Clinico-Epidemiological Study on Neoadjuvant Chemotherapy Followed by Chemoradiotherapy in Muscle-Invasive Bladder Cancer at Assiut University Hospital

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Abstract

Background:

Radical cystectomy is reference management of muscle-invasive bladder cancer (MIBC), with a reduced quality of life after cystectomy.

Our study aimed to assess the efficacy of neoadjuvant chemotherapy (NAC) followed by concurrent chemoradiotherapy (CCRTH).

Patients and Methods:

Our study was conducted at Assiut University Hospital's Clinical Oncology Department from 2015 to 2019. The study was approved by the Ethical Committee at the Faculty of Medicine, Assiut University (IRB17101267). Data were extracted from the medical records of 36 patients with pathologically confirmed MIBC (cT2-T4a N0M0) treated by 3 cycles of NAC (cisplatin/gemcitabine); responders underwent maximum transurethral resection of the bladder tumor (MTURBT) followed by chemoradiotherapy (60-66 Gy) over 6-weeks with concurrent weekly cisplatin at 40 mg/m2.

Results:

The mean age was 61, with a male predominance of (92%). Smoking was the most common risk factor (72%). 53% were Stage III, followed by (47%) Stage II. Evaluation of treatment response in 29 patients with an overall response rate of (76%); recurrence was observed in (24%), mainly distant recurrence in (17%).

The most common adverse events of NAC were grade 1 and 2 bone marrow suppression in (46%) of patients, followed by gastrointestinal disorder in (33%).

In CCRT, less treatment toxicity was observed, mainly grade 1-2 gastrointestinal disorders (42%), followed by cystitis (41%).

Median DFS was 37 months, and the significant prognostic variables for DFS in a multivariate analysis were patients aged≥65 (HR=9.9) and non-responders to treatment (HR=7). The median overall survival (OS) was 48 months. Significant prognostic variables included patient age ≥65 (HR=19.4) and non-responders to treatment (HR=5).

Conclusion:

NAC, followed by CCRTH, seems to be a promising treatment option for patients under 65 years of age, responders to treatment who refuse surgery or are medically unfit.

Introduction:

Bladder cancer (BC) ranks as the second most common cancer among Egyptian males (1), with a male-to-female ratio of 4:1 (2). Environmental exposure to various carcinogens is linked to up to 80% of bladder cancer incidences. (3)

The majority of BCs (50%) are caused by tobacco smoke, but the associated risk varies depending on the kind of tobacco and smoking history. (4)
Invasive bladder cancer (MIBC) affects around 30% of people with bladder cancer. (5)

According to reports, 15% to 30% of neoadjuvant chemotherapy patients experience a pathologic complete response (CR), a promising efficacy. (6)

Neoadjuvant chemotherapy (NAC), followed by radical cystectomy (RC), is the currently recommended course of treatment for MIBC. NAC has a 6% greater 10-year survival rate than RC (7), but urine diversion adversely impacts social interaction and quality of life. (8)

Maximum TURBT followed by chemoradiotherapy produced comparable survival outcomes to those of radical cystectomy, potentially improving overall quality of life (QOL). (9)

Our study aimed to assess the efficacy and toxicity of NAC followed by concurrent chemoradiotherapy in MIBC at Assiut University's Clinical Oncology Department from 2015 to 2019.

Patients and Methods:

An evaluation of the effectiveness of three cycles of cisplatin/gemcitabine as a NAC for MIBC (cT2- T4a N0M0) with the absence of carcinoma in situ then followed by concurrent chemoradiation (60–66 Gy) administered over 6 weeks with weekly cisplatin at a dose of 40 mg/m. during the period (2015 – 2019) at Assiut University Hospital.

The ethics committee of Assiut University Hospital approved this protocol before data collection (IRB17101267). Data were extracted from the medical records of 36 patients over 18 years of age diagnosed with pathologically confirmed bladder cancer.

They analyzed patients and tumor characteristics, risk factors, treatment response, and toxicity.

Statistical Analysis:

The data was analyzed using a social science statistical package (IBM-SPSS) version 26.0. Qualitative data were expressed as frequency and percent. The mean or median standard deviation and range were used to define the data as a function of their distribution. The Kaplan-Meier approach was used to test disease-free survival and overall survival using the Log-rank test and Kaplan-Meier curve. A univariate Cox regression analysis was conducted to assess potential prognostic factors for DFS and OS, and relevant variables were included in a multivariate Cox regression analysis. The significance level was set at a P-value of 0.05 while performing a multivariate logistic regression analysis with significant factors included to determine potential predictors for overall response among bladder cancer patients.

Results:

Patient's and Disease Characteristics:

The mean age ± SD of the enrolled patients was 60.64 ± 4.49 years; out of those patients, about 27/36 (75%) were <65 years old, with a male predominance in 33 (92%) of patients. Smoking was the significant risk factor seen in 26/36 (72%) patients, followed by bilharziasis in 10 (28%) patients. The most common presenting complaints were hematuria in 32 out of 36 cases (89%) and dysuria in 27 out of 36 cases (75%). All cases were diagnosed as transitional cell carcinoma (TCC). Stage III was in 19/36 (53%) of patients, followed by Stage I in 17/36 (47%) of patients (Table 1).

Treatment Response and Pattern of Recurrence:

Evaluation of treatment response in 29 patients (as 4 missed and 3 died) with an overall response rate of 22/29 (76%), mainly CR in 21/29 (72%), DP occurring in 7/29 (24%).

Recurrence was observed in 7/29 (24%) of patients, mainly distant in 5/29 (17%) of patients (mainly non-regional lymph node in 2 (7%) of patients, and bone in 2 (7%) of patients (Table 2).

Patients who did not respond to trimodality protocol and developed metastasis were switched to second-line systemic treatment.

Treatment Toxicity:

The majority of adverse effects associated with neoadjuvant chemotherapy (NAC) and chemoradiotherapy (CRT) were grade 1 or 2. The most common adverse effect of NAC and CRT was bone marrow suppression, observed in 13 out of 29 patients (46%), followed by gastrointestinal disorders such as nausea, vomiting, and diarrhea, experienced by 10 out of 29 patients (33%). Five patients (17%) experienced grade 3 toxicity, either bone marrow suppression or gastrointestinal disorders, leading to dose reduction of chemotherapy according to CTCAE version 5 criteria.

Regarding CRT, fewer treatment-related toxicities were observed, with gastrointestinal disorders being the most common, affecting 12 out of 29 (42%), followed by urological disorders in 12 out of 29 patients (41%) (Table 3).

Prognostic Factors Related to Disease-Free Survival (DFS):

The median DFS in all patients was 37 months. The significant prognostic factors linked to DFS by univariate Cox regression analysis were patients ≥65 were 5.5 times more hazardous than <65 (HR= 5.5), non-responded to treatment were 8 times more hazardous than responder (HR=8), patients with recurrence were 4.5 times hazardous than non-recurrent (HR=4.5).

These significant variables were entered into **a multivariate Cox logistic regression** model, and the significant prognostic variables were patients ≥65 (HR=9.9) and non-responders to treatment (HR=7) (Table 4).

Prognostic Factors Related to Overall Survival (OS):

Median OS in all patients was 48 months and was significantly higher among patients <65, stage II of the tumor who responded to treatment, and patients with no recurrence.

In Univariate Cox Regression Analysis, the significant prognostic factors associated with OS were patients ≥65 were 6 times more hazardous (HR= 6), stage III were more hazardous 3 times, non-responded to treatment were 6.8 times hazardous (HR=6.8), patients with recurrence were 3.3 times hazardous (HR=3.3).

These significant variables were entered in a **multivariate Cox** logistic **regression** model, and the significant prognostic variables were patients ≥65 (HR=19.4) and non-responders to treatment (HR=5) (**Figure 1).**

Table 1: patients and tumor characteristics

Variable	N=36 (%)
Age (years):	
Mean ± SD (range)	60.64 ± 4.49 (42-70)
▪ <65	27 (75.0%)
▪ ≥65	9 (25.0%)
Sex:	
▪ Male	33 (91.7%)
▪ Female	3 (8.3%)
Smoking history	
▪ Smoker	26 (72.2%)
▪ Nonsmoker	10 (27.8%)
Bilharziasis	10 (27.8%)
Symptoms	
▪ Hematuria	32 (88.9%)
▪ Dysuria	27 (75.0%)
▪ Frequency	12 (33.3%)
▪ urge incontinence	11 (30.6%)
▪ lower abdominal pain	15 (41.7%)
Clinical stage:	
▪ T2	20 (55.6%)
▪ T3	16 (44.4%)
Staging	
▪ II	17 (47.2%)
▪ III	19 (52.8%)

Data were expressed as frequency and % or mean ± SD.

Table 2: Treatment response and pattern of Recurrence

Variables	N=29* (%)
Response to treatment	
Overall **response rate**	**22 (75.9%**
CR	21 (72.4%)
PR	1 (3.4%)
DP	7 (24.1%)
Recurrence	**7 (24.1%)**
Local	2 (6.9%)
Metastatic	5 (17.2%)
Site of metastasis	
LNs	2 (6.9%)
Bone	2 (6.9%)
Brain	1 (3.4%)

*** Response to treatment and recurrence calculated from patients who completed treatment** (4 missed and 3 died).

Data were expressed as frequency and %

Table 3. Adverse events of Neoadjuvant chemotherapy and Concurrent chemoradiotherapy

NAT adverse events	Total N=29* (%)	Grades 1 or 2	Grades 3
Bone marrow suppression	16/29 (55%)	13/29 (46%)	3/29(9%)
Gastrointestinal disorder	12/29 (41%)	10/29 (33%)	2/29(8%)
CRTH adverse event			
Gastrointestinal disorder	13 /29 (45%)	12/29 (42%)	1/29(3%)
Cystitis	12/29 (41%)	12/29 (41%)	

Data were expressed as frequency and %

Table 4: Prognostic factors related to DFS and OS in patients with cancer bladzer receiving neoadjuvant chemotherapy.

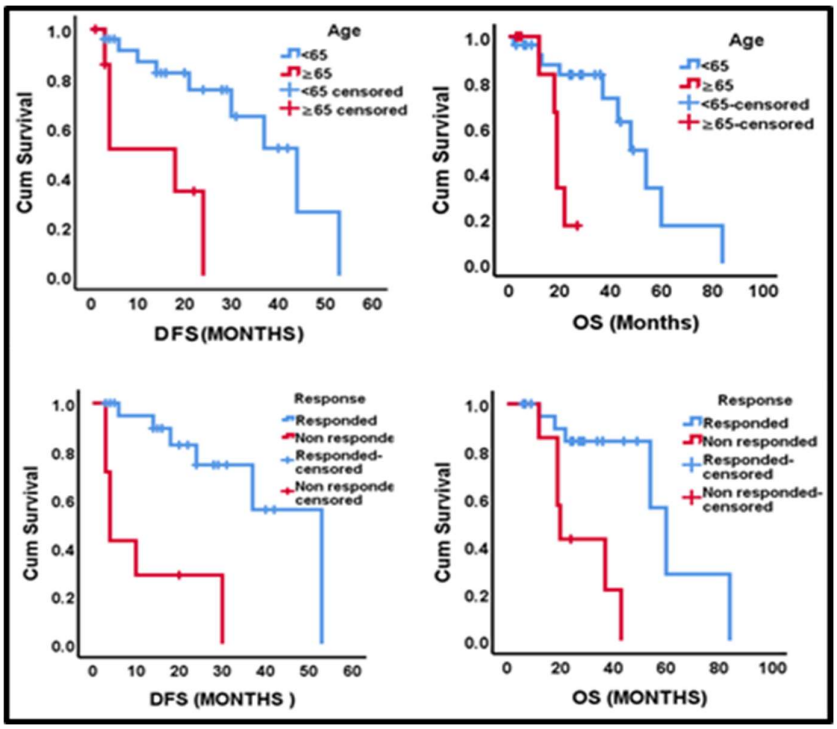
Predictors	DFS				OS			
	Univariate cox reg		Multivariate cox reg		Univariate cox reg		Multivariate cox reg	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age								
▪ <65	**Reference**		**Reference**		**Reference**		**Reference**	
▪ ≥65	**5.5 (1.6-19.2)**	**<0.001**	**9.9 (2.1-49.6)**	**0.005**	**6.1 (1.6-23.47)**	**0.008**	**19.4 (2.8-50.2)**	**0.003**
Staging								
▪ II	**Reference**				**Reference**			
▪ III	2.9 (0.9-9.7)	0.078			3.2 (1.1-10.6)	**0.051**		
Response to TTT.								
▪ Responder	**Reference**		**Reference**		**Reference**		**Reference**	
▪ non-responder	**8.1 (2.2-29.5)**	**0.001**	**7.1 (1.5-33.3)**	**0.014**	**6.8 (1.7-27.1)**	**0.007**	**5.0 (1.1-24.0)**	**0.046**
Recurrence								
▪ Yes	**4.5 (1.3-15.0)**	**0.015**			3.3 (1.1-10.8)	**0.051**		
▪ No	**Reference**				**Reference**			

Cox regression analysis

HR: hazard ratio

95% CI: 95% confidence interval

Figure (1): Kaplan Meier curve for factors associated with DFS and OS



Discussion:

Neoadjuvant chemotherapy (NACT) followed by radical cystectomy (RC) has been established as the preferred therapy for muscle-invasive bladder cancer (MIBC) according to current treatment guidelines. While a phase II trial demonstrated comparable outcomes to RC with the use of NACT before radiotherapy (RT), modern trimodal treatment (TMT) techniques often do not incorporate NACT (10) (11).

The patients in our study had an average age of 61 years, and 81% were male, consistent with the findings t reported by Ferlay J. et al. (2020) (12).

Regarding risk factors, smoking is the main risk factor in 65% of patients, with a lower bilharziasis incidence in 30% of patients, which is comparable to that reported by Amr S. et al. (2012). In contrast, SCC decreased from 78% of diagnosed bladder tumors in 1980 to (27%) of diagnosed bladder tumors, and the incidence of TCC increased from 22% in 1980 to 73% of bladders diagnosed in 2005. (13)

In our study, 88% of patients had hematuria as their primary presenting symptom, which agrees with that reported by Halaseh SA. et al. (2022) (14).

In our study, patients received 3 cycles of cisplatin/gemcitabine as an NAC for MIBC (cT2- T4a N0M0) followed by concurrent chemoradiation (60–66 Gy) administered over 6 weeks with weekly cisplatin at a dose of 40 mg/m.

The overall response rate was 76%, and the best was observed in early-stage patients with significant p-values, which correlates with the finding of Rink M et al. (2012), (15) (16).

NAC grade 3 toxicity, mainly bone marrow suppression or gastrointestinal disorder, was observed in 17% of patients, which is lower than that reported by Meleis L et al., 2020, where 41% (7/17) of the adverse effects were grades 3–4, (17).

The most common adverse events of concurrent chemoradiotherapy CRT were grades 1-2 gastrointestinal disorders, observed in 12 out of 29 patients (42%), followed by cystitis in 12 out of 29 (41%) with no recorded grade 3-4 adverse events. This contrasts with the findings of Ikeda M et al., who reported grade 3 adverse events in 36 patients (83.7%), including neutropenia in 35 (81.4%),

thrombocytopenia in 6 (14.0%), and febrile neutropenia in 6 (14.0%). Grade 3 genitourinary (GU) toxicity occurred in 11.6%, and grade 3 gastrointestinal (GI) toxicity occurred in 4.7%. (18)

Prognostic variables with $p \leq 0.1$ on univariate analysis were included in multivariate analysis. OS and DFS were significantly higher among patients <65 who responded to treatment with no recurrence, which is consistent with that reported by Mao W. et al. (2019) (19).

Conclusion:

Neoadjuvant chemotherapy followed by chemoradiotherapy appears to be a promising treatment option for patients under 65 years of age, responders to treatment who refuse surgery or are medically unfit.

Recommendations: Cessation of smoking can reduce the risk of bladder cancer.This study is phase II, and we aim for phase III to compare radical cystectomy and trimodality protocol.

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