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ROLE OF NEOADJUVANT CHEMOTHERAPY IN THE CONSERVATIVE MANAGEMENT OF NON-MUSCLE INVASIVE BLADDER CANCER (NMIBC) T1

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Aim:In this study our aim is to evaluate the benefit of neoadjuvant chemotherapy (NAC) in high risk NMIBC in preventing disease recurrence and progression while improving overall survival (OS).Patients and Methods:This prospective study included 33 patients with a pathologically confirmed NMIBC(T1) at the time of Transurethral resection of a bladder tumor (TURBT) with one or more high risk features (HRFs) during the period (2019- 2022),at Assiut University Hospital. All patients received 3 cycles neoadjuvant chemotherapy (cisplatin-gemcitabine) every 3 weeks and assessment of response was done by pelviabdomen Multi slice-CT and cystoscopy then TURBT and kept under follow up every 3 months by cystoscopy in the first 2 years. Results: A complete response (CR) was observed in 82% of the patients and disease progression (DP) to in 18% of the patients. Two year OS rate was 79% and two year disease free rate survival(DFS) was 76%.In Univariate regression t Patients with one risk features were 7 time more in 2 years DFS than patients with ≥ 2 risk features (OR= 6.90), Patients with no foci of squamous differentiation were 5 time more in 2 years DFS than patients with foci of squamous differentiation (OR= 5.25) and all factors were significant. In a multivariate regression model the significant variable only was Patients with no foci of squamous differentiation(OR= 6.92).Conclusion:NAC seems to have promising results in treatment of patients with one HRF NMIBC and a further investigation needed to determine the role of multimodal therapy in patients with two or more high risk feature NMIBC.

Keywords:*Neoadjuvant chemotherapy; Non Muscle Invasive Bladder Cancer; Transurethral resection of a bladder tumor; Overall Survival; Disease Free Survival*

INTRODUCTION

In December 2020, the Global Cancer Observatory (GLOBOCAN) estimated that bladder cancer was the third most common cancer after breast and liver cancer[1]. Bladder cancer is the second most common cancer among Egyptian males, with a 4:1 male-to-female ratio[2].

In Egypt, changes in the histopathological types of bladder cancer have been noted over the past 26 years. While Squamous Cell Carcinoma (SCC) decreased from 78% to 27% of diagnosed bladder tumour, Transitional Cell Carcinoma (TCC) increased from 22% in 1980 to 73% in 2005.[3]

A smoker's male had a 1.8-fold higher risk of urothelial carcinoma than a smoker's male who never smoked[4]. The incidence of smoking in the Egyptian population in 2010 was 22% and is increasing.[5&6]

75% of patients with bladder cancer present with non-muscle-invasive bladder cancer (NMIBC) either confined to the mucosa or invading the lamina propria (T1)[7].

Despite sharing many genetic features with muscle-invasive bladder cancers, T1 bladder cancers were classified as non-muscle-invasive or superficial tumors'[8].

In patients with NMIBC, the current gold standard of treatment is TURBT followed by six-weekly induction of intravesical Bacillus Calmette-Guérin (BCG) instillation followed by maintenance[9]**.** Local recurrence, disease

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progression, and death from bladder cancer (UC) are all common in clinical T1 high-grade (cT1HG) NMIBC[10&11]. Large and multifocal tumors' increased the risk of incomplete initial resection and were thought to be a factor in early recurrences.[12&13]

HR NMIBC recurs in 23–74% of patients after TURBT with intravesical Bacillus Chalmette- Guerin (BCG) and progresses to muscle-invasive bladder cancer in 35%–50% of patients[14&15].

In patients with low- or intermediate-risk bladder cancer, a single postoperative instillation of intravesical chemotherapy (e.g., gemcitabine, mitomycin C) within 24 hrs should be considered.[16].

In patients with high-risk NMIBC, intravesical BCG for 1-3 years is recommended to prevent recurrences[17]. Anthracycline was approved in September 1998 by the Food and Drug Administration (FDA), followed by pembrolizumab in January 2020 for NMIBC[18].

Different salvage intravesical therapies have been evaluated, but these studies are limited by a small number of patients, moderate improvements in recurrence-free survival, and no significant effects on progression or survival with the respective intravesical agent Among these are gemcitabine, docetaxel, nanoparticle albumin-bound (nab)-paclitaxel, and the sequential administration of gemcitabine and docetaxel[19-22].

According to the European Organization for Research and Treatment of Cancer Genito-Urinary, 62.8% of patients had local side effects such as cystitis with or without hematuria, and 69.5% had either local or systemic side effects such as chemical cystitis (35%), general malaise (15.5%), and 7.8% discontinued due to complications[23].

We investigate the role of neoadjuvant chemotherapy (cisplatin and gemcitabine) in preventing local recurrence, disease progression, and the use of radical cystectomy, as well as the complications of BCG that lead to discontinuation.

In recent times, several obstacles have limited the use of BCG therapy, including shortages of BCG supply and the impact of the current COVID-19 pandemic, so alternative treatment options should also be considered. This limitation highlights the dire need for novel agents in this disease setting[24].

Currently, immunotherapy with pembrolizumab and atezolizumab, anti-Programmed Cell Death Protein 1 (PD1) monoclonal antibodies (mAbs), has shown promising antitumor activity in BCG-unresponsive NMIBC in the phase II trials KEYNOTE-057 and SWOG S1605, respectively, gaining FDA approval[25] Other novel agents with different mechanisms of action, such as Nadofaragene Firadenovec and Oportuzumab Monatox, have shown efficacy in the treatment of NMIBC.[26]

The goal of this study is to assess the benefit of neoadjuvant chemotherapy in high-risk, non- muscle-invasive bladder cancer in the face of BCG shortages and financial barriers to using immunotherapy. Disease-free survival and overall survival are the primary end points.

PATIENTS AND METHODS

A prospective study at Assuit University Hospital's oncology department included 33 patients with pathologically confirmed NMIBC (T1) with any high-risk feature from 2019 to 2022. Before data collection, the Assuit University Hospital Ethics Committee approved this protocol (IRB no: 17200467) All patients received three cycles of neoadjuvant chemotherapy (cisplatin-gemcitabine) every three weeks, and response was assessed using pelviabdomen MSCT and cystoscopy, followed by TURBT, and meticulous follow-up every three months by cystoscopy for the first two years. Patients were managed appropriately in cases of progression or recurrence.

Inclusion Criteria

Patients above eighteen years old with pathologically confirmed NMIBC (T1), Eastern Cooperative Oncology Group performanous status (ECOG) 0-1, and adequate renal and haematological function

Exclusion Criteria

Stage 0, T1a, evidence of nodal or distant metastases, and patients not fitting a cisplatin-based NAC.

Statistical analysis

Data analysis using SPSS version 26. data were presented in form of frequencies and percentages. All numerical variables were tested before evaluation to determine the normality of the data by the Shapiro-Wilk test,

the mean ± SD for normally distributed data, or the median and range for not normally distributed data. Fisher Exact tests were used to compare proportions between groups according to 2-year DFS and response to treatment. A log rank test was used to compare mean DFS and OS among patients according to different variables. A univariate and multivariate logistic regression analysis was done to identify factors affecting 2 years' DFS.

DFS is defined as the amount of time that a patient survives after primary cancer treatment has ended without showing any signs or symptoms of the cancer. **OS** is defined as the amount of time that patients diagnosed with a disease, such as cancer, have been alive since either the date of diagnosis or the start of treatment.

RESULTS AND DISCUSSION

Results

Thirty-three patients with HR NMIBC (T1) received 3 cycles of neoadjuvant chemotherapy (cisplatin and gemcitabine) every 3 weeks, and assessment of response was done by pelviabdomen MSCT, cystoscopy, and TURBT. The follow-up time was 24 months.
Patient's characteristics (n = 33).

The mean age at the time of diagnosis was 62 ± 6.68 years, and 23 of 33 (30%) patients were ≥ 65 years old. Males presented in 29/33 (89%) of the patients' population, while females presented in 4/33 (12%). The most common presenting complaint was burning micturition in 15/33 (46%) of the patients, followed by hematuria in 13/33 (39%) of the patients. **(Table 1)**

Table 1: Characteristics of patients with NMIBC.

Variables	N=33	%
Age (years)		
▪ <65	23	69.7
▪ ≥ 65	10	30.3
Mean ± SD	62.06±6.68	
Gender		
▪ Male	29	87.9
▪ Female	4	12.1
Smoking		
▪ Smoker	27	81.8
▪ Nonsmoker	6	18.2
Bilharziasis	5	15.2
Main presenting symptom		
▪ Burning micturition	15	45.5
▪ Hematuria	13	39.4
▪ Suprapubic pain	3	9.1
▪ Frequency	2	6.1
Pathology		
▪ transitional cell carcinoma	25	75.8
▪ transitional cell carcinoma with squamous diff	8	24.2
High risk features		
▪ One risk feature	28	84.8
▪ Two or more risk features	5	15.2
Staging		
▪ T1b	19	57.6
▪ T1c	14	42.4
Type of high-risk features		
▪ Hydronephrosis	20	60.6
▪ Abnormal EAU	8	24.2
▪ Foci of squamous differentiation	8	24.2
▪ Multiple	1	3.0
Site of tumor		
▪ Lateral	15	45.5
▪ Posterior	9	27.3
▪ Anterior	5	15.2
▪ Dome of bladder	4	12.1

Disease characteristics

Pure transitional cell carcinoma (TCC) was the most common pathology in 25/33 (76%) of the patients, followed by TCC with squamous differentiation in 8/33 (24% of the patients). They were all high grade, primarily in the lateral wall in 15/33 (46% of the patients), and smoking was the main risk factor in 8/33 (82% of the patients). 5/33 (15%) of patients had a positive history of bilharzial infections.

The most common high-risk features were preoperative hydronephrosis in 20/33 patients (61% of patients), abnormal EUA (thickening or induration) in 8/33 patients (24% of patients), and foci of squamous differentiation in 8/33 patients (24%). Fifteen percent (5/33; 15%) of the patients presented with two or more high-risk features. **(Table 1)**

Clinical response and survival

All patients received three cycles of neoadjuvant chemotherapy (cisplatin and gemcitabine) every three weeks, and response was assessed. CR was seen in 27/33 (82%) of the patients, and DP to MIBC was seen in 6/33 (18%) of the patients, one of whom had a radical cystectomy and the others had a bladder preservation protocol (concurrent chemo radiotherapy).Two-year DFS was 76%, and the OS was 79%. 7/33 (21%) patients died due to CVI. **(Table 2), and (Figure 1).**

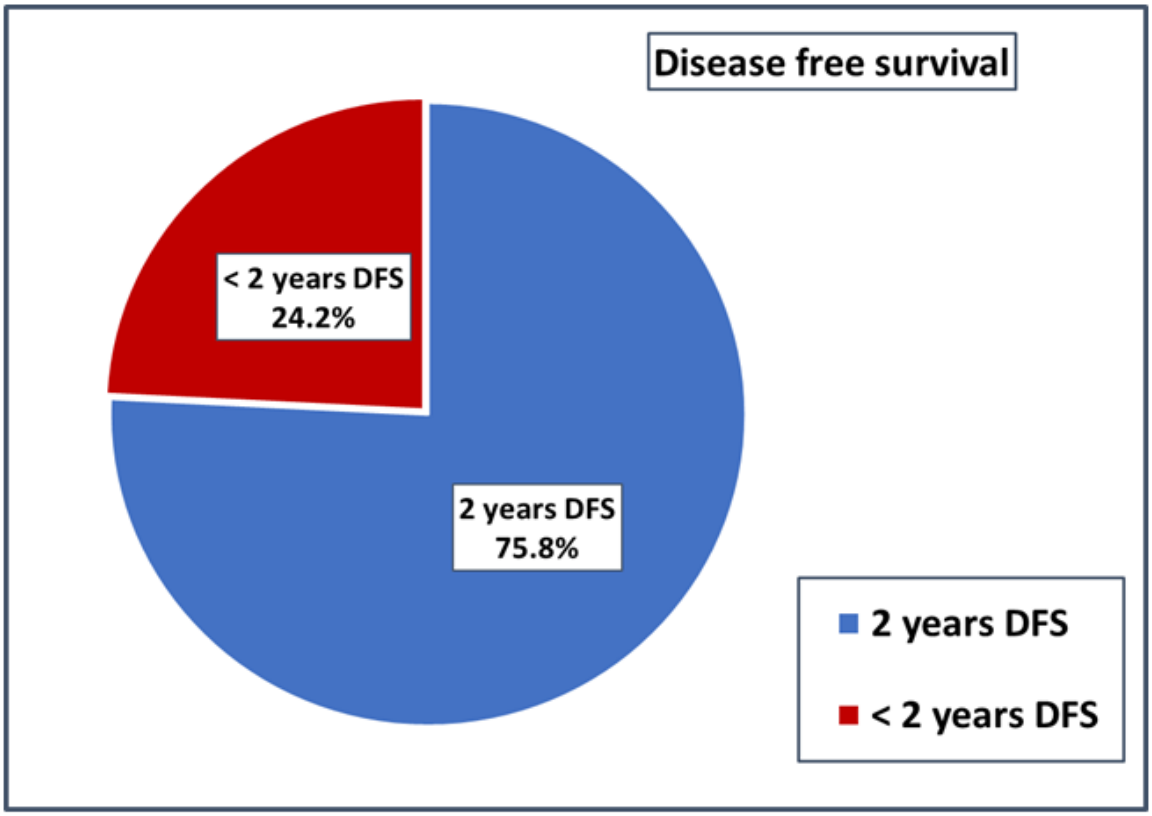

Fig. 1: 2-year disease free survival among patients with bladder cancer.

Table 2: Response and 2-year disease free survival in patients with NMIBC.

Variables	N=33	%
Response		
▪ **Complete response**	27	81.8
▪ **Disease progression**	6	18.2
2-year disease free survival	25	75.8
2-year overall survival	26	78.8

Univariate logistic regression was done on significant variables in bi variate analysis, its shows that Patients with one risk features were 7 time more in 2 years DFS than patients with ≥ 2 risk features (OR= 6.90), Patients with no foci of squamous different were 5 time more in 2 years DFS than patients with foci of squamous different (OR= 5.25) and all factors were significant. (Table 3).

The significant variables in Univariate logistic regression were entered in a multivariate logistic regression model and the significant variable only was Patients with no foci of squamous different were 7 time more in 2 years DFS than patients with foci of squamous different (OR= 6.92) . (Table 4)
Mean DFS and OS were 22 months and 23 months, respectively.

Table 3: Factors affecting 2-year disease free survival in patients with NMIBC.

Variables	2-year disease free survival		P-Value*
	2 years (n=25)	< 2 years (n=8)	
Age			
▪ <65	15 (65.2%)	8 (34.8%)	
▪ ≥ 65	10 (100.0%)	0 (0.0%)	0.071
Smoking			
▪ Smoker	21 (77.8%)	6 (22.0%)	0.616
▪ Nonsmoker	4 (66.7%)	2 (33.3%)	
Bilharziasis			
▪ Yes	4 (80.0%)	1 (20.0%)	0.999
▪ No	21 (75.0%)	7 (25.0%)	
Pathology:			
▪ Transitional cell carcinoma	**21 (84.0%)**	4 (16.00%)	**0.05**
▪ Transitional cell carcinoma with squamous different	**4 (50.0%)**	4 (50.0%)	
High risk feature			
▪ One risk feature	**23 (82.1%)**	5 (17.9%)	
▪ Two or more risk features	**2 (40.0%)**	3 (60.0%)	**0.043**
Staging			
▪ T1b	15 (78.9%)	4 (21.1%)	0.461
▪ T1c	10 (71.4%)	4 (28.6%)	
Types of risk features			
Hydronephrosis			
▪ Yes	15 (75.0%)	5 (25.0%)	0.999
▪ No	10 (76.9%)	3 (23.1%)	
Abnormal EAU			
▪ Yes	6 (75.0%)	2 (25.0%)	0.999
▪ No	19 (76.0%)	6 (24.0%)	
Foci of squamous different			
▪ Yes	**4 (50.0%)**	4 (50.0%)	
▪ No	**21 (84.0%)**	4 (16.0%)	
▪ Posterior	4 (44.4%)	5 (55.6%)	
▪ Anterior	5 (100.0%)	0 (0.0%)	
▪ Dome of bladder	3 (75.0%)	1 (25.0%)	**0.05**

Table 4: Logistic regression analysis for factors associated with 2 years DFS in patients with cancer bladder**.**

Predictors	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
High risk feature				
≥ 2 risk features	Reference		Reference	
One risk feature	6.90 (1.1-25.74)	0.046	3.55 (0.32-20.22)	0.06
Foci of squamous differentiation				
Foci of squamous differentiation	Reference		Reference	
No foci	5.25 (1.2-30.25)	0.045	6.92 (1.5-25.7)	0.041

Logistic regression analysis, OR: Odds ratio, 95% CI: 95% confidence interval.

Toxicity to neoadjuvant chemotherapy

was tolerable for the majority of patients, mostly grades I and II; improved with supportive medical treatment; and did not require treatment interruption. The most common events were neutropenia in 14/33 (42%) of the patients and renal impairment in 7/33 (21%) of the patients.

The toxicity of chemotherapy didn't affect DFS or treatment response. (Table 5**)**

Table 5: Toxicity in patients with non-muscle invasive bladder cancer.

Toxicity	N=33	%
▪ **Neutropenia**	**14**	**42.4**
▪ Grade 1	11	33.3
▪ Grade 2	3	9.1
▪ **Renal impairment**	**7**	**21.2**
▪ Grade 1	5	15.1
▪ Grade 2	2	6.1
▪ **Anemia**	**2**	**6.1**
▪ Grade 1	1	3.0
▪ Grade 2	1	3.0

Discussion

The presence of a high-risk feature in non-muscle-invasive bladder cancer was considered to represent cT3, but not introduced into current staging systems[17&27].

Transurethral resection (TUR) is the standard of care for the management of NMIBC, with a high risk of progression up to 45% and a rate of recurrence in low, intermediate, and high-risk NMIBC of 20%, 24%, and 78%, respectively.[28]

Treatment guidelines recommend TURBT and maintenance BCG for 1 to 3 years in patients with high-risk NMIBC[29]. which agree with clinical practise as regards the use of BCG induction therapy, while in most studies less than a quarter of high-risk NMIBC patients complete BCG maintenance therapy, which increases the risk of recurrence and disease progression[30&31]**.**Radical cystectomy is the preferred treatment option for BCG treatment failure[32] Chemo- radiation therapy was an alternative for radical cystectomy, with a CR rate of 88% and a 5-year survival rate of 84%.[33] Radiotherapy has no benefits in the treatment of NMIBC.[34]

Based on a similar study that showed significant improvement in OS and DSS[35]**,** and in view of the shortage of BCG vaccine in the last 3 years (the era of COVID 19), we tried to evaluate the benefit of neoadjuvant chemotherapy in HR NMIBC as an alternative treatment line.

The mean age of the patients at time of diagnosis in our study was 62 years, with a male predominance, which agrees with that reported by Michael Jet et al. (2017).[36] Patients with carcinoma insitu (CIS), lymphovascular invasion (LVI), or variant histology should be identified for consideration of upfront RC[10] However, intravesical BCG is an effective treatment for NMIBC, reducing the risk of recurrence and progression in HR NMIBC; nearly 70% of patients may achieve CR[37&38]**.**

A higher CR rate was observed in 82% of patients in our study. 18% of patients have shown DP in our study, which seems to be

comparable to that reported by van den Bosch et al. (2011)[39]. NMIBC has a wide range of progression and recurrence rates, which depend on high-risk features.[36] In our study, variant pathology and the presence of two or more high-risk features were the only prognostic variables affecting two-year DFS with a significant P-value (0.04, 0.043, respectively). Intravesical BCG complications vary from irritative urinary bladder symptoms to septicemia[40].

In our study, the most common toxicity was neutropenia in 42% of our patients, which agrees with the report by Matsubara *et al.,* that neutropenia was the most common haematological toxicity in 40% of patients[41]. NAC appears to have promising results in patients with high-risk NMIBC.

Conclusion

Neoadjuvant chemotherapy seems to have promising results in the treatment of patients with one high-risk feature in non-muscle invasive bladder cancer, and further investigation is needed to determine the role of multimodal therapy in patients with two or more high-risk features in NMIBC.

Conflicts of Interest

No conflicts of interest.

Limitations and future recommendation of our study

The small sample size and only one previous study in our research area limit our results, so a large randomized multicentric study is recommended.

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دور العلاج الكيميائي المساعد الجديد في العلاج التحفظى لسرطان المثانة الغير مخترق للعضلات

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الهدف من الدراسة هو تقييم المنفعة من استخدام علاج كيمائي المساعد للمرضي ذات خطورة عالية من سرطان المثانة الغير مخترقة للعضله في منع الارتجاع و تحسين نسبه معدل البقاء علي قيد الحياه .

المرضى والوسائل: أجريت هذه الدراسة علي ٣٣ مريض سرطان المثانه الغير مخترق للعضلة ذات خطوره عالية بقسم علاج الاورام والطب النووي - كليةالطب جامعه اسيوط في الفترة من ٢٠١٩ وحتي ٢٠٢٢. جميع المرضي تلقوا ثلاثة جلسات من العلاج الكيميائي (cisplatin-gemcitabine) جرعه كل ثلاثة اسابيع مع المتابعة بالاشاعات و عمل منظار مثانة كل ثلاثه اشهر في اول سنتين من المتابعة.

النتائج: كان متوسط عمر المرضي ٦٢ عاما و الاغلبية من الرجال ،و كانت نسبه الشفاء التام ٨٢% و معدل البقاء علي قيد الحياه ٧٩% ، و معدل البقاء علي قيد الحياه خالي من المرض ٧٦% ، وان وجود نسبه خطر واحدة او اكثر من العوامل التي اثرت احصائيا علي معدل البقاء علي قيد الحياه خالي من المرض.

التوصيات: لقد وجد ان العلاج الكيمائي المساعد له نتائج واعده في علاج مرضي سرطان المثانة الغير مخترق للعضلة ،لذا يوصي بعمل المزيد من الفحوصات لمعرفة دور استخدام اكثر من نوع واحد للعلاج لمرضي سرطان المثانة الغير مخترق للعضلة ذات خطوره عالية.