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Clinico-Pathological Outcomes of Muscle Invasive Carcinoma Bladder in Post Neoadjuvant Chemotherapy Radical Cystectomy

Prashant Pathania[1], Amit Kishore[2], Puneet Aggarwal[3]

[1]Assistant Professor, Dept of Urology, Military Hospital Jalandhar, India
[2]Assistant Professor, Dept of Urology, Command Hospital Luckhnow, India
[3]Associate Professor Dept of Urology & Renal Transplant Army Hospital (R & R), Delhi, India

ABSTRACT

Background: Neoadjuvant chemotherapy (NAC) before radical cystectomy is advocated in patients with muscle invasive urothelial carcinoma of the bladder with the goal to improve survival by downstaging the primary tumour and eradicating micro-metastasis. The use of perioperative chemotherapy for bladder cancer, particularly in the neoadjuvant setting, remains limited. This study was designed to evaluate NAC plus RC regarding pathological response, perioperative morbidity and mortality outcomes.

Methods: This is a prospective and retro prospective study that was carried out from Jan 2018 to Jan 2020 for patients with muscle invasive bladder carcinoma. All patients having operable muscle invasive bladder carcinoma, Eastern Cooperative Oncology Group (ECOG) performance status 0–1 were included. Patients found to have metastatic disease, recurrent disease, patient not able to tolerate NAC were excluded from the study.

Results: Early complications occurred within 30 days after surgery & pathological response rates, perioperative morbidity, and mortality were compared.

Conclusions: A short course of neoadjuvant chemotherapy was associated to a low incidence of serious adverse events and did not increase the post-operative morbidity. Results suggest that non-urothelial tumour showed no response to Platinum based combination chemotherapeutic regimens. After NAC, residual local disease, persistent nodal disease and status of surgical margins are the most powerful prognostic factors forpatients who underwent RC.

Keywords: Neoadjuvant chemotherapy, Muscle invasive bladder cancer, radical cystectomy with urinary diversion

INTRODUCTION

Muscle-invasive bladder cancer (MIBC) is an aggressive disease with a high-risk of early metastasis and cancer specific mortality. Bladder cancer (BC) is the ninth most common cancer worldwide with a yearly incidence of approximately 430 000 cases, and it ranks 13th in terms of yearly mortality from cancer [(1)]. There is a male predominance, and it is the seventh most common cancer worldwide in men. Urothelial BC is the most common subtype. Approximately 75% of patients present with non–muscle-invasive disease, confined to the bladder mucosa/submucosa. This stage is usually managed with local treatment

and surveillance and has a particularly high prevalence due to the nonaggressive natural history of this disease. The gold standard treatment of MIBC is radical cystectomy (RC) in conjunction with concomitant bilateral pelvic lymphadenectomy. Although the surgical technique with RC and perioperative care has improved in recent years, approximately 50 % of MIBC patients will develop distantmetastasis and eventually die of bladder cancer [(2).]

Bladder cancer death after appropriate local therapy is typically the result of systemic disease; the majority of deaths occur within 2 years of initial treatment. Non–local regional relapses arereflective of the presence of micro metastatic disease at the time of diagnosis and treatment and they continue to hamper long-term survival rates for patients with muscle-invasive disease.

Similarly, despite local definitive therapy, the average 5-year disease-specific survival (DSS) rate for patients with MIBC is reported to be only around 50 % [(3)]. Hence, effective systemic therapy is necessary to achieve better oncological outcomes. While most newly diagnosed patients have non-muscle invasive tumours,20–40% of patients develop muscle invasion.

Neoadjuvant chemotherapy (NAC) is advocated in patients with muscle invasive urothelial carcinoma of the bladder with the goal to improve survival by downstaging theprimary tumour and eradicating micro metastases. Following NAC, complete pathological response or downstaging to non-muscle invasive disease is the best clinicalindicator of biological sensitivity of the tumour to the administered agents, and the observation of downstaging is consequently associated with improved overall survival.

The survival of patients with advanced urothelial carcinoma (UC) of the bladder has improved by the use of neoadjuvant chemotherapy (NAC) before radical cystectomy (RC), providing 5%-6.5% absolute benefit in 5-year survival compared with cystectomy alone [(4,5,6)].Due to the development and implementation of neoadjuvant chemotherapy (NAC) prior to radical cystectomy, the prognosis for MIBC patients undergoing radical cystectomy has improved .The goals of neoadjuvant chemotherapy administration are to

(a) eradicate the micro metastasis, (b) avoid the release and implantation of malignant cells during cystectomy, and (c) extend the survival of these patients.

MATERIALS AND METHODS

Present study was conducted to study the clinic - pathological outcomes of muscle invasive carcinoma bladder in post neoadjuvant chemotherapy radical cystectomy in the department of Urology, Army Hospital (R & R), New Delhi from January 2018 to January 2020. As per inclusion and exclusion criteria, 32 patients were enrolled in study, however one patient lost tofollow up after first cycle of NAC and two patients opted for bladder preservation protocol.

Finally, 29 patients with MIBC received NAC and underwent surgery 4-6 weeks after their last chemotherapy cycle were included. This is a prospective and retro prospective study that was carried out from Jan 2018 to Jan 2020 for patients with muscle invasive bladder carcinoma. All patients having operable muscle invasive bladder carcinoma, Eastern Cooperative Oncology Group (ECOG) performance status 0–1 were included. Patients found to have metastatic disease, recurrent disease, patient not able to tolerate NAC were excluded from thestudy. Patients with non-metastatic MIBC (T2-T4a, N0-N2) with good performance status andanaesthetic fitness were selected for this analysis. After diagnosis and staging of MIBC, all patients were referred to medical oncology unit according to multidisciplinary team decisions.Toxicity was estimated as defined by Good Clinical Practice (GCP).

Both pre-neoadjuvant chemotherapy imaging and post chemotherapy imaging as well as post RC clinic-

pathological outcomes were recorded. Patients were followed up according to standard protocol who received platinum-based NAC. Medical records reviewed for basic demographic information, treatment response status, tumor pathology findings, recurrence, RC status. Clinical stage was be determined by physical examination, imaging, and TURBT. The study was done to evaluate the clinical and pathological outcomes following neoadjuvant chemotherapy radical cystectomy for muscle invasive bladder cancer. Typical recommendations consisted of 4 cycles of GC chemotherapy at 21-day intervals over 12 weeks or 4 cycles of M-VAC chemotherapy at 28-day intervals over 16 weeks. Patient's response to treatment was assessed after the completion of NAC with imaging. Estimation of tumor response were performed using histopathologic tumor regression grades (TRGs) which were defined as follows: TRG1: complete tumor regression (pCR); TRG2: >50% tumor regression; TRG3: 50% or less Complete response (cT0) was defined as negative cystoscopy, urine cytology, and cross-sectional imaging .Radical cystectomy with bilateral standard pelviclymphadenectomy including the external iliac, internal iliac, and obturator nodes was carried out within 04-06 weeks following the last dose of chemotherapy in patients receiving NAC. For urinary reconstruction, ileal conduit or orthotopic neobladder was selected (determined according to the surgeon's and/or patient's preference).

Protocol consisting abdominal CT urography or MRU every 3-6 months, chest x-ray or CT-chest every 3-6 months or PET/CT (if metastatic disease suspected) performed every 3-6 months for the first 1 year. Besides RFTs with electrolytes, LFTs, CBC were done every 3-6 monthly and urine cytology with urethral wash cytology (where indicated) every 6 monthly for first 1 year. Progression and recurrence were registered.

RESULTS AND OBSERVATIONS

Demographics and tumor's characteristics: They are summarized in table no.1

Table1: Patient's demographics and tumor characteristics (n=22).

Characteristics	Value (%)
Age	
Range	46-76 years
Mean±SD	64.2±7.6
Gender	
Male Female	28(90.6%) 4(9.6%)
BMI	
Range: Mean±SD	20.2 - 38.5 26.7±3.8
Smoking	
Smoker Non smoker	28 (87.5%) 4 (12.5 %)
Comorbidities	
None Diabetes Hypertension Hypertension + Diabetes 3 or more comorbidities	14 (43.75%) 6 (18.8 %) 7 (21.9%) 2(6.3%)

	3 (9.4 %)
Clinical presentation	
Haematuria	31 (96.5%)
Dysuria	15 (46.9%)
Urine retention	4 (12.5%)
Urgency and frequency	2 (6.2%)
Clinical and nodal staging (According to AJCC)	
T Tumor	
T2 T3	17 (53.1%)
T4a	13 (40.7%)
	2 (6.2%)
N Node	
N0 N+	24 (75.0%)
	8 (25.0 %)
Histopathologic type	
Urothelial carcinoma	29(90.7%)
Adeno-carcinoma	1 (3.1%)
Mixed urothelial with squamous variant	2 (6.2%)
Grade	
Low	3 (9.3%)
High	26 (81.3%)

Neoadjuvant data:

The choice of drug therapy was based on its availability at our institute and as recommended by the medical oncologist. Out of 31 patients, 26 (83.9%) patients had received GC (gemcitabine/cisplatin) and 5 (16.1%) patients had received methotrexate/vinblastine/doxorubicin/cisplatin (MVAC) neoadjuvant chemotherapy (NAC). 18 patients (58.06%) had no symptoms or signs of toxicity while 13 patients (41.9%) developed toxicity manifestations. Toxicity and undesirable effects related to NAC were collected in Table 2

Table 2: summary of toxicity and undesirableeffects related to NAC (n=31).

NAC Regimen	Number of Patients (n=31)	ercent (%)
GC	26	83.9%
Neutropenia	6/26	23.1%
Thrombocytopenia	4/26	15.4%
Mucositis	2/26	7.7%
Gastritis	7/26	26.9%
M-VAC	5	16.1%

Nephrotoxicity	1/5	20.0%
Skin eruption	1/5	20.0%

Clinical and imaging outcomes*:*

17(54.8%), 12 (38.7%) and 2 (6.5%) patients had cT2, cT3 and cT4a clinical stage prior to chemotherapy respectively. One patient clinically staged T3N2 was excluded as he lost to follow up following first cycle of chemotherapy. 12 patients showed stationary course and 19 patients showed near complete resolution of lesion following NAC. Following NAC,29 patients were lymph node negative and 2 showed persistence of lymph nodes on imaging. Both of lymph node positive patients had squamous differentiation on initial TURBT histopathological examination. Two patients refused radical cystectomy following completion of neoadjuvant chemotherapy and chosen bladder preservation protocol. Clinical and imaging outcomeswere assessed in Table3.

Table 3: clinical and imaging outcomes

Clinical staging prior to chemotherapy	**Numberof Patients(n=31)**	**linical stage afterchemotherapy**			
		To	**T2**	**T3**	**T4a**
T Tumour					
cT2	17	12	05	0	0
cT3	12	7	1	4	0
cT4a	2	0	0	0	2
N Node					
N0	24	29	0	0	0
N+	07	2	0	0	0

Pathologic response*:*

After histopathologic examination of the specimens, the frequency of TRGs (Tumor regression grade) 1, 2, and 3 in the primary tumor's were n=6 n=7, and n=16; corresponding data from the lymph nodes were n=25, n=3, and n=1.Thirteen specimens showed non-muscle invasive disease (44.82%) from which six showed pCR (20.68%) and sixteen showed muscle invasive disease (55.17%) (Table 4). Twenty-five showed negative nodes (86.20%) while four showed positive nodal disease (13.79%). Lympho-vascular invasion (LVI) was positivein 3 (10.34%). Urethral margins were free in all patients. Patients with SCC have no response to NAC.

Surgical outcome:

Twenty-nine patients (90.62%) underwent radical cystectomy with bilateral pelvic lymphadenectomy and suitable urinary diversion. Two patients opted for bladder preservation protocol. Two patients died within 12 months of follow up after RC due tometastatic disease. Most common surgery wasopen radical cystectomy with ileal conduit in 23 (79.4%) patients, open radical cystectomy with neobladder in 1 (3.4%), robotic radical cystectomy with ileal conduit in 2 (6.9%) and robotic radical cystectomy with neobladder in
3 (10.3%) patients. Operative data and perioperative complications are shown in Table 5,6,7.

Table 4: Pathologic response to NAC

Tumour type	Clinical stage prior to chemotherapy	Number of patients	Pathological stage after Surgery						
			T0	Tis	Ta	T1	T2	T3	T4a
TCC	cT2	15	5	1	2	2	4	1	0
	cT3	12	1	0	0	2	8	1	0
	cT4a	1	0	0	0	0	0	1	0
Squamous cell CA	cT2	0	0	0	0	0	0	0	0
	cT3	0	0	0	0	0	0	0	0
	cT4a	1	0	0	0	0	0	0	1

Table 5: Types of surgeries

VARIANT	VALUE
Operative duration Range Mean±SD	426-638 minutes 511± 65
Type of urinary diversion Ileal loop conduit Orthotopic neobladder	25(86.20%) 04 (13.79%)
Blood transfusion	17 patients
Estimated blood loss Range Mean±SD	350-1150 ml 594.82 ± 205.25
Hospital stay Range Mean±SD	10-33 days 13.8 ± 5.6

Table 6: Summary of operative

Type of Surgical Procedure	Number of Patients (n=29)	ercent(%)
Open Radical Cystectomy with Ileal Conduit	23	79.4%
Open Radical Cystectomy with Neobladder	1	3.4%
Robotic Radical Cystectomy with Ileal Conduit	2	6.9%
Robotic Radical Cystectomy with Neobladder	3	10.3%

Table 7: Summary of perioperativecomplications after RC

postoperative complications (1-30 days)	Of Patients(n=29)	(%)
Prolonged ileus	**4**	**13.8%**
Wound infection	**4**	**13.8%**
Pneumonia	**3**	**10.3%**
Burst abdomen	**2**	**6.9%**
Pelvic collection	**2**	**6.9%**
Metabolic abnormalities	**2**	**6.9%**
DVT	**1**	**3.4%**

Late postoperative complications		
Refluxing Pyelonephritis	**1**	**3.4%**
Incisional Hernia	**1**	**3.4%**
Urinary Incontinence	**1**	**3.4%**

Follow up and survival outcomes*:* Total thirty- two patients were included in study initially, however one patient lost to follow up following completion of first cycle of NAC. Out of remaining thirty-one patients, two opted for bladder preservation protocol following completion of chemotherapy with complete response. Twenty-nine patients who finally underwent radical cystectomy with urinary diversion, were followed up to 12 months. However, two patients developed distant metastases after 6 months & 8 months of surgery, one of them received palliative chemotherapy and died at 10 months post radical cystectomy and the other was not fit for chemotherapy and died 11.5 months after radical cystectomy. Both patients were urothelial locally advanced (T3N1, T4N2) and show no response with neoadjuvant therapy. Pathologically, both patients showed nodal invasion with lympho vascular invasion after surgery. In twenty-seven patients were with no evidence of disease (NED) after median follow-up of 12 months.

DISCUSSION

Neoadjuvant therapy is an effective strategy to improve the outcome. The use of NAC has improved 5-year survival those patients and provided about 5 to 6.5% absolute overall survival benefit compared with cystectomy alone. Finally, 29 patients with MIBC received NAC and underwent surgery 4-6 weeks after their last chemotherapy cycle were included. Majority of patients were male - 28 (90.6%). The Mean ± SD age of the patients was 64.2±7.6 years (Range: 46 - 76 years). About 50% patients were overweight and 12 (37.5%) patients had normal BMI. Majority of patients – 28 (87.5%) were smokers. Most common clinical presentation was haematuria in 31 (96.5%) followed by dysuria 15 (46.9%), urine retention – 4 (12.5%) and urgency & frequency 2 (6.2%). Most common clinical stage was T2 in 17 (53.1%) followed by T3 – 16 (40.7%) and T4a – 2 (6.2%) whereas 24 (75.0%) patients had nodal stage N0 and 8 (25.0%) had nodal stage N+. On histopathology findings, 29 (90.7%) patients had urothelial carcinoma, 1 (3.1%) patient adeno carcinoma and 2 (6.2%) patients had mixed carcinoma with squamous differentiation. Out of 31 patients, 26 (83.9%) patients had received GC (gemcitabine/cisplatin) and 5 (16.1%) patients had received methotrexate/vinblastine/doxorubicin/cisplatin (M-VAC) neoadjuvant chemotherapy (NAC). 11 patients showed stationary course of lesion and 19 patients showed near complete resolution following NAC. Following NAC,29 patients were lymph node negative and 2 showed persistence of lymph nodes on imaging. Both of lymph node positive patients had squamous differentiation on initial TURBT histopathological examination. Out of 26 patients who had received GC, 6 (23.1%) patients had neutropenia, in 4 (15.4%) patients had thrombocytopenia, 2 (7.7%) patients had mucositis and 7 (26.9%) patients had gastritis. Out of 5 M-VAC, nephrotoxicity and skin eruption were observed in one patient each. (54.8%), 12 (38.7%) and 2 (6.5%) patients had cT2, cT3 and cT4a clinical stage prior to chemotherapy respectively. Twenty-nine patients (90.62%) underwent radical cystectomy, bilateral pelvic lymphadenectomy and suitable urinary diversion, and two patients opted for bladder preservation protocol.

Blood transfusion required in 17 (58.6%) patients and mean estimated blood loss was 594.8±205.2(Range:350-1150). Mean hospital stay (days) was 13.8±5.6 (Range: 10 - 33). Prolonged ileus and wound infection observed in 4 (13.8%) patients respectively, pneumonia – 3 (10.3%), burst abdomen, pelvic collection and metabolic abnormalities in 2 (6.9%) patients respectively and DVT in 1 (3.4%) patient. Refluxing pyelonephritis, incisional hernia and urinary incontinence were observed in 1 (3.4%) patient each.

After histopathologic examination of the specimens, the frequency of TRGs (Tumor regression grade) 1, 2, and3 in the primary tumor's were n=6 n=7, and n=16; corresponding data from the lymph nodes were n=25, n=3, and n=1.Thirteen specimens showed non-muscle invasive disease (44.82%) from which six showed pCR (20.68%) and sixteen showed muscle invasive disease (55.17%) (Table 4). Twenty-five showed negative nodes (86.20%) while four showed positive nodal disease (13.79%). Lympho-vascular invasion (LVI) was positive in 3(10.34%). Urethral margins were free in all patients. Patients with SCC have no response to NACT. Two patients developed distant metastases after 6 months & 8 months of surgery, one of them received palliative chemotherapyand died at 10 months post radical cystectomy and the other was not fit for chemotherapy and died 11.5 months after radical cystectomy. In twenty-seven patients there was evidence of disease after median follow-up of 12 months

CONCLUSION

Toxicities during NAC were expected and if professionally well managed, no patient had a delay in surgery due to adverse events and no remarkable differences in complications. A short course of neoadjuvant chemotherapy was associated to a low incidence of serious adverse events and did not increase the post-operative morbidity. Treatment of MIBC requires coordinated multidisciplinary care that often stretches across practice settings. Aiming to improve survival, neoadjuvant chemotherapy has been used for treatment of MIBC. Present results suggest that non-urothelial tumor showed no response to Platinum based combination chemotherapeutic regimens.

After NAC, residual local disease, persistent nodal disease and status of surgical margins are the most powerful prognostic factors for patients who underwent RC. Findings suggested that a higher incidence ofcancer absent upon pathological staging in the NAC arm led to a better outcome in survival following RC.In conclusion, our data support the neoadjuvant treatment for muscle-invasive bladder cancer. Future studies should focus on identifying clinical and molecular factors associated with a pathologic complete response after NAC. Aiming to improve survival, neoadjuvant chemotherapy has been used for treatmentof MIBC targeting the micro-metastatic deposits and to down-stage the disease

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