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Randomized Phase III Trial of Dose-dense Methotrexate, Vinblastine, Doxorubicin, and Cisplatin, or Gemcitabine and Cisplatin as Perioperative Chemotherapy for Patients with Muscle-invasive Bladder Cancer. Analysis of the GETUG/AFU V05 VESPER Trial Secondary Endpoints: Chemotherapy Toxicity and Pathological Responses

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Abstract

Background: Perioperative chemotherapy (neoadjuvant or adjuvant) has been developed to increase overall survival for nonmetastatic muscle-invasive bladder cancer (MIBC). Retrospective studies or prospective phase II trials have been reported to use dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (dd-MVAC) or gemcitabine and cisplatin (GC). As dd-MVAC has shown higher response rates in metastatic disease, better efficacy is expected in the perioperative setting.

Objective: We designed a randomized phase III trial to compare the efficacy of dd-MVAC or GC in MIBC perioperative (neoadjuvant or adjuvant) setting.

Design, setting and participants: A total of 500 patients were randomized from February 2013 to March 2018 in 28 centers and received either six cycles of dd-MVAC every 2 wk or four cycles of GC every 3 wk.

Outcome measurements and statistical analysis: The primary endpoint (progression-free survival at 3 yr) was not reported. We focused on secondary endpoints: chemotherapy toxicity and pathological responses.

Results and limitations: In the neoadjuvant group, 218 patients received dd-MVAC and 219 received GC. Of the patients, 60% received six cycles in the dd-MVAC arm and 84% received four cycles in the GC arm; 199 (91%) and 198 (90%) patients underwent surgery, respectively. Complete pathological response (ypT0pN0) was observed in 84 (42%) and 71 (36%) patients, respectively ($p = 0.2$). An organ-confined status ($<ypT3pN0$) was obtained in 154 (77%) and 124 (63%) patients, respectively ($p = 0.001$). In the adjuvant group, 40% of patients received six cycles in the dd-MVAC arm and 60% received four cycles in the GC arm. Most of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 toxicities concerned hematological toxicities, reported for 129 (52%) patients in the dd-MVAC group and 134 (55%) patients in the GC group. Gastrointestinal (GI) grade ≥ 3 disorders were more frequently observed in the dd-MVAC arm ($p = 0.003$), as well as asthenia of grade ≥ 3 ($p < 0.001$).

Conclusions: The toxicity of dd-MVAC was manageable with more severe asthenia and GI side effects than that of GC in perioperative chemotherapy. A higher local control rate (complete pathological response, tumor downstaging, or organ confined) was observed in the

dd-MVAC arm ($p = 0.021$). However, such data have to be confirmed on progression-free survival, with primary endpoint data expected in mid-2021.

Patient summary: The authors have designed a randomized phase III controlled study comparing the efficacy of gemcitabine and cisplatin, and dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (dd-MVAC) in patients for whom chemotherapy has been decided, before or after radical cystectomy. Higher toxicity regarding asthenia and gastrointestinal side effects along with a better bladder control rate were observed in the dd-MVAC arm. However, such data have to be confirmed on progression-free survival, with primary endpoint data expected in mid-2021.

1. Introduction

Radical cystectomy (RC) is the local treatment for nonmetastatic muscle-invasive bladder cancer (MIBC); nevertheless, many patients die of distant metastases within 2 yr after cystectomy, suggesting the presence of micrometastases at the time of surgery [1,2]. Perioperative chemotherapy (neoadjuvant or adjuvant) has been developed to increase overall survival (OS), with an absolute benefit of 5% reported for neoadjuvant chemotherapy (NAC). International guidelines recommend available NAC [3,4], but the optimal chemotherapy regimen to be delivered remains open to discussion. Therefore, level I of evidence was validated for schedules as standard methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) or CMV, which are no longer currently used. In the past decade, retrospective studies or prospective phase II trials using dose-dense (dd) MVAC or gemcitabine and cisplatin (GC) have been reported, but without any randomization design. As dd-MVAC has been shown to be associated with higher response rates in metastatic disease [5], better efficacy can also be expected in the perioperative setting.

We designed a randomized phase III controlled study comparing the efficacy of GC and dd-MVAC in terms of progression-free survival (PFS) in patients for whom chemotherapy has been decided, before or after radical cystectomy. We report the results of the French GETUG/AFU V05 VESPER trial on chemotherapy toxicity and pathological responses.

2. Patients and methods

2.1. Study design

Our randomized phase III trial assesses the efficacy of dd-MVAC or GC perioperative chemotherapy in patients with bladder cancer disease defined by cT2, cT3, or cT4a N0 (pelvic

lymph nodes ≤ 10 mm on CT scan) M0 staging for patients receiving NAC or pT3 or pT4 or pN+ and M0 for patients receiving adjuvant chemotherapy.

The primary objective was the evaluation of the PFS at 3 yr. Final results for the primary endpoint will be available in mid-2021. Secondary objectives of the trial were to assess toxicity NCI Common Terminology Criteria for Adverse Events (CTCAE; v 4.0), assess the response rate in patients treated in the neoadjuvant setting according to RECIST 1.1 criteria, assess OS and time to progression, and also study the correlation between response rate, time to progression, OS, and biological parameters.

2.2. Patient selection

The key inclusion criteria were primary tumor of the bladder; histologically confirmed infiltrating urothelial carcinoma (variants accepted if combined with classical urothelial carcinoma); disease defined by cT2, cT3, or cT4a N0 (lymph node ≤ 10 mm on computed tomography [CT] scan) M0 staging for patients receiving NAC or pT3 or pT4 or pN+ whatever pT and M0 for patients receiving adjuvant chemotherapy; age ranging from ≤ 18 to ≤ 80 yr; general condition 0 or 1 as per the World Health Organization scale; absence of previous chemotherapy for muscle-invasive disease; normal blood function; normal liver function; calculated creatinine clearance of ≥ 50 ml/min; and patients covered by a social security scheme and having signed the informed consent form.

The key exclusion criteria were pure adenocarcinoma or pure squamous carcinoma or mixed or pure small-cell neuroendocrine carcinoma, ventricular ejection fraction of $< 50\%$, history of cancer in the 5 yr prior to entry in the trial other than skin basal cell carcinoma or in situ carcinoma of the cervix, and pregnant woman or woman currently breastfeeding.

2.3. Study procedures

As previously described in the design [6], chemotherapy schedules were as follows: the standard GC arm—gemcitabine 1250 mg/m^2 on days 1 and 8, and cisplatin 70 mg/m^2 on day 1, every 3 wk for a total of four cycles; the experimental dd-MVAC arm—methotrexate 30 mg/m^2 on day 1, vinblastine 3 mg/m^2 on day 2, doxorubicin 30 mg/m^2 on day 2, and cisplatin 70 mg/m^2 on day 2 with associated granulocyte colony-stimulating factor (G-CSF) from day 3 to day 9, every 2 wk for a total of six cycles (same period of 3 mo of chemotherapy before or after surgery). Randomization was stratified by the mode of administration of the

chemotherapy (neoadjuvant or adjuvant) and the involvement or not of the lymph nodes. No blinding procedure was planned.

At baseline before screening, a CT scan with contrast of the chest, abdomen, and pelvis was performed for all patients, in association with a systematic bone scan and a complete biological evaluation. Follow-up visits, and their schedules and measurements are described clearly in Figure 1.

A dose reduction of chemotherapy in case of toxicity was allowed. The cisplatin dose was adapted to renal function for the GC group (standard arm) and the dd-MVAC group (experimental arm): creatinine clearance >60 ml/min, 70 mg/m²; creatinine clearance between 50 and 60 ml/min, 50 mg/m²; creatinine clearance between 50 and 45 ml/min, 40 mg/m²; and creatinine clearance <40 ml/min, end of the chemotherapy. For hematological toxicity (neutropenic fever) or other grade IV toxicity, a dose reduction of 15% was recommended for the different chemotherapy drugs used in the GC or the dd-MVAC arm. In the absence of hematological or other toxicity recovery within 14 d, or in case of grade IV toxicity despite a dose reduction of 15%, chemotherapy was stopped.

This study was conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki. All patients signed the informed consent form to be enrolled in our randomized phase III study, approved by the Ethics Committee CPP ROUEN NO on April 19, 2012 and the competent authority on February 27, 2012 (Clinical trial registry: clinicaltrials.gov—NCT 018 12369).

2.4. Statistical analyses

This secondary endpoint analysis was mainly descriptive. Quantitative data were reported as means and standard deviation, and qualitative data as frequency and percentage, by the chemotherapy treatment arm. Univariate analyses were also performed to compare the GC and MVAC groups on baseline characteristics, toxicities of initial treatments, and pathological response staging. Comparisons between the GC and dd-MVAC groups were computed with parametric Student *t* or chi-square tests. A *p* value of <0.05 indicated a statistical difference. Some analyses were performed by subgroups to take into account the mode of administration of the chemotherapy (neoadjuvant or adjuvant). All statistical analyses 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).

3. Results

From February 2013 to March 2018, a total of 500 patients have been randomized in the French GETUG/AFU V05 trial, including 28 participating centers with referent urologist and oncologist investigators. After the exclusion of seven patients who did not meet the inclusion/exclusion criteria, 493 patients remained in the intent-to-treat population. Baseline characteristics by the chemotherapy arm are reported (Table 1), whereas tumor staging at randomization by the type of perioperative chemotherapy are detailed (Table 2).

3.1. Treatment delivery

The chemotherapy delivery was separately detailed in the two groups of the protocol (neoadjuvant and adjuvant), taking into account patients with six complete cycles, six incomplete cycles, and fewer than six cycles for the dd-MVAC arm, and patients with four complete cycles, four incomplete cycles, and fewer than four cycles for the GC arm (Fig. 2).

In the neoadjuvant group ($n = 437$ patients), the median delay of surgery from the last course of chemotherapy D1 was 48 d (95% range [27; 97]) for GC and 51 d (95% range [23; 130]) for dd-MVAC. For the dd-MVAC regimen, 58% of patients received the total dose of six cycles, whereas a reduction of the chemotherapy schedule was observed in 39% of patients: five cycles, 11%; four cycles, 14%; and fewer than four cycles, 14%; (Fig. 2). Radical cystectomy was performed in 91% of cases (199 patients). The surgery was declined because of chemotherapy toxicity in 10 cases and refused by the patient in five cases. A disease progression was observed in two cases. When considering the GC regimen, 66% of patients received four complete cycles, but 16% of patients received fewer cycles (Fig. 2). Radical cystectomy was performed as planned in 198 patients (90%). The main reasons for not performing surgery were patient's refusal (nine cases), disease progression (six cases), and toxicity of chemotherapy (five cases).

In the adjuvant group ($n = 56$ patients), only 11 patients (37%) received six cycles of dd-MVAC and 12 patients (46%) received four cycles of GC. The median time of chemotherapy D1 from the date of surgery was 74 d (95% range [43; 90]). Patients received fewer than six cycles of dd-MVAC in 60% of cases, whereas fewer than four cycles of GC were delivered in 19% of cases.

3.2. Chemotherapy toxicities

Most CTCAE grade ≥ 3 toxicities were hematological toxicities, reported for 129 patients (52%) in the dd-MVAC arm and 134 (55%) patients in the GC arm, but severe anemia was observed most frequently in the dd-MVAC arm ($p < 0.001$). Asthenia was reported for 35

(14%) patients in the dd-MVAC arm and 10 (4.1%) patients in the GC arm ($p < 0.001$), whereas gastrointestinal (GI) grade ≥ 3 disorders with nausea/vomiting were observed more frequently in the dd-MVAC arm ($p = 0.003$; Table 3). Four deaths occurred during chemotherapy, including three patients in the dd-MVAC arm: sudden death, pulmonary embolism, and septic shock (Table 4).

3.3. Pathological responses

Complete pathological response (ypT0pN0) was observed in 84 patients (42%) in the dd-MVAC arm and 71 patients (36%) in the GC arm ($p = 0.2$). Nevertheless, a higher local control rate (complete pathological response, tumor downstaging, or organ confined) was observed in the dd-MVAC arm ($p = 0.021$). The non-muscle-invasive status ($<ypT2pN0$) control rate was observed in 126 patients (63%) in the dd-MVAC arm and 98 patients (49%) in the GC arm ($p = 0.007$). An organ-confined status ($<ypT3pN0$) was obtained in 154 patients (77%) in the dd-MVAC arm and 124 patients (63%) in the GC arm ($p = 0.001$; Table 5).

4. Discussion

Despite the pivotal randomized studies and meta-analyses demonstrating the survival benefit of cisplatin-based combination chemotherapy before cystectomy [7,8], low implementation of this approach was observed in daily practice [9–12]. The objective of the French GETUG/AFU V05 Vesper phase III trial was to compare the efficacy of six cycles of dd-MVAC or four cycles of GC regimens (3 mo of chemotherapy) in terms of PFS in patients for whom chemotherapy has been decided, before or after radical cystectomy.

Zargar et al [13] have reviewed the clinical data of 319 patients with cT3-4a N0M0 bladder cancer who underwent NAC before cystectomy from 2000 to 2015 in 20 institutions. A total of 100 patients received dd-MVAC, whereas 219 patients were treated with GC. Baseline characteristics were similar between the two groups except for age and the proportion of variant histology features. A lower rate of pathological complete response (ypT0N0) was observed in the GC group (15% vs 28%, $p = 0.005$). The pathological partial response rate (ypT1N0 or less) was 30% for the GC arm compared with 41% for the dd-MVAC arm, suggesting that dd-MVAC could be the optimal regimen for the neoadjuvant setting with longer OS (7 vs 4.6 yr, $p = 0.001$). Similarly, the data of the GETUG/AFU V05 Vesper trial suggest a better local control in the dd-MVAC arm. A trend was observed only for complete

pathological response (ypT0pN0). These data may be explained by fewer advanced stages and/or a greater number of chemotherapy cycles, especially for the dd-MVAC arm.

Choueiri et al [14] and Plimack et al [15] reported results from two phase II trials using dd-MVAC as NAC in MIBC. After three to four cycles, the pathological downstaging (ypT1N0) was quite similar (49% and 53%); the pathological complete response rates (ypT0) were 26% and 38%, respectively. A large majority of the patients achieved the planned number of cycles without any life-threatening toxicity. Data analysis of chemotherapy delivery in our experience suggests that the treatment was not optimal in the adjuvant group; 60% of patients received fewer than six cycles of dd-MVAC and 19% of patients fewer than four cycles of GC. These results strongly confirm that delivering chemotherapy after surgery is often difficult and that six cycles of dd-MVAC is really not the recommended schedule. When considering the neoadjuvant group, interestingly we observed that 144 patients (66%) received the total dose of four cycles for the GC regimen and 127 patients (58%) received the total dose of six cycles for the dd-MVAC regimen. Moreover, radical cystectomy was performed as planned in most of the cases (90%) irrespective of the chemotherapy arm. Finally, surgery was declined because of chemotherapy toxicity in only 10 cases, suggesting that neoadjuvant dd-MVAC is not so pernicious, whereas patients with tumor progression during chemotherapy were definitively not good candidates for surgery.

Chemotherapy toxicity remains a very important parameter during the perioperative setting for patients with MIBC. When using dd-MVAC in metastatic disease, Sternberg et al [5] reported that 25% of patients were alive in the dd-MVAC arm versus 13% in the classic MVAC regimen with a median follow-up of >7 yr. There was a trend toward more whole blood cell toxicity in the MVAC arm, in contrast with the dd-MVAC arm, most probably due to the use of G-CSF. In the dose-dense regimen, grade 3–4 hematological toxicity was observed in only 20% of the patients. In the phase III Vesper trial, we reported similar reassuring data on chemotherapy toxicity, as most of the CTCAE grade ≥ 3 hematological toxicities were reported in the GC arm (55%) and not in the dd-MVAC arm (52%). Nevertheless, GI grade ≥ 3 disorders were more frequently observed in the dd-MVAC arm ($p = 0.003$), as well as asthenia of grade ≥ 3 ($p < 0.001$). Finally, four deaths (three in the dd-MVAC arm) occurred during chemotherapy.

A trend of a higher response rate was observed for the dd-MVAC schedule; the real question today was to confirm such benefit in PFS and OS. It could be the case since several studies have shown a strong relationship between the complete response rate and PFS or OS [16]. A

substantial high rate of morbidity (66%) or risk of perioperative mortality (4%), and a negative impact on the quality of life have been reported after radical cystectomy. The subgroup of patients downstaged to pT0N0 after NAC usually achieves a survival benefit beyond noncomplete responders; however, the real benefit of surgery remains unclear today [17,18]. Robins et al [19] reported, at the Colombia University Irving Medical Center, an interesting series of 48 patients with MIBC who were at cT0 after NAC and also refused radical cystectomy. Five-year cancer-specific survival was 87%, disease-free survival was 58%, and cystectomy-free survival was 79%. Finally, bladder preservation for patients with complete clinical response after NAC is not recommended currently; nevertheless, the pathological downstaging (ypT1N0 or less) and the rate of pathological complete response (ypT0) could be significant prognostic factors in NAC response [20].

5. Conclusions

We reported the secondary endpoint analysis of the first prospective, large, randomized GETUG/AFU VESPER phase III trial on chemotherapy toxicity and pathological responses. Toxicity of the dd-MVAC arm was manageable with more severe asthenia and GI side effects than that of the GC arm in perioperative chemotherapy. A higher local control rate (complete pathological response, tumor downstaging, or organ confined) was observed for the dd-MVAC schedule. However, such data have to be confirmed on PFS, with primary endpoint data expected in mid-2021.

Author contributions: Christian Pfister 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.

Study concept and design: Pfister, Culine.

Acquisition of data: All authors.

Analysis and interpretation of data: Pfister, Culine, Harter, Allory.

Drafting of the manuscript: Pfister, Culine, Harter, Allory.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Harter.

Obtaining funding: All authors.

Administrative, technical, or material support: Pfister, Culine.

Supervision: Pfister, Culine.

Other: None.

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References

- [1] Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer. Long-term results in 1054 patients. *J Clin Oncol* 2001;19:666–75.
- [2] Shariat SF, Karakiewicz PI, Palapattu GS, et al. Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the Bladder Cancer Research Consortium. *J Urol* 2006;176:2414–22.
- [3] Milowsky MI, Rumble RB, Booth CM, et al. Guidelines on muscle invasive and metastatic bladder cancer. American Society of Clinical Oncology clinical practice guideline endorsement. *J Clin Oncol* 2016;34:1945–52.
- [4] Witjes A, Lebreton T, Comperat EM, et al. Updated 2016 EAU guidelines on muscle invasive and metastatic bladder cancer. *Eur Urol* 2017;71:462–75.
- [5] Sternberg CN, de Mudler P, Schornagel JH, et al. Seven year update of an EORTC phase III trial of high dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumors. *Eur J Cancer* 2006;42:50–4.
- [6] Pfister C, Harter V, Allory Y, Radvanyi F, Culine S, the Vesper Trial Investigators. Design of a randomized controlled phase III study of dose dense methotrexate, vinblastine, doxorubicin and cisplatin (dd-MVAC) or gemcitabine and cisplatin (GC) as peri-operative

- chemotherapy for patients with locally advanced transitional cell cancer of the bladder. The French GETUG/AFU V05 VESPER trial. *Contemp Clin Trials Commun* 2020;17:100536.
- [7] Advanced Bladder Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer meta-analysis collaboration. *Eur Urol* 2005;48:202–5.
- [8] Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003;349:859–66.
- [9] Reardon ZD, Patel SG, Zaid HB, et al. Trends in use of peri-operative chemotherapy for localized and locally advanced muscle invasive bladder cancer: a sign of changing tides. *Eur Urol* 2015;67:165–70.
- [10] Booth CM, Karim S, Brennan K, et al. Peri-operative chemotherapy for bladder cancer in the general population: are practice patterns finally changing? *Urol Oncol* 2018;36:89.e13–20.
- [11] Hermans TJ, Fransen Van de Putte EE, Harenblas S, et al. Peri-operative treatment and radical cystectomy for bladder cancer. A population based trend analysis of 10 388 patients in the Netherlands. *Eur J Cancer* 2016;54:18–26.
- [12] Culine S, Allory Y, Pfister C. Editorial. Refining the use of neoadjuvant chemotherapy in locally advanced bladder cancer: from conviction to optimization. *Transl Androl Urol* 2018;7:757–9.
- [13] Zargar H, Shah JB, Van Rhijn BW, et al. Neoadjuvant dose dense MVAC versus gemcitabine and cisplatin in patients with cT3-4a N0M0 bladder cancer treated with radical cystectomy. *J Urol* 2018;199:1452–8.
- [14] Choueiri TK, Jacobus S, Bellemut J, et al. Neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin and cisplatin with pegfilgrastim support in muscle invasive urothelial cancer: Pathologic, radiologic and biomarker correlates. *J Clin Oncol* 2014;32:1882–94.
- [15] Plimack ER, Hoffman-Censits JH, Viterbo R, et al. Accelerated methotrexate, vinblastine, doxorubicin and cisplatin is safe, effective and efficient neoadjuvant treatment for muscle invasive bladder cancer. Results of a multicenter phase II study with molecular correlates of response and toxicity. *J Clin Oncol* 2014;32:1895–901.
- [16] Kassouf W, Spiess PE, Brown GA, et al. P0 stage at radical cystectomy for bladder cancer is associated with improved outcome independent of traditional clinical risk factors. *Eur Urol* 2007;52:769–74.
- [17] Petrelli F, Coinu A, Cabiddu M, et al. Correlation of pathologic complete response with survival after neoadjuvant chemotherapy in bladder cancer treated with cystectomy: a meta-analysis. *Eur Urol* 2014;65:350–7.
- [18] Herr HW. Outcome of patients who refuse cystectomy after receiving neoadjuvant chemotherapy for muscle invasive bladder. *Eur Urol* 2008;54:126–32.
- [19] Robins D, Matulay J, Lipsky M, et al. Outcomes following complete response to neoadjuvant chemotherapy for muscle invasive urothelial carcinoma of the bladder in patients refusing radical cystectomy. *Oncology* 2018;11:116–21.
- [20] Magers MJ, Kaimakliotis HZ, Barboza MP, et al. Clinico pathological characteristics of ypT0N0 urothelial carcinoma following neoadjuvant chemotherapy and cystectomy. *J Clin Pathol* 2019;72:550–3.

Fig. 1 – Study procedures, schedule, and parameters of the patients’ follow-up. ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; BMI = body mass

index; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; dd-MVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; FU = follow-up; GC = gemcitabine and cisplatin; PAL = alkaline phosphatase; PS = performance status.

Fig. 2 – Treatment delivery in the (A) adjuvant and (B) neoadjuvant groups for the dd-MVAC and GC arms. d = day; dd-MVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; GC = gemcitabine and cisplatin.

Baseline

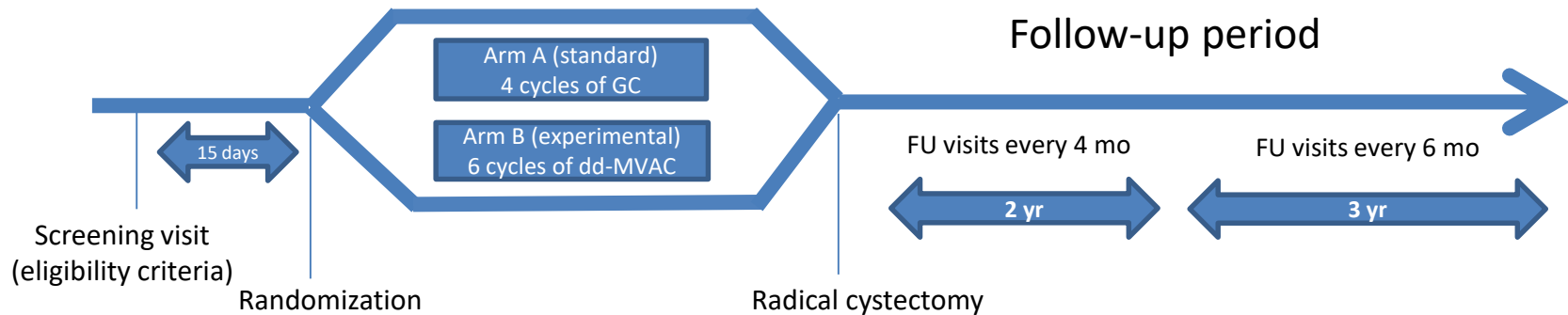
- Medical history
- Clinical parameters (PS and BMI)
- Hematology blood count
- Liver and renal function tests (bilirubin, ALAT, ASAT, PAL, creatinine clearance)
- CT of the chest, abdomen, and pelvis (with contrast)
- Bone scan
- Audiometric, cardiac evaluation

Treatment phase

- Before each cycle of chemotherapy :
 - Clinical parameters
 - Hematology blood count
 - Liver and renal function tests (bilirubin, ALAT, ASAT, PAL, creatinine clearance)
 - Toxicities (CTCAE V4.0)
 - Concomitant treatments
- Audiometric assessment >3 cycles

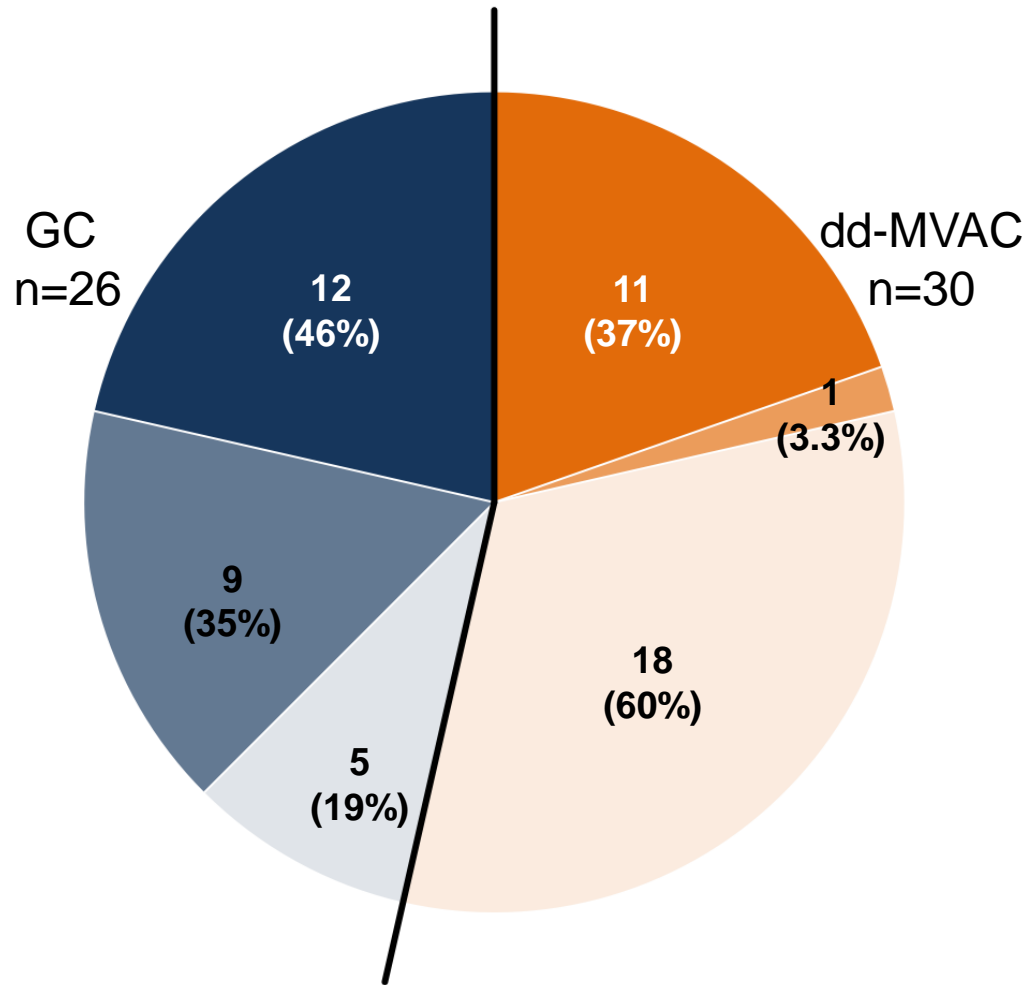
Follow-up period

- Clinical parameters (PS and BMI)
- Hematology blood count
- Liver and renal function tests (bilirubin, ALAT, ASAT, PAL, creatinine clearance)
- Tumor response (RECIST V1.1)
- CT of the chest, abdomen, and pelvis
- Bone scan if clinical symptoms
- Toxicities collected up to 3 yr



A

Adjuvant chemotherapy



GC : Gemcitabine (d1,d8), Cisplatin (d1)

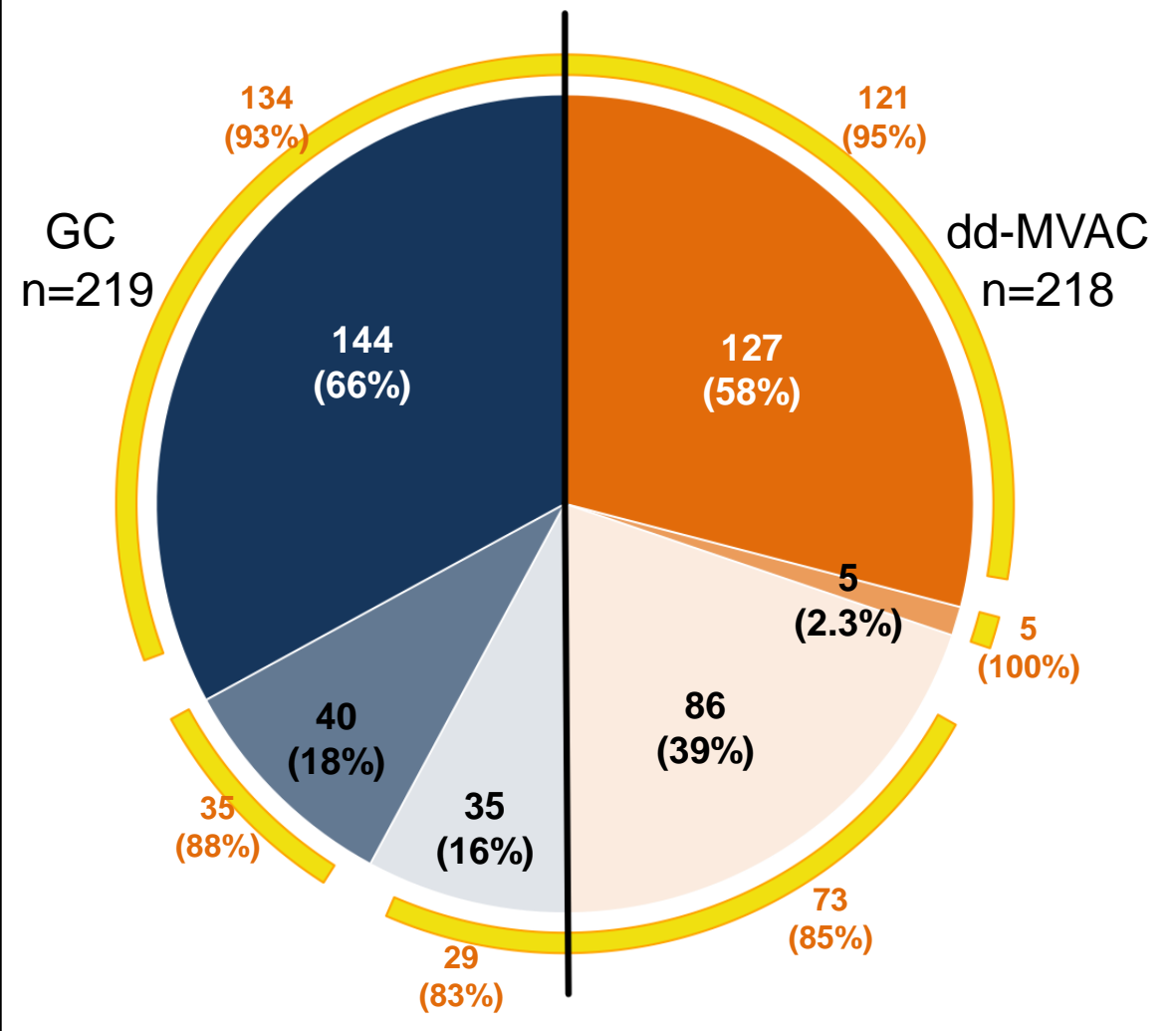
- Four complete cycles
- Four incomplete cycles
- Less than 4 cycles

dd-MVAC : Methotrexate (d1), Vinblastine (d2),
Doxorubicin (d2), Cisplatin (d2)

- Six complete cycles
- Six incomplete cycles
- Less than 6 cycles

B

Neoadjuvant chemotherapy



Cystectomy performed



Table 1 – Baseline characteristics reported by chemotherapy arm (GC or dd-MVAC)

	GC (n = 245)	dd-MVAC (n = 248)
Demography		
Age	63 (59–69)	63 (58–68)
Sex	Male	202 (81%)
Physical examination		
Body mass index	26.3 (23.4–29.0)	25.7 (23.0–29.0)
Body surface area	1.92 (1.79–2.05)	1.90 (1.75–2.05)
WHO status	0	165 (67%)
	1	82 (33%)
	Not done	2 (0.82%)
Medical history		
Any medical history	235 (96%)	242 (98%)
Neuropathy	3 (1.2%)	1 (0.40%)
Hearing disorder	35 (15%)	46 (19%)
High blood pressure	100 (43%)	89 (37%)
Infarction	9 (3.7%)	11 (4.4%)
Coronary	5 (2.0%)	9 (3.6%)
insufficiency		
Diabetes	14 (5.7%)	4 (1.6%)
Tobacco use	198 (84%)	197 (81%)
Aromatic amine	14 (5.7%)	7 (2.8%)
exposure		
Biology and renal function		
Hemoglobin (g/100 ml)	14 (13–15)	14 (13–15)
Neutrophil polynuclear cells (1000/mm ³)	5.0 (4.0–6.4)	4.6 (3.6–5.9)
Platelets (1000/mm ³)	267 (217–314)	259 (213–319)
Total bilirubin (mg/l)	4.4 (3.2–6.0)	4.7 (3.4–6.4)
ALT (UI/l)	20 (14–28)	21 (16–27)
AST (UI/l)	19 (16–23)	19 (16–23)
Alkaline phosphatase (UI/l)	73 (62–88)	73 (60–88)
Creatinine (mg/l)	9 (8–11)	9 (8–10)
Clearance of creatinine (ml/min)	86 (70–102)	89 (72–103)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; dd-MVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; GC = gemcitabine and cisplatin; WHO = World Health Organization.

Median (first quartile–third quartile) was used for quantitative data and frequency (percentage) was used for qualitative data.

Table 2 – Staging at randomization by type of perioperative chemotherapy and regimen

		Adjuvant chemotherapy		Neoadjuvant chemotherapy		
		GC (n = 26)	dd-MVAC (n = 30)		GC (n = 219)	dd-MVAC (n = 218)
Tumor	pT1	1 (3.8%)	1 (3.3%)	cT1	0	0
	pT2a	0	1 (3.3%)	cT2	207 (95%)	197 (90%)
	pT2b	3 (12%)	2 (6.7%)			
	pT3a	8 (31%)	12 (40%)	cT3	8 (3.7%)	12 (5.5%)
	pT3b	3 (12%)	6 (20%)			
	pT4a	11 (42%)	8 (27%)	cT4a	4 (1.8%)	9 (4.1%)
Nodes	pN0	7 (27%)	12 (40%)	cN0	219 (100%)	218 (100%)
	pN1	12 (46%)	7 (23%)	cN1	0	0
	pN2	7 (27%)	11 (37%)	cN2	0	0
Metastasis	cM0	26 (100%)	30 (100%)	cM0	219 (100%)	218 (100%)

dd-MVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; GC = gemcitabine and cisplatin; pTNM = pathological TNM; TNM = tumor, node, metastasis; TURBT = transurethral resection of bladder tumor.

Data are presented as frequency (percentage). For adjuvant chemotherapy, pTNM staging is performed on cystectomy. For neoadjuvant chemotherapy, TNM staging is performed on TURBT. Staging was done according to the 2009 TNM classification.

Table 3 – CTCAE grade ≥ 3 hematological toxicities reported for patients of the dd-MVAC and GC arms

	GC (<i>n</i> = 245)	dd-MVAC (<i>n</i> = 248)	<i>p</i> value
Anemia	19 (7.8%)	54 (22%)	<0.0001
Neutropenia	113 (46%)	97 (39%)	0.14
Febrile neutropenia	6 (2.4%)	16 (6.5%)	0.053
Thrombopenia	41 (17%)	49 (20%)	0.5
At least one grade ≥ 3 hematological toxicity	134 (55%)	129 (52%)	0.6

CTCAE = Common Terminology Criteria for Adverse Events; dd-MVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; GC = gemcitabine and cisplatin.

Data are presented as frequency (percentage). Comparisons between the GC and dd-MVAC groups are performed with a chi-square test. A *p* value of <0.05 would assume a statistical difference between the GC and dd-MVAC groups.

Table 4 – CTCAE grade ≥ 3 nonhematological toxicities reported for patients of the dd-MVAC and GC arms

	GC (<i>n</i> = 245)	dd-MVAC (<i>n</i> = 248)	<i>p</i> value
Nausea/vomiting	7 (2.9%)	24 (9.7%)	0.003
Diarrhea	2 (0.81%)	3 (1.2%)	–
Asthenia	10 (4.1%)	35 (14%)	<0.001
Cardiovascular	17 (6.9%)	16 (6.5%)	>0.9
Kidney	13 (5.3%)	15 (6.0%)	0.9
Liver	13 (5.3%)	7 (2.8%)	0.2
Neuropathy	0	2 (0.81%)	–
Chemotherapy-related deaths	1	3	–

CTCAE = Common Terminology Criteria for Adverse Events; dd-MVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; GC = gemcitabine and cisplatin.

Data are presented as frequency (percentage). Comparisons between the GC and dd-MVAC groups are performed with a chi-square test when enough events were observed. A *p* value of <0.05 would assume a statistical difference between the GC and dd-MVAC groups.

Table 5 – Pathological responses observed after neoadjuvant chemotherapy and cystectomy for the dd-MVAC and GC arms

		GC (<i>n</i> = 198)	dd-MVAC (<i>n</i> = 199)	<i>p</i> value
Complete response	ypT0 pN0	71 (36%)	84 (42%)	0.021
	ypTis or ypTa or ypT1 and ypN0		42 (21%)	
	≥ ypT2 and ypN0	63 (32%)	51 (26%)	
	ypN+	35 (18%)	20 (10%)	
	Uncertain staging	2	2	
Non-muscle invasive	<ypT2 pN0	98 (49%)	126 (63%)	0.007
	≥ypT2 or ypN+	99 (50%)	72 (36%)	
	Uncertain staging	1	1	
Organ-confined disease	<ypT3 pN0	124 (63%)	154 (77%)	0.001
	≥ypT3 or ypN+	73 (37%)	43 (22%)	
	Uncertain staging	1	2	

dd-MVAC = dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; GC = gemcitabine and cisplatin.

Data are presented as frequency (percentage). Comparisons between the GC and dd-MVAC groups are performed with a chi-square test. A *p* value of <0.05 would assume a statistical difference between the GC and dd-MVAC groups.