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Original Research Article

Comparative Toxicity of Neoadjuvant Gemcitabine-Cisplatin Versus Dose-Dense Methotrexate, Vinblastine, Doxorubicin, and Cisplatin in Muscle-Invasive Bladder Cancer: A Single-Center Retrospective Experience in an Oncology Center in Meknes, Morocco

Touimri Youssef[1]*, Toreis Mehdi[1], Bazine Aziz[1], Fetohi Mohammed[1]

[1]Department of Medical Oncology, Moulay Ismail Military Hospital of Meknes, Morocco

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Abstract: ***Background:*** Neoadjuvant chemotherapy (NAC) with either Gemcitabine-Cisplatin (GC) or Dose-Dense Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (DD-MVAC) is a standard approach for muscle-invasive bladder cancer (MIBC). While efficacy is established, toxicity profiles may differ and impact treatment delivery. This retrospective study compares the toxicity of GC and DD-MVAC regimens at the Moulay Ismail Military Hospital in Meknes. ***Methods:*** We retrospectively analyzed the records of 21 patients with MIBC treated with NAC between January 2020 and December 2023 (*Corrected Date*): 14 received GC (Gemcitabine 1000 mg/m² D1, D8; Cisplatin 70 mg/m² D1, q21 days) and 7 received DD-MVAC (Methotrexate 30 mg/m² D1; Vinblastine 3 mg/m² D2; Doxorubicin 30 mg/m² D2; Cisplatin 70 mg/m² D2, q14 days with G-CSF support). Toxicities were graded according to NCI-CTCAE v5.0. Results were compared descriptively and contextualized with published data. ***Results:*** In the GC group (n=14), the most frequent grade ≥3 toxicities were neutropenia (21.4%), anemia (14.3%), and thrombocytopenia (7.1%). Grade 1-2 renal toxicity occurred in 21.4%. In the DD-MVAC group (n=7), grade ≥3 neutropenia (42.9%) and mucositis (28.6%) were predominant. Two cases (28.6%) of febrile neutropenia were observed in the DD-MVAC arm (*Corrected Number*). Grade 1-2 renal toxicity was noted in 28.6% of DD-MVAC patients, and one case (14.3%) of Grade 3 renal toxicity occurred. All patients completed their planned NAC regimen, except for one patient (DD-MVAC arm) who discontinued due to Grade 3 renal toxicity. ***Conclusion:*** In our small cohort, both NAC regimens induced significant toxicity. DD-MVAC appeared associated with higher rates of severe neutropenia and mucositis compared to GC. These findings, although limited by sample size, underscore the need for vigilant monitoring and proactive toxicity management for both regimens in our setting, potentially favoring GC in patients perceived as more vulnerable to DD-MVAC toxicities.

Keywords: Muscle-Invasive Bladder Cancer, Neoadjuvant Chemotherapy, Gemcitabine, Cisplatin, Dose-Dense MVAC, Toxicity.

INTRODUCTION

Bladder cancer is a common malignancy, and muscle-invasive bladder cancer (MIBC) requires aggressive multimodal management [1]. Neoadjuvant chemotherapy (NAC) followed by radical cystectomy is the standard of care for eligible patients with MIBC, providing an absolute overall survival benefit of 5-8% at 5 years compared to cystectomy alone, as demonstrated by large meta-analyses [2, 3].

Cisplatin-based combination chemotherapy is the cornerstone of NAC. Historically, the MVAC regimen (Methotrexate, Vinblastine, Doxorubicin, Cisplatin), administered over 28 days, was the reference standard [1]. Subsequently, the combination of Gemcitabine and Cisplatin (GC), administered over 21 days, emerged as an alternative, demonstrating similar efficacy to classic MVAC in the metastatic setting but with a generally more favorable toxicity profile, notably less myelosuppression and mucositis [4, 5]. More recently, the dose-dense MVAC (DD-MVAC) regimen,

***Corresponding Author:** Touimri Youssef
Department of Medical Oncology, Moulay Ismail Military Hospital of Meknes, Morocco

administered every 14 days with mandatory granulocyte colony-stimulating factor (G-CSF) support, was developed [6].

In the neoadjuvant setting, both GC and DD-MVAC are now widely used options [7]. Studies like that by Fransen van de Putte et al. have retrospectively compared DD-MVAC, classic MVAC, and GC, finding similar pathological complete response (pCR) rates and overall toxicity rates between DD-MVAC (29%) and GC (32%) [8]. However, specific toxicity profiles may differ, and real-world data, particularly from diverse healthcare settings, remain valuable.

The objective of this study was to retrospectively evaluate and compare the toxicity profiles of NAC using GC versus DD-MVAC in patients treated for MIBC at the Medical Oncology Department of the Moulay Ismail Military Hospital in Meknes, Morocco, and to compare these findings with the established literature.

MATERIALS AND METHODS

Study Design and Population

We conducted a single-center retrospective study. We reviewed the medical records of all patients diagnosed with MIBC who received NAC at the Medical Oncology Department, Moulay Ismail Military Hospital, Meknes, Morocco, between January 2020 and December 2023 (*Corrected Date*). Patients were included if they had histologically confirmed urothelial carcinoma of the bladder, stage cT2-T4a N0 M0 or cTany N1-3 M0, were deemed fit for cisplatin-based chemotherapy (ECOG performance status 0-1, adequate renal function [creatinine clearance >50-60 mL/min], adequate cardiac and hematologic functions), and had received at least one cycle of GC or DD-MVAC as curative-intent NAC before planned local treatment (cystectomy or radiotherapy). Patients receiving chemotherapy for metastatic disease or with palliative intent were excluded. The total population was 21 patients.

Chemotherapy Regimens:

- GC (n=14): Gemcitabine 1000 mg/m² intravenously (IV) on days 1 and 8, and Cisplatin 70 mg/m² IV on day 1, repeated every 21 days.
- DD-MVAC (n=7): Methotrexate 30 mg/m² IV on day 1, Vinblastine 3 mg/m² IV on day 2, Doxorubicin 30 mg/m² IV on day 2, and Cisplatin 70 mg/m² IV on day 2, repeated every 14 days. Prophylactic G-CSF (e.g., Pegfilgrastim or daily Filgrastim) was routinely administered 24-48 hours after chemotherapy completion, consistent with standard practice for this regimen.
- The planned number of cycles was typically 3-4 for GC and 4 for DD-MVAC.

Data Collection and Toxicity Assessment:

Data were extracted from patient records, including baseline demographic, clinical, and pathological characteristics, chemotherapy regimen received, number of cycles administered, and adverse events (AEs). Toxicities occurring between the start of NAC and the planned start of local therapy (or treatment discontinuation) were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 5.0. We focused on grade ≥3 toxicities and specific AEs of interest (e.g., febrile neutropenia, renal toxicity).

Statistical Analysis:

Due to the small sample size, analyses were primarily descriptive. Frequencies and percentages were calculated for categorical variables (e.g., types and grades of toxicity). Means and standard deviations (or medians and ranges) were used for continuous variables (e.g., age). Data were tabulated, and comparisons between the GC and DD-MVAC groups were made descriptively.

RESULTS

Patient Characteristics:

A total of 21 patients met the inclusion criteria: 14 received GC and 7 received DD-MVAC. Baseline characteristics are summarized in Table 1. The groups were small but appeared broadly similar in terms of age distribution and performance status.

Table 1: Patient Characteristics

Characteristic	GC Group (n=14)	DD-MVAC Group (n=7)
Mean Age (years)	56	53
Sex (Male/Female)	11 / 3	6 / 1
ECOG Performance Status 0/1	14 (100%)	7 (100%)
Clinical T Stage (T2/T3/T4a)	4 / 7 / 3	1 / 2 / 4
Clinical N Stage (N0/N+)	4 / 10	1 / 6

Treatment Administration: All patients completed their neoadjuvant chemotherapy protocol, except for one patient due to grade 3 renal toxicity.

Toxicity: The incidence of grade ≥3 toxicities is presented in Table 2, and specific adverse events are detailed in Table 3.

Table 2: Grade ≥ 3 Toxicities by Regimen

Toxicity	GC Group (n=14)	DD-MVAC Group (n=7)
Hematologic		
Neutropenia	3 (21.4%)	3 (42.9%)
Anemia	2 (14.3%)	1 (14.3%)
Thrombocytopenia	1 (7.1%)	0 (0%)
Non-Hematologic		
Mucositis/Stomatitis	0 (0%)	2 (28.6%)

Table 3: Specific Adverse Events of Interest

Adverse Event	GC Group (n=14)	DD-MVAC Group (n=7)
Febrile Neutropenia	0 (0%)	2 (28.6%)
Renal Toxicity (G1-2)	3 (21.4%)	2 (28.6%)
Renal Toxicity (G3-4)	0 (0%)	1 (14.3%)
Nausea/Vomiting (G≥2)	4 (28.6%)	4 (57.1%)
Fatigue (G≥3)	3 (21.4%)	3 (42.9%)

KEY OBSERVATIONS

Hematologic Toxicity:

Grade ≥3 neutropenia was the most frequent severe toxicity, observed in 21.4% of GC patients and 42.9% of DD-MVAC patients. Febrile neutropenia occurred only in the DD-MVAC group (2 patients, 28.6%). Grade ≥3 anemia was seen in 14.3% of patients in each group. Grade ≥3 thrombocytopenia was infrequent (7.1% in the GC group, 0% in the DD-MVAC group).

Non-Hematologic Toxicity:

Grade ≥3 mucositis was notable in the DD-MVAC group (28.6%) but absent in the GC group. Grade 1-2 renal toxicity was observed in both groups (GC 21.4%, DD-MVAC 28.6%). One case of Grade 3 renal toxicity occurred in the DD-MVAC arm (14.3%), leading to treatment discontinuation. Significant nausea/vomiting (Grade ≥2) was reported in 28.6% of GC patients and 57.1% of DD-MVAC patients. Grade ≥3 fatigue was reported in 21.4% of GC and 42.9% of DD-MVAC patients.

DISCUSSION

This retrospective study provides insight into the toxicity associated with two standard NAC regimens, GC and DD-MVAC, for MIBC within a Moroccan medical oncology center. Our findings confirm that both regimens carry a significant risk of adverse events, consistent with the general literature [4, 5, 6, 8, 9, 10].

In our cohort of 21 patients, DD-MVAC (n=7) appeared associated with a higher incidence of grade ≥3 neutropenia (42.9%) and mucositis (28.6%) compared to GC (n=14) (21.4% and 0%, respectively). The occurrence of febrile neutropenia (28.6%) exclusively in the DD-MVAC arm, despite mandatory G-CSF support, is noteworthy, although the absolute number is small (2 patients). This contrasts somewhat with the results from the larger study by Fransen van de Putte et al. [8], where DD-MVAC, despite a 7.6% rate of febrile neutropenia, had an overall G3-4 toxicity rate (31.6%) similar to GC (43.6%). The pivotal trial by Sternberg *et al.*, in the metastatic setting even showed significantly less febrile neutropenia with DD-MVAC (10%) compared to classic MVAC (26%) [6]. The higher rates of neutropenia and mucositis observed in our DD-MVAC group compared to these larger studies could be due to several factors: the very small sample size (especially n=7) leading to unstable estimates, potential differences in patient baseline characteristics or comorbidities not fully captured, variations in supportive care practices beyond G-CSF, or inherent population differences in drug metabolism or tolerance.

The toxicity profile observed for GC in our study (e.g., 21.4% G≥3 neutropenia, 14.3% G≥3 anemia) reasonably aligns with rates reported in large phase III trials like that by von der Maase et al. (G3/4 neutropenia 41%, anemia 8%, thrombocytopenia 8% in the GC arm) [5]. The rate of 21.4% grade 1-2 renal toxicity in the GC group and 28.6% in the DD-MVAC group (with one G3 event) underscores the nephrotoxic potential of cisplatin, requiring careful patient selection, hydration protocols, and monitoring [11].

The comparison with the study by Fransen van de Putte *et al.*, [8] remains relevant. Although they found similar overall G3-4 toxicity rates between DD-MVAC and GC, they noted specific differences. Our study, despite its limitations, suggests potentially higher myelosuppression and mucositis with DD-MVAC in our patient population.

The choice between GC and DD-MVAC for NAC often involves balancing efficacy, toxicity, and logistical factors. While efficacy in terms of pCR appears similar between the two regimens in larger studies [8, 12], the perceived or experienced toxicity profile may influence physician and patient preference. Our local experience, though limited, suggests that DD-MVAC might be more challenging to manage in terms of hematologic toxicity and mucositis.

LIMITATIONS

This study has significant limitations inherent to its design. It is retrospective, conducted at a single center, and includes a very small number of patients (N=21), particularly in the DD-MVAC arm (n=7). Toxicity data collection relied on chart review. This limits the generalizability of the findings and precludes any meaningful statistical comparison.

CONCLUSION

Within the limitations of this small, single-center retrospective study, both GC and DD-MVAC neoadjuvant chemotherapy regimens demonstrated significant toxicity in patients with MIBC treated at our institution. Our preliminary data suggest that DD-MVAC might be associated with higher rates of severe neutropenia and mucositis compared to GC in our patient population. Febrile neutropenia remains a concern with DD-MVAC despite G-CSF support. One case of Grade 3 renal toxicity led to DD-MVAC discontinuation. These findings highlight the critical need for careful patient selection, close monitoring, and proactive management of adverse events when administering NAC for MIBC.

Conflict of Interest: The authors declare no conflicts of interest.

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