NON-INVASIVE TREATMENT OF MUSCLE INVASIVE BLADDER CANCER IN PATIENTS WITH DERANGED RENAL PROFILE

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ABSTRACT

Objective: To determine the efficacy of trimodality therapy in patients with muscle invasive carcinoma of the bladder with deranged renal profile.

Study Design: Quasi-experimental study.

Place and Duration of Study: Oncology Department, Combined Military Hospital Rawalpindi over 14 months, from Sep 2015 to Nov 2016.

Patients and Methods: Forty patients (n=40) having histopathologically confirmed (urothelial) urinary bladder cancer, clinical stage II or III, aged 18 to 80 years, with Eastern Cooperative Oncology Group (ECOG) performance status ≤2 and having deranged renal functions were included in this study. After maximal transurethral resection of bladder tumour (TURBT), they received 4 courses of chemotherapy with mitomycin and 5 fluorouracil, followed by concurrent chemoradiation using same chemotherapy received 50 Grays in 20 fractions. Response was assessed using RECIST criteria.

Results: Efficacy; defined in terms of complete and partial response, was observed in 85% (n=34) of patients. Treatment efficacy was better in males as compared to females (90.6% vs. 62.55: $p<0.05$). Patients with better ECOG-PS (0-1) and early stage (2) responded well to treatment while response was almost same in different age groups, ($p>0.05$ in all cases). Thirty-seven patients were able to complete the full study protocol, 2 had severe mucositis and hand-foot syndrome while one patient died after septicaemia.

Conclusion: Trimodality treatment with TURBT, chemotherapy and chemo-radiation is a feasible option for bladder preservation in muscle invasive bladder cancer patients with compromised renal functions if we use 5-fluorouracil and mitomycin chemotherapy.

Keywords: Concurrent chemo-radiation therapy, Deranged renal profile, Muscle invasive bladder cancer, Organ preservation, Trimodality therapy.

INTRODUCTION

Bladder cancer is the eleventh most common malignant disease in the world[1]. In Pakistani males, urinary bladder cancer is included in top ten malignancies and the commonest urological malignancy in both genders[2]. Traditionally radical cystectomy is considered to be the gold standard treatment for muscle invasive bladder cancer[3]. Oncologists have been looking for treatment options resulting in bladder preservation. Highly selected patient population with normal renal functions has benefitted from trimodality treatments in the form of transurethral resection of bladder tumour (TURBT) followed by chemotherapy and concurrent chemoradiation[4,5]. Patients with deranged renal functions are poor candidates for radical cystectomy because of the increased chances of peri-operative complications and mortality[6,7]. Such patients have benefitted from bimodality treatment of TURBT followed by concurrent chemoradiation using Mitomycin and 5-Florouracil.

Bladder preservation has the inherent advantage of retaining the natural reservoir. The quality of life is also far superior with bladder preservation when compared to radical cystectomy resulting in ileal conduit or even other continent diversion procedures[8]. Recent studies have shown that trimodality bladder preserving

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therapy, with combined transurethral resection, chemotherapy and radiation provides, disease-specific survival, progression-free survival or overall survival, at 5 or 10 years, comparable with radical cystectomy[9].

In 15-20% of muscle invasive bladder cancer patients, who fit into criteria of bladder preservation, have deranged renal profile[10] and cannot receive cisplatin, which forms the backbone of MVAC (Methotrexate, Vinblastine, Adriamycin, Cyclophosphamide) and GP (Gemcitabine, Cisplatin) chemotherapy protocols. These patients are equally poor candidates for radical cystectomy. In such cases, renal-friendly combination like mitomycin and 5-FUhas been successfully used in combination with radio-therapy[11]. Studies have also shown response and bladder preservation rates up to 89%[12].

The rationale of present study is to give a chance of bladder preservation to patients with deranged renal profile and to find a safe chemotherapy regimen for these patients. So we investigated the efficacy of Mitomycin/5 fluorouracil combination in the neoadjuvant as well as concurrent chemoradiation settings.

Our objective was to determine the efficacy of trimodality therapy in patients with muscle invasive carcinoma of the bladder with deranged renal profile.

PATIENTS AND METHODS

After getting approval from the ethical review committee of the hospital, the study was conducted at Oncology Department of Combined Military Hospital, Rawalpindi. Duration of the study was 14 months (September 2015 to November 2016). Raosoft® online sample size calculator was used that gave the required number of 40 for the study. Non-probability Consecutive sampling technique was used. Chemo-naïve patients, aged 18 to 80 years, with histopathologically proven urothelial carcinoma of urinary bladder, clinicalstage II or III, having creatinine clearance <40 ml/min, with Eastern Cooperative Oncology Group – Performance Status (ECOG PS) ≤2 and normal peripheral blood counts and liver functions were enrolled in the study. From all the patients participating in the study, an informed consent was obtained. Demographics, findings on baseline physical examination and investigations were documented on specified proforma. Study protocol as shown in figure.

Four courses of neo-adjuvant chemotherapy with Mitomycin (10mg/m^2) on day 1 combined with 5 FU (500 mg/m^2) day 1-3 at 3 weekly intervals was given before chemoradiation. Chemoradiation comprised of same protocol of chemotherapy in first and last week of radiation combined with external beam radiotherapy at a dose of 50 Grays in 20 fractions (2.5 Gray/day), 5 days a week with Saturday/Sunday off. Three-dimensional conformal radiation therapy (3D CRT) planning was done with Siemens Somatom CT simulator and radiation therapy was delivered using Siemens linear accelerator machine (Primus). Parallel opposed antero-posterior/posteroanterior radiation fields were delivered using 6 MV photons while the parallel opposed lateral fields were delivered using 15 MV photons. Weekly evaluation with history, physical examination and complete blood count, serum urea/creatinine and liver function tests were done to monitor the potential side effects of the treatment. Response to treatment was evaluated using contrast enhanced CT scan of

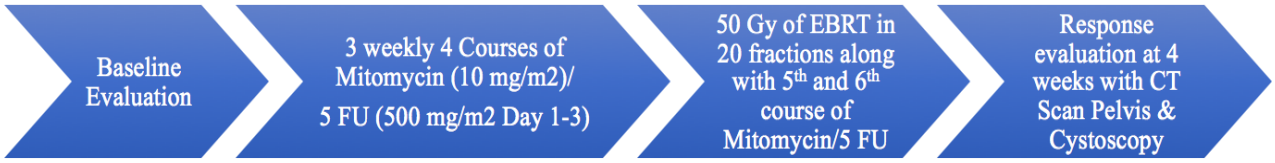

Figure: Study protocol.

pelvis after discussion with radiologist regarding possibility of contrast if not possible then non contrast enhanced scan was used, applying (RECIST criteria) and cystoscopy 6 weeks after completion of treatment. All data was recorded in a predesigned proforma. Data was entered and analyzed in SPSS version 22. Mean and standard deviation were calculated for quantitative variables like age, height, weight and BSA. Frequency and percentages were computed for qualitative variables like gender and efficacy. Effect modifiers like age, gender, stage, ECOG-PS were controlled by stratification. Post stratification chi-square test was applied. A *p*-value ≤0.05 was considered significant.

Treatment response was assessed in terms of complete response, partial response, stable disease and progressive disease. In patients as per RECIST criteria, out of 40 patients, complete response was documented in 16 (40%) patients, partial response was there in 7 (17.5%) patients, stable disease was seen in 6 (15%) patients while 8 (20%) patients had progressive disease. Overall 29 (72.5%) patients had clinical benefit from the treatment. Data was stratified for gender, age, ECOG-PS and clinical stage to deal with effect modifiers. Treatment efficacy was better in males when compared to females (90.6% vs. 62.5%) with a *p*-value of <0.05. Patients with ECOG PS 0 and 1 responded better than those with ECOG PS 2 and all the 3 patients who dropped out had ECOG PS 2 (table-I). Response evaluation to stage revealed that patients with stage II disease responded to treatment better than those with stage III disease and this was also statistically significant (table-II).

Table-I: Response according to ECOG-PS.

ECOG	No	Response					*p*-value
		CR	PR	SD	PD	DO	
0	6	6	Nil	Nil	Nil	Nil	<0.001
1	21	10	5	4	3	Nil	
2	13	Nil	2	2	5	3	
Total	40	16	7	6	8	3	40

CR=Complete response, PR=Partial response, SD=Stable disease, PD=Progressive disease, DO=Drop-out

Table-II: Response according to stage of disease.

Stage	No	Response					*p*-value
		CR	PR	SD	PD	DO	
II	15	10	4	1	Nil	Nil	<0.01
III	25	6	3	5	8	3	
Total	40	16	7	6	8	3	40

CR=Complete response, PR=Partial response, SD=Stable disease, PD=Progressive disease, DO=Drop-out

RESULTS

A total of forty (n=40) histopathologically confirmed stage II or III carcinoma of urinary bladder patients between age 18 to 80 years with ECOG performance status ≤2 and compromised renal function were recruited in this study. There were 32 males and 8 females (M:F::4:1) with a mean age of 56.4 years. Six patients had ECOG PS 0, 21 had ECOG PS 1 and 13 had ECOG PS 2. Fifteen patients had stage II disease while 25 had stage III disease. Thirty seven patients were able to complete the full study protocol, 2 had severe mucositis and hand-foot syndrome while one patient died after septicaemia.

DISCUSSION

Traditionally radical cystectomy has been considered as the treatment of choice for muscle invasive stage of disease. Radical cystectomy is associated with 1 to 2 percent risk of a treatment-related mortality[13]. In patients with comorbidities (cardiopulmonary and renal dysfunction), there is even more risk of mortality. Furthermore, the median age of urothelial carcinoma diagnosis is 73 years, this older population is not good

candidate for major surgeries[14]. The perioperative mortality rates for 90-days increase with increasing age and reach up to 9 percent in more than 80 years old patients[15].

Alternative, bladder sparing treatment approaches have been explored in order to avoid the morbidities of radical cystectomy and to improve the functional and social outcome of the patients[4]. Recently treatment paradigm has a shifted towards bladder preservation using trimodality approach including transurethral resection of bladder tumor (TURBT), chemotherapy and concurrent chemo-radiation therapy (CCRT). Patients who received combined modality therapy had significantly better general health-related, patient-reported quality of life than patients who had a radical cystectomy. Combined modality therapy also had better equivalent urinary quality of life and bowel quality of life compared with radical cystectomy[8]. Recent studies have shown that trimodality bladder preserving therapy provides survival comparable with radical cystectomy[9]. In patients having invasive bladder cancer, five year survival with bladder preservation was improved in the long term survivors who maintained a functional bladder, with no apparent cost in terms of survival.

There has been a systemic review from 1980-2013 to assess modern bladder preservation treatment modalities in muscle invasive bladder cancer. They have recommended trimodality therapy[16]. Outcome of trimodality therapy depends upon the extent of transuretheral resection[17,18]. Reduced salvage cystectomy rate and improved survival were observed with complete transuretheral resection of bladder tumor prior to bladder preservation[18]. For trimodality bladder preservation strategy, neoadjuvant chemotherapy is given[19,20].

In the past decade, most of trials have used single agent Cisplatinor 5–fluorouracilfor radio-sensitization during radiotherapy. In an attempt to improve safety and to increase efficacy, newer studies of multimodality therapy were done, including chemotherapeutic agents that have recently shown excellent activity in metastatic urothelial cancers, such as gemcitabine and mitomycin. Several phase II trials demonstrated that gemcitabine combined with cisplatin was active regimen and have shown excellent response rates and bladder preservation rates in patients with normal renal profile. Almost all studies of bladder preservation used cisplatin[21]. About 15-20% of patients reporting to our department have deranged renal profile. Cisplatin being nephrotoxic cannot be used in this patient population. Alternatives for these patients include gemcitabine/carboplatin which is a myelotoxicregimen. Radiosensitization can be done by using a combination of 5-fluorouracil and mitomycin C[22]. Synchronous chemotherapy with mitomycin C and fluorouracil combined with radiotherapy significantly improved locoregional control, disease free survival and overall survival of bladder cancer, as compared with radiotherapy alone[11].

We wanted to check the efficacy of fluorouracil and mitomycin chemotherapy as a trimodality therapy. This chemotherapy has been tried in international studies and no significant difference was found in survival, as compared to other regimens[23]. Out of 40 patients included in our study, complete response was documented in 16 (40%) patients. When we compare this with South West Oncology Group study[24], which had a complete response rate of 49% with standard cisplatin based chemotherapy.

We had a partial response in 7 (17.5%) patients, stable disease was seen in 6 (15%) patients while 8 (20%) patients had progressive disease. Overall 29 (72.5%) of the patients had clinical benefit from the treatment. The present study showed that mitomycin/capecitabine is an acceptable alternative to nephrotoxic drugs like cisplatin. Side effects of this treatment are minimal as only 3 (7.5%) patients had grade III or grade IV toxicities, in ours study. Our set of patients had less grade 3,4 toxicities as compared to study of James *et al*[11], in which 36% of patients had toxicity. Reasons for this reduced toxicity

were, a reduced dose of mitomycin from 12 mg/m^2 to 10 mg/m^2 and also a decreased dose of radiotherapy from 55 Gy to 50 Gy.

The combination of chemotherapy used by us, is being used in other international studies. The TUXEDO is a phase I trial[25] examining concurrent chemo-radiotherapy in muscle invasive bladder cancer has been completed with good response rate. Phase-II trial is currently underway in UK. It is also using fluorouracil and mitomycin chemotherapy but with addition of cetuximab.

CONCLUSION

Trimodality treatment with maximal TURBT, chemotherapy and chemoradiation is a feasible and effective option for bladder preservation in muscle invasive bladder cancer patients with compromised renal functions if we use 5-fluorouracil and mitomycin as chemotherapy. Trimodality treatment improved locoregional disease control, in renal function compromised patients.

RECOMMENDATIONS

Trimodality treatment can be used for bladder preservation in renal compromised patients. Further studies with large number of patients are required for better understanding and making this protocol a treatment standard.

CONFLICT OF INTEREST

This study does not have any conflict of interest to announce.

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