

Original Research

## Cisplatin-Based Neoadjuvant Chemotherapy for Elderly Patients with Muscle-Invasive Bladder Cancer: Is It Feasible?

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### Abstract

Cisplatin-based neoadjuvant chemotherapy (C-NAC) has been the standard of care in localized muscle-invasive bladder cancer (MIBC). However, the feasibility and benefit of C-NAC in elderly patients remain uncertain since this population has always been underrepresented in pivotal trials and is often barred from chemotherapy in routine practice because of their perceived frailty. Therefore, in order to evaluate the effectiveness of C-NAC in elderly patients with MIBS, we retrospectively reviewed the medical files of patients (cT2-4, N0-3, and M0)



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treated at our institution and aged 75 or older at the time of the first chemotherapy cycle. From May 2012 to March 2020, 51 patients aged 75 to 90 received C-NAC. Among them, 38 patients received methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) and 13 patients received gemcitabine and cisplatin (GC). In this study, the primary endpoint was the feasibility of C-NAC, evaluated as the percentage of patients who underwent at least four chemotherapy cycles. Overall feasibility of a complete four-cycle chemotherapy course was 75% (dose-dense MVAC [dd-MVAC]: 76%; GC: 69%). Incidence of grade 3-4 adverse events was 57%, mostly driven by hematological toxicity from dd-MVAC, and the incidence of febrile neutropenia was 6%. These results indicate the feasibility of C-NAC in elderly patients without any contraindication to cisplatin. A coordinated multidisciplinary approach, including a geriatric oncologist, may help to identify patients at increased risk for chemotherapy-induced toxicity, especially in patients aged 85 or older.

### **Keywords**

Bladder cancer; neoadjuvant chemotherapy; elderly patients; cisplatin

## **1. Introduction**

Muscle-invasive bladder cancer (MIBC) is associated with early metastasis and high mortality, leading to a poor prognosis. Radical cystectomy (RC) remains the gold standard local treatment for non-metastatic MIBC; however, it has been observed that many patients die of distant metastases within two years of RC, suggesting the presence of micro-metastases at the time of surgery [1, 2]. In past decades, the delivery of perioperative chemotherapy before (neoadjuvant) or after (adjuvant) RC was utilized for treating micro-metastases, thereby increasing overall survival. However, presently, only cisplatin-based neoadjuvant combination chemotherapy regimens (C-NAC) are being utilized as it has an absolute benefit of 5% on overall survival with Level I evidence in international guidelines [3-5].

Outcome data on elderly patients treated with C-NAC are limited in both clinical trials and retrospective series. Results of subgroup analyses in prospective trials indicate that C-NAC is beneficial for patients  $\geq 65$  years. However, several studies have reported the underutilization of C-NAC in real life, which may be due to factors like toxicity concerns, increased perioperative complications, etc., as well as higher comorbidity scores in elderly patients as primary factors associated with lower use of C-NAC [6-8]. In the present report, we assessed the feasibility of C-NAC in a cohort of 51 consecutive patients aged 75 years or above who were treated at our institution in the last decade.

## **2. Patients and Methods**

### **2.1 Patient Identification and Data Retrieval**

In order to identify the patients, we screened our database from January 2011 to March 2020. These patients were treated at our institution with at least one cycle of C-NAC for histologically proven pure or predominant urothelial MIBC and evidence of cT2-4a, cN0-N3, and M0 disease. In

this study, patients with non-muscle-infiltrating disease, inoperable locally advanced disease, and non-urothelial bladder cancer were excluded.

## **2.2 Treatment Plan**

Two chemotherapy regimens were used: Gemcitabine/cisplatin (GC) and dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (dd-MVAC). The standard doses of GC were gemcitabine 1250 mg/m<sup>2</sup> on days one and eight and cisplatin 70 mg/m<sup>2</sup> on day one every three weeks. The dosage of dd-MVAC included methotrexate 30 mg/m<sup>2</sup> on day one, vinblastine 3 mg/m<sup>2</sup> on day two, doxorubicin 30 mg/m<sup>2</sup> on day two, and cisplatin 70 mg/m<sup>2</sup> on day two every 14 days. Both regimens were delivered in an inpatient setting, and all patients received granulocyte-colony stimulating factor (G-CSF). The type of regimen, as well as dose reductions, were at the discretion of the treating physician. The planned number of cycles was four for GC and six for dd-MVAC; however, in case of excessive toxicity or disease progression, chemotherapy could be discontinued prematurely at the discretion of the treating physician. At the end of chemotherapy, further treatments were decided according to a multidisciplinary approach and patients' preference (RC and lymphadenectomy, pelvic chemoradiotherapy, or surveillance).

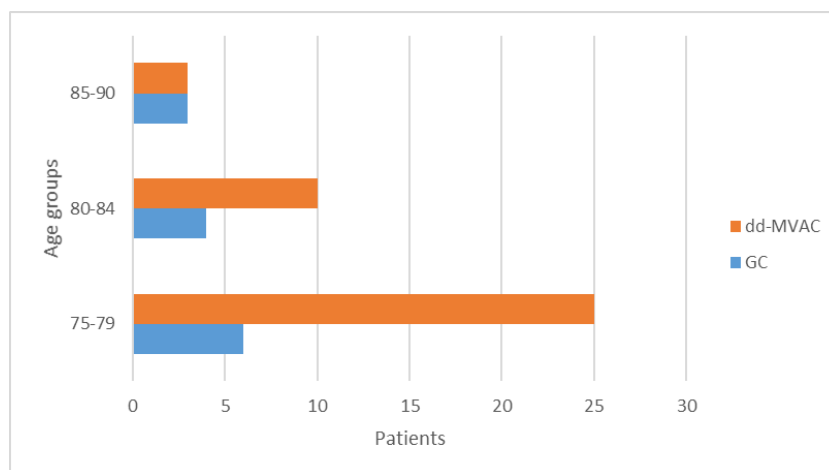
## **2.3 Safety Assessment**

Clinical toxicities and significant laboratory values were 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 5.0), based on individual medical reports. Reasons for changes in the planned chemotherapy cycles were notified.

## **3. Results**

### **3.1 Patients**

From May 2012 to March 2020, 51 patients aged 75 to 90, with a median age of 79 years, received C-NAC (dd-MVAC: 38; GC: 13). Twenty (39%) patients were older than 80 years; out of them, six patients were above the age of 85. Age distribution according to the chemotherapy regimen is shown in Figure 1. Initial characteristics of the patient population indicated that they were suitable candidates for C-NAC, with good performance status and adequate renal function (Table 1).



**Figure 1** Age distribution of patients according to the chemotherapy regimen.

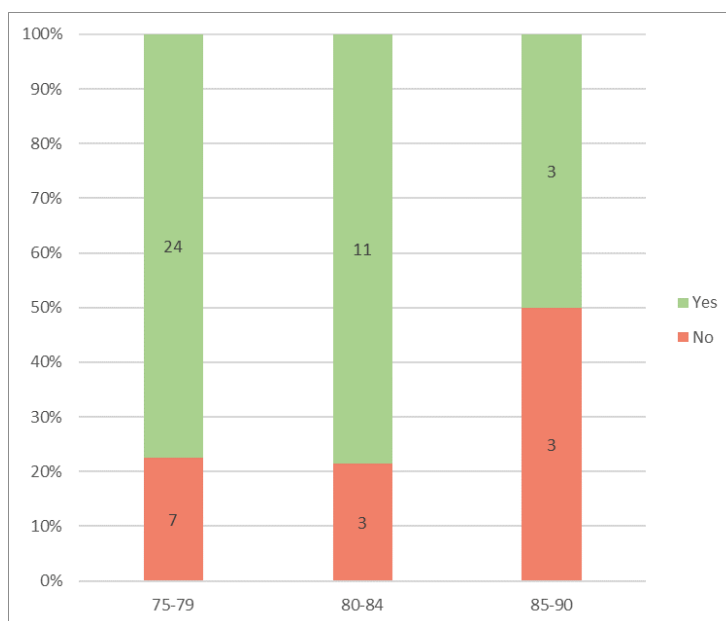
**Table 1** Patient characteristics.

Characteristics	Value	Number
Age, median (range)	79 (75-90)	
Sex, Female/Male		8/43
Medical history		
Tobacco use, Yes/No		38/13
Pelvic radiotherapy, Yes/No		9/42
Non-muscle-invasive cancer, Yes/No		10/41
High blood pressure, Yes/No		20/21
Diabetes, Yes/No		8/43
Atheromatous arterial disease, Yes/No		6/45
Physical examination		
Body mass index, median (range)	26 (19-34)	
Performance status, 0/1/2		23/25/3
Biology		
Albumin (g/L), median (range)	40 (30-48)	
Creatinine clearance (mL/min), median (range)	64 (33-96)	
	82 (42-121)	
Staging		
cT2, N0		29
cT3-4, N0		14
cTany, N1-3		8

### 3.2 Treatment Delivery

Two patients received reduced cisplatin doses at the first cycle because of impaired renal function. The median number of cycles was four for both regimens. Eighteen (47%) patients treated with dd-MVAC received more than four cycles of chemotherapy. Overall feasibility of a complete 4-cycle chemotherapy course was 75%, regardless of the chemotherapy regimen (dd-MVAC: 76%; GC: 69%). No differences were observed in the completeness of chemotherapy between patients aged

75 to 79 and patients aged 80 to 84 (Figure 2). The feasibility of chemotherapy seemed to drop in patients aged 85 or above; however, it should be noted that the number of patients was small in this subset. Dose reductions were done in 57% of the patients (dd-MVAC: 55%; GC:62%). Thirteen (25%) patients discontinued chemotherapy before the fourth cycle, and the reasons included toxicity in ten patients, planned surgery in one patient, COVID-19 infection in one patient, and death from an unknown cause (sudden death) in one patient. Toxicities responsible for chemotherapy discontinuation, possibly multiple, were renal in five patients, hematological in four patients, infectious in two patients, and general in two patients. One patient discontinued dd-MVAC because of nephrotoxicity and pursued chemotherapy with carboplatin and gemcitabine.



**Figure 2** Completeness of chemotherapy in patients according to age groups (digits indicate the number of patients).

At the end of C-NAC, 27 patients underwent surgery, 12 patients were treated with chemoradiotherapy, and three patients underwent active surveillance. Other six patients did not receive any locoregional treatment (the reason was disease progression in one patient). Details on post-chemotherapy locoregional management were unavailable for two patients.

### 3.3 Safety

All patients experienced at least one adverse event from C-NAC. Overall, grade 3-4 adverse events were noted in 57% of patients, mostly due to hematological toxicity. Red blood cell transfusion was performed in 29% of patients, and 8% underwent platelet transfusion. The incidence of febrile neutropenia was 6%. Grade 5 adverse event occurred in only one patient aged 79, who died from an unknown cause shortly after a single dd-MVAC cycle. When considering only the first four chemotherapy cycles in all patients (i.e., disregarding toxicity from cycles five and six in dd-MVAC patients), the incidence of grade 3-4 adverse events dropped to 47%. Adverse events according to chemotherapy regimens are detailed in Table 2. Grade 3-4 adverse events were significantly more common with dd-MVAC than with GC (68% vs. 23%;  $p = 0.008$ ).

**Table 2** Adverse events according to chemotherapy regimens.

	dd-MVAC		GC	
	All grades	Grades 3-4	All grades	Grades 3-4
Neutropenia	55%	47%	62%	15%
Febrile neutropenia	8%	8%	0%	0%
Anemia	95%	29%	92%	8%
Thrombopenia	79%	18%	38%	8%
Fatigue	82%	0%	92%	8%
Nausea	66%	3%	46%	0%
Vomiting	47%	3%	31%	8%
Diarrhea	32%	3%	15%	0%
Constipation	39%	0%	38%	0%
Stomatitis	47%	11%	0%	0%
Peripheral neuropathy	26%	0%	23%	0%
Hearing loss	8%	0%	0%	0%
Weight loss	50%	5%	23%	0%
Creatinine increase	68%	5%	62%	0%
Thrombosis	8%	0%	8%	0%
Infection (non-neutropenic)	11%	5%	8%	0%
All adverse events	100%	68%	100%	23%

dd-MVAC: methotrexate, vinblastine, doxorubicin, cisplatin; GC: gemcitabine, cisplatin.

#### 4. Discussion

Bladder cancer is an age-associated malignancy, with the median age at diagnosis being 73 years. More than 30% of new cases are observed in patients aged 75 or above. The age-related decline in performance status and increase in comorbidities significantly affect the risk of treatment-related toxicities; therefore, elderly patients are less likely to receive standard of care treatments, thereby making them prone to undertreatments [9].

Presently, the standard of care for patients with MIBC is a combination of C-NAC and RC. Any deviation in the delivery of these treatments jeopardizes the chances of cure. However, a well-known important limitation to the use of C-NAC is cisplatin itself, since adequate renal, cardiovascular, and hearing functions, as well as the absence of neuropathy, are required for an optimal delivery [10]. In addition, compliance with contraindications is likely to exclude up to 50% of patients from undergoing C-NAC, particularly in older populations. Despite all these limitations, cisplatin is the most active cytotoxic agent against MIBC. [11].

Retrospective studies have clearly shown that C-NAC is underutilized worldwide, although recent surveys indicate an increase in its application since 2010 [12, 13]. The potential clinical reasons contributing to the underutilization of C-NAC in elderly patients include older age as well as higher comorbidity scores [6-8]. Based on a national database from the United States and Porto-Rico, Carvalho et al. reported that only 18.8% of patients aged  $\geq 75$  received C-NAC. Of the 81.2% of patients who did not receive C-NAC, only 2.5% were ineligible due to true contraindication. In addition, 68% of patients did not receive C-NAC simply because it was not planned, implying that

this treatment option may not even be offered or discussed by some providers after the initial diagnosis of MIBC [8].

Renal function, in particular, is often compromised in older patients with MIBC due to smoking, comorbidities, and/or obstructive nephropathy. Given the potential for renal toxicity with cisplatin-based chemotherapy, adequate renal function is a prerequisite for C-NAC. Clinical trials and medical oncologist community surveys have arrived at the common eligibility threshold of measured or calculated creatinine clearance (CrCl) of  $\geq 60$  mL/min [10]. However, no robust data exist to support a specific renal function threshold and an optimal methodology to assess the eligibility of patients for receiving the treatment as well as dose adaptations of cisplatin throughout C-NAC in MIBC. To overcome this, an algorithm that eliminates an absolute CrCl threshold and emphasizes a multidisciplinary, patient-centered approach was recently proposed [14].

Results of this study indicate that chronologic age itself should not directly affect treatment options. In a selected population of elderly patients with no standard contraindication for cisplatin, overall feasibility of 75% was achieved, when considering a 4-cycle chemotherapy course (regardless of the chemotherapy regimen). More serious adverse events were observed in patients who received dd-MVAC, mainly because of its higher hematological toxicity. Also, the 6% febrile neutropenia rate was similar to those described in pivotal studies with younger patients, and only 8% of the patients needed a platelet transfusion. No toxic death was observed, although one patient died from an unknown cause shortly after a single dd-MVAC cycle. However, the optimal modalities for C-NAC, including the number of cycles as well as the quality of drugs combined with cisplatin, remain a matter of debate. In a French randomized trial comparing four cycles of GC to six cycles of dd-MVAC, the local control rate was greater in the dd-MVAC arm, but the potential impact on survival is still unknown [15].

The first limitation of our study is linked to its retrospective nature, as the incidence of adverse events could be underestimated. Second, we did not incorporate a formal geriatric assessment as a routine in the clinical evaluation of our patients prior to the decision to undertake chemotherapy. Although a clear selection was made regarding the contraindications to cisplatin, the implementation of routine use of geriatric assessment tools may have potentially allowed for a better selection of vulnerable patients. Finally, we did not report outcome data. However, several studies indicate that in elderly patients with MIBC deemed suitable for C-NAC, survival and other outcomes were similar to that of their younger counterparts [16, 17].

In conclusion, C-NAC is a feasible treatment approach even in elderly patients without any contraindication to cisplatin. A coordinated multidisciplinary approach, including a geriatric oncologist, may help to identify patients at increased risk for chemotherapy-induced toxicity and, therefore, optimize the use of NAC in older patients with MIBC [11].

### **Author Contributions**

Conception and design: Clément Dumont, Stéphane Culine. Provision of study materials or patients: Clément Dumont, Madeleine Lefèvre, Alexandra Masson-Lecomte, Evangelos Xylinas, Hélène Gauthier, Virginie Fossey-Díaz, Amélie Aregui. Collection and assembly of data: Clément Dumont, Quiterie Aussédát, Pierre-Louis Régnier. Data analysis and interpretation: Clément Dumont, Stéphane Culine. Manuscript writing: Clément Dumont, Stéphane Culine. Final approval of manuscript: all authors.

## Competing Interests

The authors state they have no conflict of interest.

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