dose of cisplatin (mg/m²)</u>							
<u>GC arm</u>							
≥ 270 (4 cycles)	134	-		-		-	
< 270	64	0.46 (0.23-0.89)	0.022	0.49 (0.26-0.91)	0.024	0.47 (0.25-0.88)	0.019
<u>dd-MVAC arm</u>							
≥ 410 (6 cycles)	65	-		-		-	
340 to 410 (5 cycles)	62	0.56 (0.27-1.15)	0.12	0.61 (0.28-1.29)	0.19	0.89 (0.33-2.37)	0.8
270-340 (4 cycles)	38	0.85 (0.38-1.93)	0.7	0.67 (0.28-1.59)	0.4	0.44 (0.16-1.20)	0.11
< 270 (< 4 cycles)	34	0.67 (0.28-1.58)	0.4	0.55 (0.23-1.32)	0.18	0.39 (0.14-1.10)	0.074

Covariates age, sex, OMS status, cT tumor stage, tobacco, diabetes were excluded from each final model with the stepwise selection. Chemotherapy arm and its interaction with total dose of cisplatin were forced in the selections.

Figure 1 – Flow diagram from enrollment to end of primary treatment

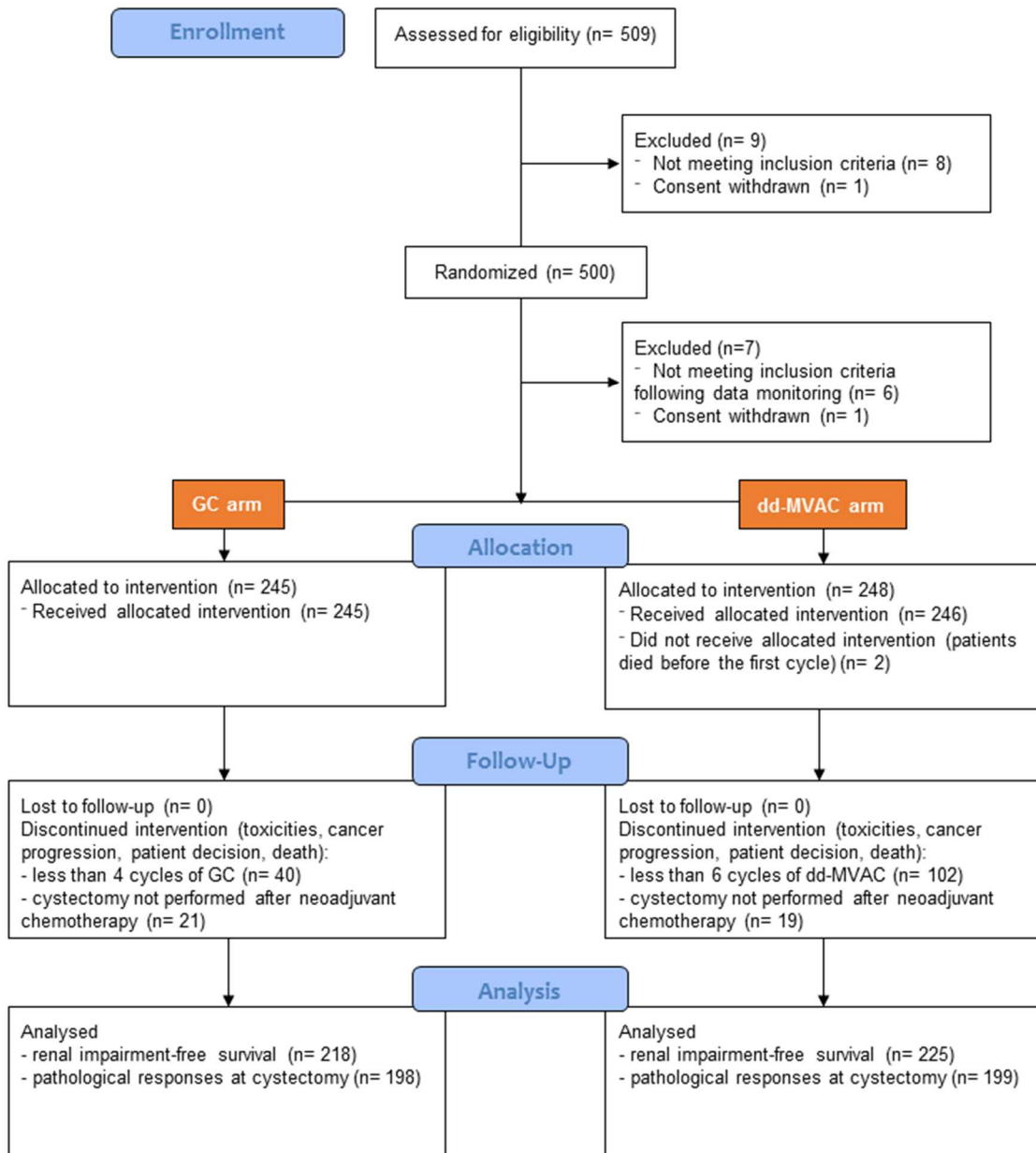


Figure 2 – Evolution of median creatinine clearance from baseline to the end of chemotherapy

Whole patient sample (A), According to treatment arms (B) According to baseline creatinine clearance (C).

For A and B, the q1-q3 interval is presented with a colored area. For each curve, the number of patients assessed at the baseline is indicated, then for each cycle the percentage of these patients whose creatinine clearance was evaluated.

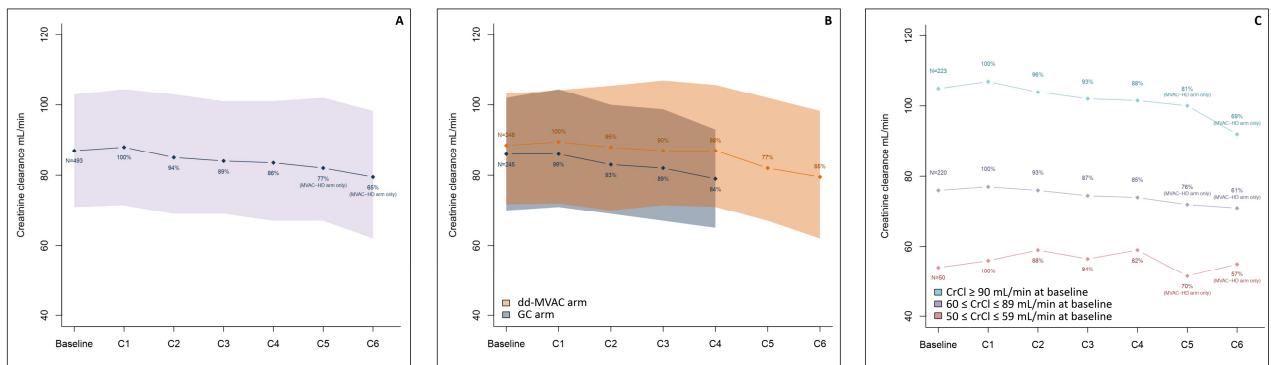


Figure 3 – Renal impairment-free survival curves

Kaplan-Meier curves with 95% confidence area according to treatment arms (A, N=493) and according to baseline creatinine clearance (B, N=443, patients with creatinine clearance < 60 mL/min at baseline are not presented).

