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Evaluation of Neoadjuvant Chemotherapy in Treatment of Muscle Invasive Urothelial Bladder Tumors in Upper Egypt

Mohamed A. Khateeb [1], Diaa A. Hameed [1], Ahmed M. Moeen [1], Tareq Salah [2], Hosney M. Behnsawy [1], Yasser M. Abdelsalam [1], Samir Shehata [2], Magdi A. El-Akkad [1]

[1] Urology University Hospital, Faculty of Medicine, Assiut University, Assiut, Egypt; [2] Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Assiut University, Assiut, Egypt.

Background: Bladder cancer is a common health problem is Egypt where it is the 3rd common cancer (6.9%) in both sexes and the 2nd common (10.7%) among males. Neoadjuvant chemotherapy has proven benefits in treatment of muscle invasive bladder cancer (MIBC), yet it is still underutilized.
Aim: To study the response to neoadjuvant chemotherapy in patients with MIBC and their attitude towards definitive treatment after completion of neoadjuvant therapy.
Methods: In this prospective study, 85 patients with MIBC were recruited between September 2013 and September 2014. They were scheduled to receive three cycles of gemcitabine (1000 mg/m^2, on days 1 and 8) plus cisplatin (75 mg/m^2 on day 1) or carboplatin (AUC=5 on day 1) in patients with impaired renal function prior to definitive treatment.
Results: Sixty-seven patients were evaluable for response and toxicity. The majority (79%) were males and their median age was 61 years (range: 38-84). The initial T stage was T3 or T4 in 72% of patients. Complete response was documented in 6 (9%) patients, partial response in 41 (61.2%), stationary disease in 5 (7.5%) and progressive disease in 15 (22.4%). Grade III and IV toxicities were infrequent (5%) with no chemotherapy-related mortality. After completion of the treatment, 9 (13.4%) patients were shifted to bladder preservation treatment due to complete radiological response and refusal of surgery.
Conclusion: Neoadjuvant chemotherapy is feasible in MIBC patients in our setting as it gives good clinical response. If offered in a proper way, it doesn't preclude the patients' chances for definitive treatment.

Keywords: Bladder cancer, Neoadjuvant chemotherapy, Bladder preservation, Uro-oncology, Upper Egypt
Corresponding Author: Tareq Salah, M.D.; Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Assiut University, Assiut, Egypt; Email: tareqsalah41@yahoo.com
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INTRODUCTION

Bladder cancer (BC) is one of the most common cancers worldwide. In Egypt, it is the 3rd common cancer (6.9%) in both sexes after liver and breast cancers and the 2nd common (10.7%) among males [1]. There is geographical variability in the incidence of BC which is higher in Upper Egypt (7.4%) than in Lower Egypt (5.9%) [1]. The golden standard for the management of muscle invasive bladder cancer (MIBC) is radical cystectomy with pelvic lymphadenectomy [2]. Despite potentially curative surgery almost half of MIBC patients develop local recurrence and/or distant metastasis which affect their survival [3, 4].

To improve the results of surgery for MIBC, neoadjuvant chemotherapy (NAC) has been explored. Radical cystectomy provides the best local control of the 1ry bladder tumors; however, cancer is a systemic disease and so chemotherapy aims at eradicating the possible micrometastatic disease in addition to its local effect on the 1ry tumor [5]. The rationale behind NAC is multifactorial. The use of NAC in locally advanced BC permits a rapid in vivo assessment of pathological response [6]. It may reduce the 1ry tumor volume and give the chance for some patients to have a curative surgery. Furthermore, patients may best tolerate chemotherapy while they are in the best possible performance before receiving local treatment whether surgery or radiotherapy that may affect their performance status [7]. Local treatments may also affect drug delivery to the 1ry tumor by alternating the blood supply. Collectively, NAC has the potential to deliver the drugs more efficiently and at higher doses than in the adjuvant setting in addition to the opportunity to in vivo testing response of the tumor to chemotherapy [8].

To the best of our knowledge, NAC for MIBC hasn't been studied in our locality till now. The reluctance to use NAC in this setting doesn't seem to be peculiar to Upper Egypt. Although the benefits are well established [9], the clinical practice is still lagging behind [10]. In this study we aimed to evaluate the clinical and radiological responses and the side effects of NAC in a cohort of MIBC patients in Upper Egypt and the attitude of these patients towards definitive treatment following NAC.

METHODS

This prospective study has been carried out between September 2013 and September 2014 at the Urology and Clinical Oncology departments, Assiut University, Assiut, Egypt. The ethical committee of the Faculty of

Medicine, Assiut University approved the study. The nature of the study and the expected treatment related toxicity were explained to participants and an informed consent was obtained before enrollment.

Eighty-five patients were enrolled and underwent the following pre-treatment evaluation: detailed history taking and clinical examination; examination under anesthesia and transurethral resection biopsy; chest, abdomen and pelvis computerized tomography (CT) scan or magnetic resonance imaging (MRI) in patients with elevated serum creatinine; bone scan was done if there was clinical suspicion of metastases in the form of bone pain or elevated serum alkaline phosphatase. Laboratory investigations (complete blood count and renal and liver function tests) were done at baseline and before each chemotherapy cycle.

Selection of patients

Eligible patients were adults (>18 years of age) who have: histopathologically proven urothelial BC; stage T2, T3 or T4a, N0, M0; performance status ≤1 by the Eastern Cooperative Oncology Group (ECOG) scale; adequate bone marrow reserve (neutrophil count >1500/μL, platelet count >100000/ μL and hemoglobin >10 gm/dL); creatinine clearance >60 ml/min and serum bilirubin and aminotransferases ≤2.5 times the upper limit of normal.

Patients were excluded if they have any of the following: serious or uncontrolled concurrent medical illness, pregnancy or lactation, history of previous cancer, non-urothelial BC, prior systemic chemotherapy or radiotherapy to the bladder, or major surgery within 4 weeks of starting chemotherapy.

Neo-adjuvant chemotherapy (NAC) regimen

Eligible patients received 3 cycles of NAC that included cisplatin on day 1 and gemcitabine on days 1 and 8.

One hour after intravenous pre-hydration with 1000 ml normal saline, cisplatin (75mg/m^2) was administered intravenously + 12.5 gm mannitol in 500 ml 0.45% normal saline over one hour. This was followed by intravenous post-hydration with 1000 ml normal saline + 10 q KCI/L + 8 mEq magnesium sulfate over 1 hour. Cisplatin was substituted with Carboplatin in 4 patients because of grade II renal impairment after starting treatment (creatinine clearance <60 ml/min) or decline in performance status. Carboplatin was administered with dose targeting area under the curve 5 (AUC=5).

Gemcitabine (1000mg/m^2) was administered intravenously in 250 ml normal saline over 30 minute.

Post-treatment evaluation

History taking, clinical examination and chest, abdomen and pelvis CT scans or MRI were done to evaluate tumor response. The response was determined according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 [11] as follows:

- Complete Response (CR): Disappearance of all target lesions.
- Partial Response (PR): At least a 30% decrease in the sum of the longest diameters of target lesions.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
- Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions or the appearance of one or more new lesions.

Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 [12].

Statistical analysis

Data was analyzed using the Statistical Package for Social Sciences (SPSS) software version 14.0. Chi square test was used to compare categorical data. P value <0.05 was considered significant.

RESULTS

Sixty-seven out of 85 (79%) recruited patients were evaluable with a dropout rate of 21%. Three patients discontinued treatment after the 2nd cycle due to severe local symptoms and preferred to undergo surgery immediately. Another 3 patients were excluded due to the discovery of undetected distant metastasis (2 patients) or the development of grade 4 renal impairment (1 patient). One female patient who aged 71 years with pT4a tumor died during the 2nd cycle. Her death was not treatment-related. The other 11 patients were withdrawn from the study because of their preference to receive treatment in other centers near their localities.

Table 1: Characteristics of 67 patients

	No.	%
Age		
Median (range)	61 (38-84)	
Sex		
Male	53	79.1
Female	14	20.9
T Stage		
T2	19	28.4
T3	34	50.7
T4	14	20.9
Grade		
Low	5	7.5
Intermediate	6	9
High	56	83.6
Squamous differentiation		
Yes	33	49.3
No	34	50.8
Smoking history		
Active	51	76.1
Passive	8	11.9
None	8	11.9

The baseline characteristics of the evaluable 67 patients are shown in table 1. All patients had no radiological evidence of lymph node metaststses (N0) and no evidence of distant metstases (M0). All active smokers were males and all passive smokers were females.

The response to NAC was CR in 6 (9%) patients, PR in 41 (61.2%), SD in 5 (7.5%) and PD in 15 (22.4%). The overall response rate (CR+PR+SD) was 77.6%. It differed significantly according to the T stage of tumors, age of patients and smoking history as shown in table 2. Younger (≤ 60 years) patients, those with T2 and T3 stage and non-smokers had better overall response rate. Among the 8 non-smokers, 5 achieved CR and 3 PR. The other studied variables did not correlate significantly with response to NAC.

Table 2: Variables with significant correlation with the overall response rate

	No.	CR,PR,SD (n=52)	PD (n=15)	P-value
		n (%)		
Age (years)				
≤ 60	43	35 (81)	8(19)	0.036
> 60	24	17 (70)	7 (30)	
T stage				
T2	19	14 (74)	5 (26)	0.02
T3	34	30 (88)	3 (12)	
T4	14	8 (57)	6 (43)	
Smoking history				
No	8	8 (100)	0	<0.05
Yes	59	44 (75)	15 (25)	

CR: Complete response; **PR**: Partial response; **SD**: Stable disease; **PD**: Progressive disease

All the evaluable 67 patients completed the scheduled 3 Cycles of NAC. The toxicity pattern is shown in table 3. Grade III and IV toxicities were infrequent and occurred in only 5% of patients. There was no chemotherapy-related mortality.

The most common haematological toxicity was anemia, mostly of grade I. Only 2 patients developed grade III anemia which was corrected with blood transfusion and the course of therapy was completed. Vomiting was universal in all cases with no grade IV vomiting reported. The only reported grade IV toxicity was nephrotoxicity in one patient which was corrected with haemodialysis and supportive measures.

After concluding NAC, we followed up the patients to know their attitude towards definitive treatment. All patients (6, 9%) who achieved pathologically confirmed CR by cystoscopic biopsy were shifted to bladder preservation treatment with radical radiotherapy. Of the 46 patients who had PR, 40 (59.7%) patients underwent cystectomy. The other 6 PR patients were satisfied with the results of the treatment (disappearance of symptoms) and they refused to have cystectomy, 3 (4.5%) of them preferred radiotherapy and the remaining 3 (4.5%) refused any form of definitive treatment in spite of our advice. The remaining 15 (22.4%) patients had PD on treatment and were referred to radiotherapy, 2nd line chemotherapy or salvage cystectomy.

In total, after completion of NAC, 9 (13.4%) patients were shifted to bladder preservation treatment (according to patient preference) due to CR in 6 of them and major PR in the other 3 patients who refused cystectomy.

DISCUSSION

The dropout rate (21%) in the current study is the usual rate in our center which serves a very wide geographic area covering nearly half of the Egyptian area. Hence, a patient may prefer to complete his treatment or his follow up in a nearby facility, after being offered the initial treatment, or the plan of treatment in our hospital.

Although considered as the state of the art in treatment of MIBC and being highly recommended in nearly every considerable guideline [13-16], NAC in treatment of MIBC isn't widely practiced as recommended [10]. This may be attributed to the urologists' fear of missing the chance to operate on the patient in the "appropriate time" due to the duration needed for NAC and the possible side effects of the treatment.

In this study, we investigated the feasibility of NAC in MIBC, its side effects and how it affects the delivery of definitive treatment to the patients in our locality. We assigned our patients for 3 cycles of neo-adjuvant gemcitabine-cisplatin combination which is as effective as the standard methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) combination NAC with fewer side effects [17].

Larger studies that investigated standard cisplatin based regimen confirmed the survival benefits of NAC in MIBC especially when CR is achieved [13]. The response rate in our study (9% CR, 61% PR, 7.5% SD and 22.4% PD) is very similar to single institute studies with small number of patients [18]. In an Egyptian Phase II study done by Khaled et al., 57 previously untreated patients with stage III/IV BC (65% had transitional cell carcinoma) received neoadjuvant gemcitabine-cisplatin. The overall response rate was 59% with 9% CR and 50% PR [19]. Galsky et al., reported an overall response rate of 56% in 25 patients treated sequentially with dose dense MVAC and gemcitabine [20].

Overall, the gemcitabine-cisplatin regimen was well tolerated by our patients with grade III-IV toxicity in only 5% of patients. In a large randomized multicenter phase III study, gemcitabine-cisplatin was compared with MVAC. The trial revealed a similar efficacy with respect to response between the 2 treatment arms, whereas gemcitabine-cisplatin was significantly less toxic [17]. This is the foundation of using the "alternate regimen" instead of the "standard regimen" in our study. Herchenhorn et al used a similar regimen to ours and reported an incidence of 85% grade I toxicity, 28% grade II, 33% grade III and 4% grade IV [18]**.** Kaneko et al reported grade III-IV neutropenia in 14.3% of patients, anemia in 2.4 % and thrombocytopenia in 21.4% of patients [21]**,** which is higher than we encountered in our study.

None of the patients included in this study died because of treatment-related cause. The NAC treatment related mortality is usually reported to be in the range of 0 to 1% [13, 22].

Table 3: Neoadjuvant chemotherapy – related acute toxicities

	No Toxicity	Grade I	Grade II	Grade III	Grade IV
			***n* (%)**		
Hematological					
Anemia	14 (20.8)	48 (71.6)	3 (4.5)	2 (3)	0
Leukopenia	61 (91)	6 (9)	0	0	0
Thrombocytopenia	60 (89.5)	7 (10.4)	0	0	0
Non-hematological					
Vomiting	0	58 (86.6)	4 (6)	5 (7.5)	0
Renal Impairment	53 (79)	7 (10.4)	4 (6)	2 (3)	1 (1.5)
Neuropathy	65 (79)	2 (3)	0	0	0
Weight loss	48 (71.6)	16 (24)	3 (4.5)	0	0

Since there are no tumor markers yet that can beforehand detect responders to NAC, certain clinico-pathological factors were suggested to affect the treatment response. The relation between the response rate and stage of the 1ry tumor was previously proved in a trial done by Schultz et al who reported overall response rates after neoadjuvant MVAC in patients with T3b and T4a tumors to be approximately 81% and 9%, respectively [23]. In the present study the overall response rate in patients with T3 was 88% and in patients with T4 was 57% (p = 0.02). In our study patient's age was significantly associated with response, as younger patients (≤60 years) responded better than older (>60 years) patients. Other researchers didn't find a significant difference between younger and older patients and concluded that any fit patient of any age group can benefit from the treatment [24].

As regards smoking, Kim PH et al investigated the impact of smoking on the pathologic response to cisplatin-based NAC in patients with MIBC and found that smoking is not considered to be predictive of response [25]. On the contrary, in our study there was a significant association between smoking history and response to NAC which was better among non-smokers. Gender and grade were not found to be significantly affecting the response of NAC in the current study.

NAC does not prevent patients from undergoing cystectomy and does not increase the risk of perioperative complications. This was confirmed in a randomized controlled trial in which 317 patients with MIBC were randomized to radical cystectomy alone or 3 cycles of neoadjuvant MVAC followed by radical cystectomy. Cystectomy was performed as planned for 82% of patients assigned to NAC and 81% of those assigned to cystectomy alone [22]**.** This wasn't the case in our study. Only 9 (13.4%) of our patients were shifted to bladder preservation due to CR in 6 patients in addition to another 3 who refused cystectomy after successful NAC treatment that resulted in disappearance of their symptoms due to major PR. This seems not to be unique to our patients. Herr reported on the outcome of 63 patients who refused cystectomy after receiving NAC for their MIBC [5]. We believe that multidisciplinary team management for BC patients and discussion of treatment options and expectations and better communication with the patient before starting treatment is necessary. It should be stressed on that NAC may result in CR, yet it does not mean a cure from MIBC without definitive local therapy. This can make the patients' expectations more realistic and improve the percentage of patients accepting cystectomy after NAC and hence, improving treatment outcomes.

Conclusions

Neoadjuvant chemotherapy is feasible to use with our patients as it gives good clinical response in the form of local control of the disease with tolerable side effects, and if offered in a proper way, it doesn't preclude the patients' chances for definitive treatment.

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