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Real-Life Experience with Neo-Adjuvant Chemotherapy in Muscle Invasive Bladder Cancer and Its Outcome

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Abstract

Objectives: Muscle-invasive bladder cancer (MIBC) has a poor prognosis with a 5-year overall survival rate of 50%. Current guidelines recommend the use of neoadjuvant chemotherapy (NAC) followed by radical cystectomy in these patients. However, its application remains limited and underutilized in clinical practice. This study aims to delineate, in real-life practice, the clinical characteristics and outcomes of patients with muscle-invasive bladder cancer (MIBC) who received NAC and were subsequently candidates for cystectomy. **Methods:** This study is a retrospective observational analysis of patients with muscle-invasive bladder cancer (stages T2-T4aN0M0 and T1-T4aN1M0) who received neoadjuvant chemotherapy prior to total cystectomy. The data, collected over a six-year period from 2018 to 2024, originates from Hotel Dieu de France University Hospital in Beirut. Various factors were analyzed, including age, sex, history of smoking, stage of disease at diagnosis, presence of carcinoma *in situ* (CIS), and any prior history of Bacillus Calmette-Guérin (BCG) treatment or T1 or Ta disease. Additionally, the study evaluates renal function prior to neoadjuvant chemotherapy (NAC), specifies the type and number of chemotherapy cycles administered, the pathological complete response (pCR) following cystectomy and calculate both overall survival and disease-free survival rates. **Results:** A total of 36 patients were analyzed, with a median age of 71.6 years. 77.7% were male, 22.2% were female, and 77.8% were smokers. 55.6% of the patients presented with *de novo* muscle-invasive bladder cancer (MIBC), 44.4% had a history of Ta or T1 stage tumors and 100% had urothelial histology and lower tract location. Among these 36 patients, 27.8% had received intravesical Bacillus Calmette-Guérin (BCG) treatment, while 72.2% did not. 86.1% of patients had a creatinine clearance greater than 60, whereas

13.9% had a clearance below 60 but still above 50. At the time of diagnosis, 61.1% were at stage II, 13.9% were at stage IIIa, and 25.0% were at stage IIIb. All the patients received the combination of gemcitabine and cisplatin with a median number of 3.9 cycles per patient. Out of the 36 patients, 5 experienced disease progression and did not undergo radical cystectomy, while another 5 opted for trimodal therapy (TMT) after evaluation by cystoscopy showing no residual lesion. The remaining 26 patients proceeded with radical cystectomy. Among these 26 cystectomized, 30.8% demonstrated a complete pathological response. During the follow-up period, 75% of these 36 patients did not experience disease progression, with a median disease-free survival of 9.5 months and a mean disease-free survival of 19.72 months. No deaths were recorded in this study, and overall survival data could not be determined. **Conclusion:** In our real-world experience, approximately one-third of patients who received gemcitabine and cisplatin NAC followed by radical cystectomy achieved a pathological complete response. Extended follow-up is necessary to assess long-term outcomes, including median overall survival. Future research should focus on investigating and comparing between triple modality therapy and cystectomy, both after neoadjuvant chemotherapy.

Keywords

Bladder Cancer, Muscle Invasive, Cystectomy, Neoadjuvant Chemotherapy, Trimodality Therapy

1. Introduction

Bladder cancer is not a rare disease, with estimated new cases in 2023 of 82,290 (n = 62,420 in men and n = 19,870 in women) and 16,710 deaths (about 12,160 in men and 4550 in women) [1]. Bladder cancer has one of the highest incidence rates in Lebanon, it accounts for 9% of all newly diagnosed cancers, it is ranked second in males and ninth in females [2]. Bladder cancer may present as painless hematuria or irritative urinary symptoms, and it is typically diagnosed via transurethral resection of bladder tumor (TURBT). The most frequent pathologic type is transitional or urothelial carcinoma [3], which is most associated with smoking. Additional risk factors include industrial exposures, chronic catheters, and chronic bladder infections, including schistosomiasis in endemic areas.

Muscle-invasive bladder cancer (MIBC) is a common and deadly disease, but potentially curable if treated promptly. It has a poor prognosis with a 5-year overall survival (OS) of 50%. Staging for patients with MIBC includes a CT scan of the abdomen and pelvis, chest imaging, and, if clinically indicated, a bone scan. FDG PET can be used to rule out distant metastases, but since FDG is excreted through the urinary tract, it is less helpful for evaluating bladder masses, local extension, and local nodal involvement [4].

The therapeutic goal in MIBC is to maximize the chance of cure by using a multimodality approach including primary chemotherapy followed by surgery or

by bladder preservation therapy, called the trimodality therapy (TMT) [5]-[7]. Bladder preservation therapy may be considered in selecting patients, who are usually unfit for surgery or who refused cystectomy, using the TMT approach: maximal TURBT followed by concurrent chemotherapy and pelvic radiotherapy (RT) [8].

Neoadjuvant chemotherapy (NAC) is recommended for patients with MIBC who are eligible for cisplatin-based therapy and cystectomy. Radical cystectomy after four cycles of cisplatin-based NAC is considered the classical standard approach in MIBC [1].

Despite the standardization of MIBC approach for decades, the NAC procedure remains shy and under used in reel-life practice [9]. Characterization of NAC-treated patients as well as their clinical outcomes in daily practice needs to be repeatedly reviewed and reported accordingly. The objective of this study is to describe the clinical characteristics and outcomes of patients with MIBC treated by NAC who were candidates for cystectomy in our University Hospital during the last six years.

2. Patients and Methods

2.1. Data Source and Patients' Population

It is a retrospective observational study collecting data of muscle invasive bladder cancer patients who received NAC before a planned total cystectomy, during a 6-year period (2018-2024), at Hotel Dieu de France University Hospital, Beirut, which is a tertiary medical center serving around 20% of the Lebanese population. The approval of the ethical committee CeHDF was obtained under number 2337.

2.2. Inclusion and Exclusion Criteria

2.2.1. Inclusion Criteria

- Patients are diagnosed with MIBC with or without local lymph node involvement. (T2-T4a, N1-3, M0)
- Patients treated with neoadjuvant chemotherapy prior to radical cystectomy.
- Diagnosis between 2018 and 2024.
- Absence of metastases at the time of diagnosis.
- Absence of another malignancy.

2.2.2. Exclusion Criteria

- Metastatic bladder cancer at the time of diagnosis.
- Absence of muscle invasion.
- Patients not treated with chemotherapy before radical cystectomy.
- Diagnosis before 2018 or after 2024.

Included patients are those diagnosed with MIBC with or without clinical local lymph node enlargement (T2-T4a, N1-3, M0), in the absence of distant metastases and other previous history of cancer disease. Those patients were treated with NAC prior to a prescheduled radical cystectomy.

Patient characteristics are selected from hospital files, pathology reports and documents from private oncology clinics if needed. These variables were collected: sex, age, year of diagnosis, tobacco consumption, renal function, previous history of T1 - Ta, history of BCG therapy, staging at diagnosis, presence of carcinoma-*in-situ*, type of chemotherapy, pathology results at assessment and at cystectomy (Table 1). All patients were followed until death or till July 2024, the final date of analysis.

The primary objective of this study is to investigate the characteristics and outcomes of patients diagnosed with muscle-invasive bladder cancer (MIBC) who were candidates for cystectomy following NAC. Secondary objectives include reasons for skipping cystectomy, if it was not performed, the pathological findings from cystectomy specimens, disease-free survival (DFS) and overall survival (OS).

2.3. Statistical Analysis

We performed descriptive statistics on the clinical characteristics of the patients included in this study. Patient characteristics are presented as mean and standard deviation (SD) in the case of continuous data, and absolute and relative frequencies in the case of categorical data. To investigate the association between categorical variables, we employed Fisher's exact test due to its suitability for small sample sizes. A p-value of <0.05 was considered statistically significant. Disease-free survival (DFS) was estimated using the Kaplan-Meier method. The survival curves were plotted to visualize the DFS distributions. The analyses were performed using R statistical software version 4.1.2 (packages prettyR and survival).

3. Results

During the last 6 years period, 36 patients were identified with MIBC who received NAC followed by either cystectomy or bladder preservation therapy. The mean age of the patients is 71.64 years with a standard deviation of 7.93. The gender distribution shows 28 males (77.8%) and 8 females (22.2%). Among these patients, 28 (77.8%) have a history of smoking, and 8 (22.2%) do not. 16 patients (44.4%) have a history of Ta or T1 stage tumors, while 20 (55.6%) were diagnosed *de novo* as MIBC. 10 patients (27.8%) had carcinoma *in situ* (CIS), while 26 patients (72.2%) did not. At diagnosis, 22 patients (61.1%) were at stage II, 5 patients (13.9%) at stage IIIa, and 9 patients (25.0%) at stage IIIb. Histologically, 27 patients (75.0%) have urothelial tumors, 2 (5.6%) have sarcomatoid components, 6 (16.7%) have epidermoid components, and 1 (2.8%) has a neuroendocrine component (Table 1). Renal function data shows 31 patients (86.1%) with clearance greater than 60, and 5 patients (13.9%) with clearance between 50 and 60. Out of all the patients, 10 (27.8%) have received intravesical BCG treatment, whereas 26 (72.2%) have not.

All the patients in the study were treated using the association Gemzar + Cisplatin rather than ddMVAC (dose dense MVAC). 2 patients (5.6%) had less than 4 cycles considering that the treatment is still in progress, and 34 patients (94.4%)

Table 1. Patients characteristics.

Patient characteristics (N = 36)	
Age, mean (SD)	71.64 (7.93)
Gender	No. (%)
Male	28 (77.8)
Female	8 (22.2)
History of smoking	No. (%)
Yes	28 (77.8)
No	8 (22.2)
History of Ta or T1	No. (%)
Yes	16 (44.4)
No	20 (55.6)
History of BCG	No. (%)
Yes	10 (27.8)
No	26 (72.2)
Staging at diagnosis	No. (%)
Stage II	22 (61.1)
Stage IIIa	5 (13.9)
Stage IIIb	9 (25.0)
Renal function	No. (%)
Clearance >60	31 (86.1)
Clearance <60 and >50	5 (13.9)
Number of cycles	No. (%)
<4 cycles	2 (5.6)
4 cycles	34 (94.4)
Presence of CIS	No. (%)
Yes	10 (27.8)
No	26 (72.2)
Chemotherapy toxicities	No. (%)
no	22 (61.1)
Nausea/vomiting	10 (27.8)
Acute renal impairment	3 (8.3)
Deep vein thrombosis	1 (2.8)
Histological type	No. (%)
Urothelial	36 (100.0)
Sarcomatous component	2 (5.6)
Epidermoid component	6 (16.7)
Neuroendocrine component	1 (2.8)
Surgical procedures	No. (%)
TMT	5 (13.8)
Radical cystectomy	26 (72.2)
Residual disease post cystectomy	No. (%)
Absence residual disease	8 (30.8%)
Presence of residual disease	16 (61.5%)
Presence of CIS	2 (7.7%)

completed all 4 cycles (median number of 3.9 cycles per patient). Chemotherapy toxicity was observed only in 14 patients, with 10 experiencing nausea/vomiting (27.8%), 3 acute renal impairment (8.3%), and 1 deep vein thrombosis (2.8%). There was no chemotherapy related alopecia.

8 patients (22.22%) were assessed by TURB before radical cystectomy, 7 of which (87.5%) showed no residual disease, while one patient (12.5%) showed residual disease. 3 out of the 7 patients with pCR on cystoscopy opted for TMT.

A surgical removal of the bladder (radical cystectomy) was performed in 26 patients (72.22%). 5 patients (13.88%) went through TMT (Two of these patients are over 80 with comorbidities and they did not consent to the surgery, and the three other patients declined the cystectomy in favor of TMT, particularly after achieving a complete pathological response on cystoscopy, as they are concerned about the potential complications of the surgery). The other 5 patients (13.88%) showed signs of progression on CT scan after completing four cycles of chemotherapy and subsequently moved on to a different type of treatment.

After cystectomy, among the 26 patients, 8 patients (30.8%) showed an absence of residual disease, 16 patients (61.5%) had the presence of residual disease, and 2 patients (7.7%) were found to have carcinoma *in situ* (CIS). All patient characteristics are summarized in Table 1.

Disease-free survival ranges from 2 to 67 months, with a median of 9.5 months. Most patients (75%) did not experience disease progression or death during the study period (censored). Only 22.22% of patients experienced disease progression or death, as indicated by the mean status of 0.2222 and the maximum value of 1. With a median DFS of 9.5 months and a mean of 19.72 months, these findings suggest a generally positive response, with some patients having notably extended periods without disease progression (Figure 1).

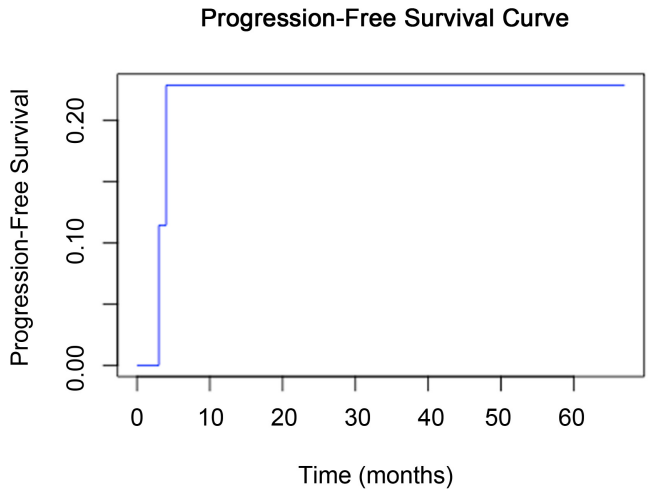

Figure 1. Progression free survival.

After performing Fisher's exact tests to evaluate the associations between several pairs of qualitative variables, results indicate that none of the tested associations

are statistically significant at the 5% level (Response to NAC and histological type: p-value = 0.6537. Response to NAC and presence of CIS: p-value = 0.4423. Response to NAC and history of BCG: p-value = 0.1991. Response to NAC and staging at diagnosis: p-value = 0.6158. Histological type at diagnosis and histology of residual disease post-cystectomy: p-value = 1).

4. Discussion

Bladder cancer incidence is 3 to 4 times higher in men compared to women, with a median age at diagnosis of 73 years [7]. Cigarette smoking is strongly linked to an increased risk of bladder cancer in both men and women. In the United States, the risk of developing bladder cancer among former and current smokers has risen compared to never smokers. Although quitting smoking is associated with a reduced risk, former smokers still face an elevated risk compared to those who have never smoked, even after more than a decade of cessation [8]. In our study, the median age of patients was 71.64 years, which is close to the global median, and the incidence among men was 3.5 times higher than that among women. Additionally, 77.8% of our patients had a history of smoking.

Urothelial carcinoma can occur throughout the urinary tract, with over 90% of these tumors originating in the bladder. Mixed histology lesions typically represent variants of urothelial carcinoma, including micropapillary, sarcomatoid, rhabdoid, and plasmacytoid forms. In the United States, urothelial carcinoma accounts for 92% of lower urinary tract tumors, while squamous cell carcinoma makes up 5%, adenocarcinoma 2%, and small-cell carcinoma 1%. In our study, all the tumors are located in the lower tract, all the tumors were urothelial, 5.6% had sarcomatoid components, 16.7% had squamous components, and 2.8% had neuroendocrine features. The high percentage of squamous components in our cohort may suggest a possible association with infection, although none of our patients had a history of schistosomiasis. Squamous cell carcinoma (SCC) is classified into two subtypes: bilharzial-associated SCC (B-SCC), linked to schistosomiasis, and non-bilharzial-associated SCC (NB-SCC). These subtypes differ in their epidemiology, natural history, and clinicopathological characteristics [1]. B-SCC is predominantly found in areas where schistosomiasis is endemic, such as the Middle East, Southeast Asia, and South America [9]-[11].

Cisplatin-based NAC has been widely used in MIBC, with the combination of cisplatin and gemcitabine being the most administered and the most preferable regimen. In our study, all patients were treated with the gemcitabine and cisplatin regimen. The VESPER clinical trial compared the efficacy of 6 cycles of dose-dense MVAC (ddMVAC) with 4 cycles of gemcitabine and cisplatin (GC), showed that fewer patients completed all 6 cycles of ddMVAC compared to GC. However, at the 3-year mark, progression-free survival (PFS) was 64% in the ddMVAC group versus 56% in the GC group. Additionally, the cumulative cisplatin dose and associated side effects were higher in the ddMVAC group compared to the GC regimen [12]. The most frequently reported side effects of NAC include anemia

(8%), nausea and vomiting (3%), and asthenia/generalized weakness (4%) [13]. In our study, chemotherapy toxicity was observed in 14 patients: 10 experienced nausea/vomiting (27.8%), 3 had acute renal impairment (8.3%), and 1 developed deep vein thrombosis (2.8%). The relatively high incidence of nausea and vomiting is likely attributed to non-compliance with medication. However, among the 14 patients, there was only a treatment delay in 2 patients, without any treatment discontinuation.

Although NAC can achieve a complete response in some patients, radical cystectomy is currently recommended for all individuals with MIBC to evaluate or confirm pathological responses and to remove any residual disease. While combining chemotherapy with cystectomy improves overall survival (OS), relying solely on chemotherapy for bladder preservation presents challenges, as it is difficult to definitively determine which bladders are entirely free of residual tumors. Pathological complete response (CR) rates after NAC and at the time of cystectomy range from 20% to 40%. Consequently, chemotherapy alone cannot replace the definitive treatment of bladder cancer provided by surgery or radiation therapy (RT). However, some patients are either ineligible for cystectomy due to medical comorbidities or prefer a bladder-sparing approach. For appropriately selected patients, TMT, which includes transurethral resection (as complete as safely possible), followed by definitive RT plus radio sensitizing chemotherapy, has achieved long-term disease-free survival (DFS) and OS rates comparable to those seen with radical cystectomy [13]. TMT is now recommended as a category 1 option in the NCCN guidelines, alongside cystectomy. In our study, 13.8% of patients underwent TMT using 20 mg/m^2 weekly cicpaltin as radiosensitizer, while 72.2% had radical cystectomy. Three out of the 5 patients who chose TMT had a complete response on cystoscopy after 4 cycles of chemotherapy and opted to forgo cystectomy in favor of TMT.

According to the literature, Pathological complete response (pCR) rates following NAC at the time of cystectomy typically range from 20% to 40% [1]. In our study, among patients undergoing cystectomy, 30.8% had pCR, 61.5% had residual disease, and 7.7% were found to have carcinoma *in situ* (CIS).

The survival benefit of neoadjuvant MVAC chemotherapy is associated with tumor downstaging to pT0, which corresponds to an 85% 5-year survival rate for patients who achieve a pathological CR. A meta-analysis of neoadjuvant chemotherapy demonstrated a significant overall survival (OS) benefit with platinum-based combination regimens, showing a 14% reduction in the risk of death and a 5% absolute survival benefit at 5 years (with OS increasing from 45% to 50%) [14]. In our study, 75% of patients did not experience disease progression or death during the follow-up period. Only 22.22% of patients experienced disease progression or death, as reflected by the mean status of 0.2222 and the maximum value of 1. These results suggest that most patients did not experience disease progression or death during the study period. The median progression-free survival was 9.5 months, with a mean of 19.72 months, indicating an overall favorable response to

treatment, with some patients experiencing notably extended periods without disease progression. The overall survival was not reached in this study, as no deaths occurred during the follow-up period.

The interaction results of our study indicate that none of the tested associations are statistically significant at the 5% level. A 2017 cohort study also found no significant association between CIS status at diagnosis or patients who had a history of BCG treatment and the response to NAC [15]. Furthermore, a review of patients who underwent radical cystectomy (RC) for clinical T2-3 muscle-invasive bladder cancer (MIBC) from 2005 to 2018 indicated that patients could be stratified into high-risk (e.g., lymphovascular invasion, variant histology, hydronephrosis, clinical T3b) versus low-risk (no risk factors) groups, and into progressive MIBC (≤pT1 treated with at least induction BCG who progressed to ≥cT2) versus *de novo* MIBC. The study found that treatment with NAC led to comparable pathological responses and survival outcomes in both *de novo* and progressive MIBC cases treated with BCG [16].

In a population-based analysis involving 1175 patients, the prognosis for MIBC patients receiving NAC followed by radical cystectomy (NAC + RC) was found to be superior compared to those receiving TMT [17]. Additionally, a macro-microstimulation model constructed with TreeAge Pro, analyzing outcomes for 500,000 patients with newly diagnosed MIBC, indicated that younger patients who underwent RC had a greater quality-adjusted life expectancy (QALE) and longer life expectancy (LE) compared to those treated with TMT. Conversely, elderly patients had better outcomes with TMT. Overall, 39.4% of patients undergoing TMT experienced bladder recurrence [18].

A retrospective cohort study of 140 patients, published in January 2024, investigated the demographic and clinical profiles, neoadjuvant treatment patterns, and clinical outcomes among patients with muscle-invasive bladder cancer (MIBC) undergoing RC with NAC. The study found that cisplatin-based NAC, particularly the combination of cisplatin and gemcitabine, was widely used. Notably, approximately one-third of patients who received neoadjuvant treatment followed by RC achieved a pCR [19]. Research indicates that patients who achieve pCR after NAC for MIBC tend to have favorable cancer-specific survival (CSS) and overall survival (OS). As the number of patients receiving NAC increases, and with about 40% achieving pCR at RC, there is growing interest in bladder preservation strategies. However, clinical decision-making should be guided by accurate clinical staging, recognizing the discrepancy between clinical complete response (cCR) and pCR. There is currently insufficient evidence to justify changing NAC protocols based solely on cCR. Although local treatment options are evolving, bladder-preserving protocols (BPPs) for patients with cCR post-NAC should be applied cautiously due to potential staging inaccuracies and the risk of micro-metastases.Vigilant monitoring and salvage cystectomy remain essential for managing recurrence [20].

Our study represents a real-life experience of NAC in MIBC and its outcome,

with several limitations due to its retrospective design and the small sample size, also the patient population treated at Hotel-Dieu De France hospital may not fully represents the broader population. Future prospective trials are needed to evaluate bladder preservation strategies after cisplatin-based NAC, with an emphasis on standardizing restaging procedures and validating molecular diagnostics to assess NAC response comprehensively. Ongoing clinical trials aim to clarify these approaches and may potentially shift MIBC treatment paradigms if favorable outcomes are demonstrated using clinical, radiological, and molecular criteria.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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