Bladder Preservation with Concurrent Radiotherapy and Gemcitabine following Maximal Transurethral Resection for Muscle Invasive Bladder Cancer: Single Institutional Experience

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Abstract

Objectives: For bladder preservation, cisplatin is widely used radiosensitizer with concurrent chemoradiation (CRT). We aimed to evaluate the safety profile and potential benefit of gemcitabine as a radiosensitizer in bladder preservation.

Patients and methods: During July 2006 to January 2007, consecutive 32 patients with T2-T4N0M0 bladder cancer underwent transurethral resection of bladder tumor (TURBT) followed by concurrent chemoradiation with weekly gemcitabine 100 mg/m². Conformal radiotherapy was given with a shrinking field technique. Complete response was defined as no visible tumor on cystoscopy and biopsy.

Results: Of total, 26 patients received a median of 7 (3–8) cycles of gemcitabine and median cumulative radiation dose of 65 Gy. Grade 3 hematologic toxicities seen were; neutropenia (3.8%) and thrombocytopenia (7.7%). Grade 3 non-hematologic toxicities were; diarrhea (19.2%), nausea/vomiting (7.7%) and cystitis (15.4%). Complete response was achieved in 18 patients (69.2% [95% CI: 60–89%]). At median follow up of 36 months, four patients had local recurrences (two superficial and two muscle invasive). The overall intact bladder and overall survival rates were 75.1% and 56.3%, respectively.

Conclusion: CRT with weekly gemcitabine was found feasible and highly active in the treatment of muscle invasive bladder cancer, as the 3 year intact bladder survival rates were promising.

Keywords: Muscle invasive bladder cancer; Bladder preservation; Gemcitabine; Radiosensitizer; Intact bladder and overall survival

Introduction

In Saudi Arabia, bladder cancer is the 10th and the 20th most common cancer in males and females and the smoking is main cause of bladder cancer according to the King Faisal Specialist Hospital and Research Center (KFSH & RC) Cancer Registry [1], which is much lower as compared to the most of developing countries; where bladder cancer is most common urologic malignancy [2]. According to the treatment, bladder cancer is categorized into, superficial (non-invasive), muscle invasive and metastatic disease [3]. Muscle invasive bladder cancer is traditionally treated with radical cystectomy with long term survival rates around 50% [4]. Even the new surgical techniques including construction of neobladder with continent urinary diversion cannot substitute for the original bladder [5]. An alternative option is the bladder preservation incorporating maximal transurethral resection of bladder tumor (TURBT) and concurrent chemoradiation (CCRT) and it has demonstrated similar overall survival around 50% to radical cystectomy [6,7]. Cisplatin is commonly used as a radiosensitizer; however, this agent has significant toxicity, limiting its utility. In Radiation Therapy Oncology Group (RTOG) 85-12, for example, only 30 of 42 assessable patients were able to complete the entire therapy per protocol [8].

Gemcitabine, a nucleoside analog has shown significant activity as a radiosensitizer in various preclinical and clinical studies [9,10]. Additionally, cisplatin is not a choice as radiosensitizer in patients with compromised renal functions.

On the basis of these data, this study was undertaken prospectively to determine the complete response rates, safety profile with radiation, disease free and overall survival rates with intact functional bladder in

conjunction with a weekly gemcitabine concurrent with radiation as a bladder preservation option.

Patients and Methods

After taking written consent, consecutive patients with muscle invasive bladder cancer were enrolled between July 2006 and January 2007 and were followed up until January 2010.

Eligibility

After protocol approval by institutional review board, patients were enrolled. At time of enrollment, eligible patients were required to have; histopathological proven muscle invasive transitional cell carcinoma of bladder; European Cooperative Oncology Group (ECOG) performance status 0-2; American Joint Committee on Cancer (AJCC) stage T2b-T4aN0M0; baseline full capacity functioning bladder; maximum transurethral resection of bladder tumor (TURBT) at time of CCRT; normal hematology with hemoglobin ≥ 10 gm/dl, white blood cells (WBC) $\geq 4000/\text{mm}^3$, platelets $\geq 100,000/\text{mm}^3$ and

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normal renal functions (serum creatinine ≤ 2.0 mg/dl or creatinine clearance ≥ 60 ml/min) and normal electrolyte values.

Patients with concurrent Tis or superficial bladder cancer, any lymphadenopathy or distant metastasis, with poor performance status, prior chemotherapy, radiotherapy or prior history of malignancy were excluded. Hydronephrosis was not included as exclusion criteria. Attempts were made to correct renal functions by percutaneous nephrostomy (PCN) or urinary diversion.

Treatment protocol

All patients underwent CCRT within 6 weeks after maximal TURBT.

Transurethral resection of bladder tumor (TURBT): After meeting with eligibility criteria, all patients underwent cystoscopic evaluation including examination under spinal anesthesia; Bi-manual examination was carried out before and after TURBT. Cystoscopy was performed by experienced urologist and maximal TURBT was defined as no visible tumor after resection. Visually maximal TURBT in one or more attempts. The small residuals after second sitting of TURBT were also eligible.

Radiation therapy: All patients were simulated on virtual simulator and three dimensional (3D) conformal planning was performed. Radiotherapy was given with shrinking field technique

(Figure 1), (1) initial phase included whole pelvis, covered by four fields anteroposterior (AP), posteroanterior (PA), two opposing lateral fields (right and left lateral) to encompass the entire bladder, prostate, and pelvic lymph nodes. The field borders were at the L5-S1 interspace cephalad, at laterally 1cm beyond bony pelvis, and the inferior margin of obturator foramen caudally. The dose given was 45 Gy with fraction size 1.8 Gy in 25 fractions, five days/a week, (2) in boost phase; multiple radiation fields were used to cover the gross tumor volume only with 1 cm margin. The boost dose to gross tumor volume was given 20 Gy with fraction size 2 Gy in ten fractions to complete cumulative 65 Gy. The maximum doses to the posterior rectal wall and to the femoral heads were kept 55 Gy and 45 Gy, respectively. All radiation was delivered by 6 to 15 MV photons from multileaf collimator (MLC) based linear accelerator.

Chemotherapy: Gemcitabine 100 mg/m² intravenously was given weekly, 30 minutes prior to radiation for six weeks. During CRT, dose was modified on a weekly basis. If the WBC count was $<2,000/\text{mm}^3$ or platelet count was $<50,000/\text{mm}^3$, all chemotherapy for that week was omitted. If the WBC count was $<1,000/\text{mm}^3$ or platelet count was $<25,000/\text{mm}^3$, CCRT was withheld until WBC count and platelet counts recovered to $\geq 1,000/\text{mm}^3$ and $25,000/\text{mm}^3$, respectively. For grade 3 or more non-hematological toxicity gemcitabine was withheld for that week and radiation was continued if score changed to grade 2.

Figure 1: Four field Box Technique irradiating pelvic lymph nodes, along with gross tumor volume.

Toxicity and assessment evaluation

During CCRT, patients were evaluated every week for weight, performance status, hematology/chemistry and other related symptoms. The National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0, were used to score acute radiation and chemotherapy toxicity (≤ 90 days from start of radiation therapy). The Radiation Therapy Oncology Group (RTOG) Late Radiation Morbidity Scoring Criteria were used to score radiation toxicity persisting beyond 90 days from the completion of radiotherapy.

Follow-up: Check cystoscopy was performed after the completion of treatment and biopsy was taken only in selected cases with suspected residual disease. Patients were considered to have achieved a complete response (CR) if no evidence of visible tumor on cystoscopy / biopsy and urine cytology showed any malignancy. Patients with CR or only superficial tumor (Ta, Tis, or T1) at a new site were followed as bladder preservation. Patients with any residual tumor at the original tumor site or muscle-invasive tumor (T2 or greater) at a new site underwent salvage cystectomy. During the follow up period, patients underwent check cystoscopy 6 weeks after completion of concurrent chemoradiation, and then every 3 months for first year and every 6 months for following years. During follow up, superficial recurrences were treated with complete TURBT and intravesical therapy (intravesical bacilli Calmette-Guerin BCG; Connaught strain, 81 mg/50ml) over 6 weeks induction course and then each week for 3 weeks. Recurrent muscle invasive tumors were treated with salvage cystectomies. For distant metastasis, bone scan, CT chest, abdomen and pelvis were repeated every 6 months after completion of treatment.

Statistical analysis

The primary endpoints were the effectiveness of the regimen in terms of safety profile, and response rates and the secondary points were local recurrence and distant metastasis. The times to last follow up evaluation, appearance of local and distant relapse and death were calculated from date of starting treatment. Disease free survival (DFS) was defined as the duration between the entry date and the date of documented disease reappearance, death from cancer and/or last follow-up (censored). Overall survival (OS) was defined as the duration between the entry date and the date of patient death or last follow-up (censored). Probabilities of local and distant control, disease free and the overall survival were determined with the Kaplan-Meier method. The comparisons for various endpoints were performed using log rank test and Cox regression analysis. Statistical analyses were performed using the computer program SPSS version 16.0.

Results

Patient characteristics

A total 22 males and 10 females with mean age 60.06 years (range 36-75) with muscle invasive bladder cancer were treated (Table 1). 15 patients (46.9%) were with radiological stage T3N0M0. Nine patients (28.1%) had hydronephrosis at time of enrollment, for which all of these patients underwent percutaneous nephrostomy (PCN). Complete TURBT was performed in 22 patients (68.8%) in one or more attempts. All patients had ECOG performance status 0-1.

Initial response and treatment related toxicity

For 32 patients, acute non-hematological grade 3 side effects of concurrent chemoradiation were nausea & vomiting 15.6% (5 patients), diarrhea 18.7% (6 patients) and cystitis in 18.7% (6 patients). The G4 side effects were only cystitis seen in 3.0% cases. The acute

hematological grade 3 toxicities were neutropenia 3.1% (1 patient) and thrombocytopenia 6.2% (2 patients) (Figure 2). The weekly gemcitabine was omitted for one course in three patients; however, no dose reduction was seen during course of radiation.

Out of 32 patients, 26 patients underwent first check cystoscopy and biopsy at 3 months following CRT. Remaining six patients were lost to follow up. The complete response (CR) on first check cystoscopy/ tumor site biopsy at 3 months following concurrent chemoradiation, was seen in 18 patients (69.2%, 95% confidence interval {CI} 60–89). Of 8 patients, who did not achieve CR, all underwent salvage cystectomies.

Late side effects at one year after treatment were seen in only two patients (7.7%) were consistent with mild irritative bladder symptoms. No delayed gastrointestinal or hematological toxicity were observed.

Local recurrences, distant metastasis, survival and disease free survival

At the median follow-up period of 36 months (24-38 months), local recurrences were seen in 4 patients (15.4%) out of 18 initial complete responders. Two (7.7%) had superficial bladder cancers (pT1, G2) and were treated with complete TURBT followed by intravesical bacillus Calmette-Guerin (BCG). Two (7.7%) had muscle invasive cancer, for which salvage cystectomy was performed.

Variable	Number (%)
Age	60.06 years (range 36-75)
Gender	
Male	22 (68.7)
Female	10 (31.3)
Clinical Stage	
T2N0M0	10 (31.2)
T3N0M0	15 (46.9)
T4N0M0	7 (21.9)
Hydronephrosis	
No	23 (71.9)
Yes	9 (28.1)
Visible complete TURBT performed	
Yes	22 (68.7)
No	10 (31.3)
ECOG	
0-2	32 (100)
3-4	0

Table 1: Patient characteristics.

Bony metastases were seen in three patients (11.5%); and were treated with salvage chemotherapy, palliative radiotherapy for pain relief and bisphosphonates.

At the time of analysis 14 patients initial 18 complete responders (77.78%) continued to retain their original bladder and were free of disease. Using the Kaplan-Meier method, over intact bladder rates 75.1% were at 3 years and 3 year survival was found to be 56.3% (Figure 3).

On Cox-regression analysis, significant differences in survival were found between the subgroups of hydronephrosis (presence vs. absence) (log-rank p 0.0001), primary Tumor stage ($<T3$ vs. more than $T3$) (log-rank p 0.0001), initial complete response (yes vs. no) and incomplete TURBT (yes vs. no) (log-rank p 0.001).

Discussion

The current standard of care for muscle-invasive bladder cancer is radical cystectomy. Trimodality treatment, including maximal transurethral resection of the bladder tumor (TURBT) followed by concurrent chemoradiation has been shown to produce five year survival rates in the range of 50-60%, comparable with those of cystectomy [11,12]. With this bladder preservation strategy, cystectomy has been reserved for patients with incomplete response

or local invasive recurrence [8]. The majority of these trials have used cisplatin as a radiosensitizer. However, reported grade 3 and 4 hematologic and non-hematologic toxicities were considerable in the neoadjuvant or non neoadjuvant resulting in poor compliance and outcome assessment [13].

In the present study, gemcitabine was given for its proven potent radiosensitizer properties. Gemcitabine was well tolerated in our study population. Six patients could not complete the treatment protocol owing to their socioeconomic reasons. We observed more non hematological side effects including nausea, vomiting (15.6%) and diarrhea (18.7%). The possible explanation could be that, we used initial large pelvic fields to irradiate pelvic lymph nodes. However, similarly designed study by Kent E et al. reported no grade 3 gastrointestinal toxicity by using bladder fields [14]. Further, we did not see any deranged liver function tests in our patient population. In our study, all patients were treated by 3D-CRT; however the acute side effects may further increase if conventional methods of radiation are used.

We used gemcitabine 100 mg/m² weekly, different from other similar designed trials [15,16] to increase the compliance which was (100%) in our study population.

Our study resulted in 3 year overall survival rates of 56.3% and with intact bladder disease free disease free survival rates of 75.1%. These

Figure 3: 3 year local recurrence free and overall survival rates.

Study (reference)	Patients	Regimen	CR	Toxicity Grade 3
Kent E et al [14]	24	RT 60Gy + 30 fractions+ gemcitabine MTD 10-30mg/m ² twice weekly	91%	Hepatic: 3 patient Diarrhea: 1 patient Neutropenia: 1 patient
Caffo O et al. [17]	16	RT 54Gy + 30 fractions+ gemcitabine MTD 400mg/m ² weekly+ cisplatin 100mg/m ² q 3wks	100%	NA
Sangar VK et al. [18]	8	RT 52.5Gy + 20 fractions +gemcitabine MTD 150mg/m ² once weekly	88%	Cystitis: 1 patient Diarrhea: 1 patient
Present study	32	RT 65Gy +35 fractions +gemcitabine 100mg/m ² weekly	69.2%	Diarrhea: 6 patients Nausea and vomiting: 5 patients Neutropenia: 1 patient Thrombocytopenia: 2 patient Cystitis: 1 patient

NA= not available

Table 2: comparison of present study with similar other published studies.

results are comparable to other similarly designed studies (Table 2). The presence of the hydronephrosis and advanced T stage, absence of post treatment complete response and incomplete TURBT are generally considered poor prognostic factors affecting the survival in patients undergo either radical cystectomy or bladder preservation [19,20]. Our study cohort was mainly with T stage >T3 and hydronephrosis; for these patients continent diversion is difficult after radical cystectomy. Our study did not evaluate the DNA ploidy, tumor grade and HER 2 over-expression which are considered additional poor prognostic factors [21,22].

Conclusion

Although the follow up period was shorter to evaluate the prognostic factors influencing the survival and bladder preservation, bladder preservation with concurrent gemcitabine and radiation therapy is adequate option for patients with no hydronephrosis, lower T stage (<T3) and with maximum complete TURBT.

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