



Intravesical Mitomycin-C with Bladder Wall Hyperthermia in Intermediate and High-risk Non-muscle Invasive Bladder Cancers: Prospective Clinical Trial with a Single-treatment Arm

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Abstract

Objective: Bacillus Calmette-Guérin (BCG) limited availability, cost, and allergic response in some patients limit its use, leading to the search for alternative agents. We aimed to present the outcomes of intermediate- and high-risk non-muscle invasive bladder cancers treated with bladder wall thermochemotherapy (BWT) system via a single-arm prospective study.

Materials and Methods: Overall, 44 patients were enrolled and subjected to a treatment with mitomycin-C and BWT for 6 weeks, followed by a monthly maintenance for up to 1 year. The recurrence rate, progression rate, recurrence-free survival, progression-free survival, and side effects were evaluated.

Results: In the intermediate- and high-risk groups, the median follow-up duration was 14 and 17 months; recurrence rates were 28.6% and 23.3%; progression rates were 7.1% and 23.3%; the recurrence free survival at the 24th month were 78.6% and 80.0% and the progression free survival at the 24th month were 92.6% and 76.7%, respectively. All the patients suffered from dysuria lasting for 2-3 days; five of the 44 BWT application developed allergic reactions requiring treatments with oral agents.

Conclusion: BWT showed comparable recurrence and progression rates, but seemed safer than BCG when our findings were compared to those of published studies. It could be an alternative for individuals who are not suitable for BCG or in a case of BCG unavailability.

Keywords: Bladder, cancer, intravesical, mitomycin, thermo

Introduction

Among all cancers, bladder cancer (BC) ranks 10th in incidence among both sexes. At the time of diagnosis, most BCs (70%-80%) are non-muscle invasive (NMI) (1,2). It is advisable to stratify them into low-, intermediate-, and high-risk groups based on their clinical features, pathological stages, and grades because NMI-BC patients show varying risks in terms of recurrence and progression. For the low-risk group, one dose of intravesical chemotherapy immediately after transurethral resection of the BC (TURBT) is sufficient in almost all patients. However, for the intermediate- and high-risk groups, it is quite challenging

to tailor the appropriate treatment. Although intravesical chemotherapy prevents recurrences, it is not as effective in preventing their progression as intravesical Bacillus Calmette-Guérin (BCG) for the intermediate-risk group. Intravesical BCG with a one-year maintenance was demonstrated to be superior to intravesical chemotherapy in preventing BC progression in the intermediate-risk group. Intravesical BCG with 1-3 years of maintenance or radical cystectomy is another treatment option suggested for the high-risk group (3). However, the fact that BCG has serious side effects and is not always readily available from the market has escalated the search for new alternatives such as intravesical mitomycin-C (MMC) application with

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hyperthermia [thermochemotherapy (TCT)]. Several studies have compared TCT with intravesical chemotherapy alone or with BCG, which employed a microwave technology as the heating system (4,5,6). A limited number of studies have employed a conductive heating system (7,8).

This paper presents the recurrence and progression outcomes of intermediate- and high-risk NMIBC treated with the bladder wall TCT system.

Materials and Methods

Patient Selection

The study was designed as a prospective study with a single-treatment arm, including MMC with TCT. The study group included NMIBC patients who were newly diagnosed or followed-up as recurrent patients between January 2014 and February 2015. They were stratified into intermediate and high-risk groups according to the criteria defined in the European Association of Urology Guidelines on “non-muscle invasive urothelial carcinoma of bladder” (3). All of them had been histologically diagnosed with urothelial carcinoma. The exclusion criteria included low bladder capacity (<150 mL), increased post-voiding residual urine (>150 mL), untreatable or uncontrollable urinary tract infection, history of urethral stricture, presence of bladder diverticula >1 cm size, pathology other than urothelial carcinoma, World Health Organization performance status >2, and upper urinary tract urothelial carcinoma diagnosis. Before the application of TCT, complete TURBT was performed. Restaging TURBT (RE-TURBT) was conducted within four weeks for patients with initial T1 pathology. Postoperative single-dose intravesical chemotherapy was applied to all the patients. The first TCT instillation was applied at 1 month following the TURBT or the RE-TURBT.

Thermochemotherapy Application and Treatment Schedule

The bladder wall TCT (BWT) system (Elmedical, Hod-Hasharon, Israel) was used as a conductive heating modality. MMC (40 mg; MMC Kyowa Hakko Kogyo Co., Ltd., Tokyo, Japan) was mixed with 50 mL of 0.9% saline solution and applied using a disposable silicone 20 Fr 3-way TCT catheter (UniThermia catheter; Elmedical). In each session, the bladder was irrigated with MMC solution at 42 °C - 45 °C for 45 minute via the BWT system. The treatment schedule consisted of an initial 6-week instillation, followed by control cystoscopy and urine cytology in the 3rd month and monthly instillations for up to 1 year. Urine cytology and cystoscopy were performed every three months. The samples were collected from the suspected areas during cystoscopy. At the end of the first year, a control cystoscopy with random bladder biopsies was conducted. During the second year, routine controls were conducted every three months. Subsequently, follow-ups were performed every six months. In case of the development of any complication in a patient, TCT was discontinued. Before each instillation of TCT, clear urine cultures were obtained from all the patients. No prophylactic anticholinergic agent was administered prior to the intravesical

TCT. If TURBT pathology was Ta or T1 during the follow-up, it was accepted as a recurrence. If it was carcinoma *in situ* or T2, it was accepted as a progression. All the adverse events observed during the study were recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (9).

All the study protocols were approved by the local ethical committee at our institution on July, 4th, 2014 (IRB Approval number: 2014/387). An informed consent was obtained from all the patients.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 22 for windows (IBM, NY, USA) software package. Normality test was done with Shapiro-Wilks test. Survival analysis was done with Kaplan-Meier tests and survival tables.

Results

In total, 44 patients (females =2, rest were males) were enrolled in this study, of which 14 showed intermediate-risk NMIBC and 30 showed high-risk NMIBC. The patients' characteristics are summarised in Table 1. Eight patients had a history of intravesical chemotherapy or BCG. The median follow-up period was 14 months in the intermediate-risk group and 17 months in the high-risk group. In both groups, the median number of BWT instillation was 9. The recurrence rate was 28.6% (4/14) in the intermediate-risk group and 23.3% (7/30) in the high-risk group. Progression was detected in only one (7.1%) patients from the intermediate-risk group and seven (23.3%) patients from the high-risk group. Four patients showed progression to the T2 stage, three of whom received radical cystectomy and the remaining one patient was at the metastatic stage clinically and preferred a bladder-preserving treatment modality (chemo-radiotherapy). The progression pathology was carcinoma *in situ* in the remaining four patients. The initial pathology before TCT was also carcinoma *in situ* in two of them. Radical cystectomy was suggested to patients with carcinoma *in situ* after TCT, but they preferred intravesical BCG. In the intermediate- and high-risk groups, the recurrence free survival rates at the 24th month were 78.6% and 80% and the progression free survival rates at the 24th month were 92.6% and 76.7%, respectively. The Kaplan-Meier curves of recurrence-free survival and progression-free survival are shown in Figures 1 and 2.

After TCT, no patient reported bladder spasms, bladder pain, and urgency or frequency. However, all the patients reported dysuria resulting from catheterisation that lasted for 2-3 days. No action was taken other than the conservative management for dysuria. Overall, 442 TCT applications were conducted. Allergic reactions (skin rash and hyperemia) were observed in five out of the 442 TCT treated patients (1.12%), who were treated with oral anti-histaminic agents. None of these allergic attacks broke out with the first TCT, but the study protocol was discontinued for these patients. Urethral stricture developed in one patient after the 9th TCT application, upon which TCT was discontinued for them. It was hard to confirm TCT application as the reason for urethral stricture because this patient had BC

Table 1. Characteristics of intermediate and high-risk patients			
	Intermediate n=14	High n=30	Overall n=44
Gender			
• Male	13 (92.9%)	29 (96.7%)	42 (95.5%)
• Female	1 (7.1%)	1 (3.3%)	2 (4.5%)
Age in years	68.14±10.75	64.73±8.74	65.82±9.43
Previous intravesical treatment			
• No previous treatment	12 (85.7%)	24 (80%)	36 (81.8%)
• MMC	1 (7.1%)	1 (3.3%)	2 (4.5%)
• BCG	1 (7.1%)	3 (10%)	4 (9.1%)
• MMC + BCG	0	2 (6.7%)	2 (4.5%)
Grade			
• Low Grade	14	16 (53.3%)	30 (68.2%)
• High Grade	0	14 (46.7%)	14 (31.8%)
Stage			
• Ta	14	6 (20%)	20 (45.5%)
• T1	0	22 (73.3%)	22 (50%)
• CIS	0	2 (6.7%)	2 (4.5%)
Follow-up in months -median (min-max)	14 (3-41)	17 (2-47)	16.5 (2-47)
# of BWT session -median (min-max)	9 (2-16)	9 (4-16)	9 (2-16)
Recurrence	4 (28.6%)	7 (23.3%)	11 (25%)
Progression	1 (7.1%)	7 (23.3%)	8 (18.2%)
Adverse event			
• Allergic reaction	1 (7.1%)	4 (13.3%)	5 (11.4%)
• Urethral stricture	0	1 (3.3%)	1 (2.3%)
Treatment after progression			
• Radical cystectomy	1 (7.1%)	2 (6.7%)	3 (6.8%)
• Radiotherapy & chemotherapy	0	1 (3.3%)	1 (2.3%)
• BCG with maintenance	0	4 (13.3%)	4 (9.1%)
MMC: Mitomycin-C, BCG: Bacillus Calmette-Guerin, CIS: Carcinoma <i>in situ</i> , BWT: Bladder wall thermotherapy, min: Minimum, max: Maximum			

for >5 year and a history of intravesical MMC and BCG. All these adverse events were of ≤ grade 2 according to CTCAE v4.0.

Discussion

The search for new agents and administration routes for intravesical treatment to prevent recurrence and progression in NMIBC is actively ongoing. MMC, which is safer than BCG, does not have the same efficacy to prevent progression as it does for recurrence (10).

Accordingly, in an attempt to increase its efficacy, MMC application with hyperthermia has gained much attention for application and research since the past 20 years. Colombo et al. (5) reported recurrence rates of MMC alone and TCT + MMC in a median 90 months of follow-up as 80% and 14%, respectively, whereas the progression rates were 15% and 8.6%, respectively.

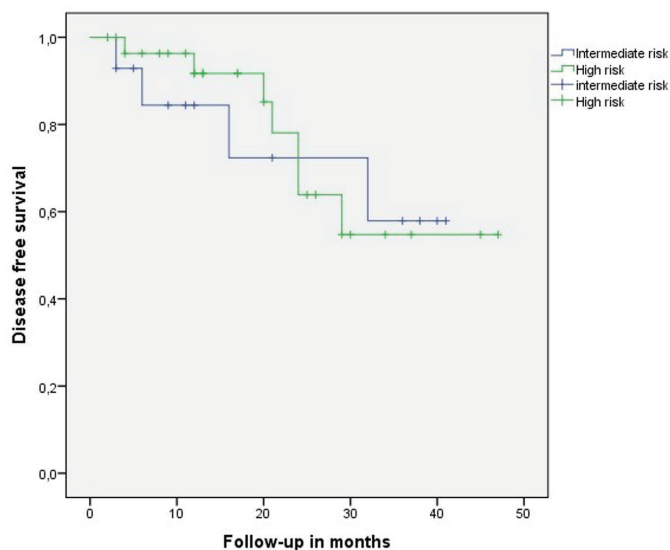


Figure 1. Kaplan-Meier curve of recurrence free survival in both groups

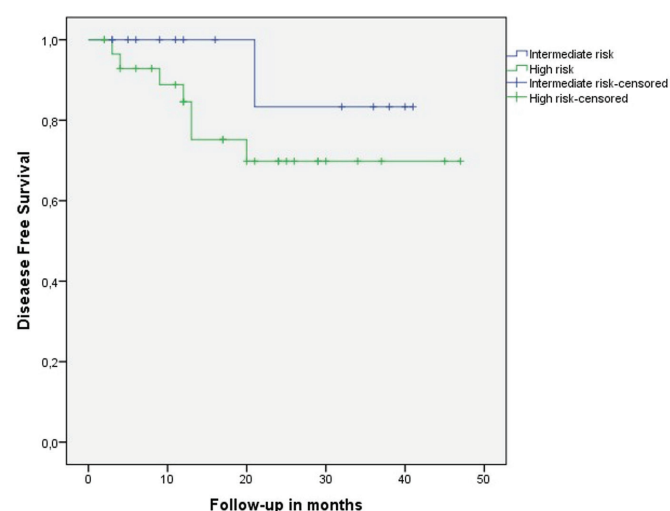


Figure 2. Kaplan-Meier curve of progression free survival in both groups

Another study (4) that used the same hyperthermia system reported a recurrence rate of 9% in the TCT group at the end of a median of 289 days of follow-up. In the multicentric phases 1 and 2 study of the conductive heating modality, the recurrence and progression rates were stated as 35.3% and 23.5% with a median follow-up of 41 months (7). In another cohort using a conductive heating system with 40 high-risk NMIBC patients, the recurrence rate was 32.5% and the median recurrence-free survival period was 23 months (8). In a randomised prospective study, the recurrence-free survival at the 24th month was 81.8% for TCT + MMC and 64.8% for the BCG arm. Progression was observed in one patient with BCG (1.4%). In addition, in the case of CIS, no statistically significant difference was noted between the BCG and TCT + MMC groups (6). Unlike in the studies in the literature, this study evaluated the intermediate- and high-risk NMIBC groups separately. Initially, we planned to compare the TCT + MMC and BCG groups, but the unavailability of BCG did not allow it. The recurrence rates of 14 intermediate-

risk and 30 high-risk patients in this study were 28.6% and 23.3%, respectively. The progression rates were 7.1%, 23.3%, respectively. As compared with the published series, the recurrence rate was better, although the progression rate was higher in the study group.

Considering the adverse events, MMC showed a better profile than BCG. In a meta-analysis comparing intravesical treatments, 27%-84% granulomatous cystitis or lower urinary tract symptoms (dysuria, urgency and frequency), 21%-72% macroscopic haematuria, and 27%-44% fever were reported as BCG side effects (10). In another study that compared MMC + TCT with BCG application, bladder spasm (14.4%) and bladder pain (14.1%) were noted as the main side effects in the MMC arm, whereas dysuria (11.7%), nocturia (10.3%), and frequency (9.9%) were the side effects noted in the BCG arm. In this study, the sole adverse event was mild allergic reactions treated with oral agents and dysuria lasting for 2-3 days. This symptomatic process was treated conservatively. All the side effects recorded were of a grade ≤ 2 .

Study Limitations

The limitations of this study were the small sample size and the single-arm approach. To attain more powerful oncologic results, there is no doubt the need for randomized double arm studies with more patients comparing MMC + BWT and BCG.

Conclusion

Comparing our results with that of the literature, MMC with BWT had comparable recurrence and progression rates as BCG, with the number of side effects being significantly lower than those with BCG. Thus, MMC + BWT can be considered as an alternative treatment option for selected cases in whom BCG cannot be applied or is not available. Furthermore, MMC + BWT costs less and produces lesser side effects compared with other hyperthermia systems, making it an attractive option.

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Ethics

Ethics Committee Approval: The study protocol was approved by the Erciyes University Clinical Research Ethics Committee (decision number: 2014/387, date: 04.07.2014).

Informed Consent: An informed consent was obtained from all the patients.

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Authorship Contributions

Concept: G.S., A.D., Design: G.S., Ak.D., A.D., Data Collection and Processing: Ş.T.T., T.D., Ak.D., Analysis and Interpretation: A.D., A.T., T.D., Literature Search: Ş.T.T., Writing: A.D.

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