The Effect of Passive Intravesical Instillation of Mitomycin C with BCG versus BCG alone in Non-Muscle Invasive Bladder Cancer: A randomized controlled trial

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Abstract

Aim and objectives: The aim of this study was to evaluate the effect of the combination of bacillus Calmette-Guerin (BCG) and mitomycin C (MMC) in comparison to BCG alone in the treatment of patients with non-muscle invasive bladder cancer.

Materials and methods: Our study is a randomized clinical trial carried out on 50 Patients diagnosed with non-muscle invasive urothelial bladder cancer, they were classified into 2 groups: Group (I): included 25 patients who received immediate single instillation of mitomycin C (MMC) after TURBT then intravesical BCG per week for 6 weeks and Group (II): included 25 patients who were treated with TURBT followed by intravesical BCG per week for 6 weeks alone (standard of care). Patients were being followed up at 3, 6, 12, 18 months by cystoscopy. The outcome measures were time to recurrence, progression of the disease to muscles or other organs, disease free survival, and treatment-related side effects.

Result: Immediate single instillation of mitomycin C (MMC) after TURBT in combination with BCG had low recurrence rate compared to BCG alone (36% vs 48% respectively, p=0.567), and longer disease free interval (64.0% vs 52.0% respectively, p=0.567). Four patients progressed to muscle invasive bladder cancer in BCG alone group. While three patients progressed to muscle invasive bladder cancer in MMC+BCG group However, this difference was not statistically significant (p= 0.896). Regarding side effects, there were no statistically significant differences between groups.

Conclusion: Immediate single instillation of mitomycin C after TURBT in combination with BCG seems to be effective in decrease recurrence rates and enhances the disease-free interval compared with TURBT followed by BCG alone at least in short term.

Keywords: Mitomycin C, Transurethral resection of bladder tumors, BCG, Recurrence, Non muscle invasive bladder cancer..

Introduction

Bladder cancer (BCa) is the seventh most common cancer in men and the eleventh most common cancer in women worldwide. Its incidence in men is 4 times greater than in women with peak incidence at the seventh decade of age. Bladder cancer has the second highest prevalence in Egypt. It accounts for 12.7% of male cancers with the majority of cases [1, 2].

90% of bladder tumours are histologically urothelial, 5% are squamous cell carcinomas, and less than 2% are adenocarcinomas or other variants. Approximately 70% of all urothelial BCa at presentation are non-muscle invasive (NMIBC), with 70% presenting in stage Ta, 20% as T1, and 10% as CIS (carcinoma in

situ) [3, 4]. These tumours are classified as NMIBC because they can be treated with transurethral resection of bladder tumours and/or intravesical instillations.
Based on EORTC risk score, NMIBC is stratified into three-risk groups; low, intermediate and high risk groups. Such stratification reflects probability of recurrence and progression, and provides the basis for surveillance protocols and adjuvant intra-vesical therapies. Low grade Ta tumors have a 50% to 70% recurrence rate, and progress in approximately 5% of cases. In contrast to high-grade T1 tumors that can recur in up to 80%, and progress in up to 50% of patients within 3 years [5-7].

Intravesical chemotherapy instillation immediately following TURBT reduced recurrence in patients with low-risk non-muscle invasive bladder cancer by 12% and intermediate risk by 17% (vs TURBT alone), with acceptable side effects, according to meta-analyses published by the European Organization for Research and Treatment of Cancer (EORTC) and the American Urological Association. As a result, guidelines from the European Association of Urology and, to a lesser degree, the American Urological Association suggested that this approach be included in the treatment strategy for all patients with non-muscle invasive bladder cancer [6, 8]. The rational explanation for effectiveness of intravesical chemotherapy instillation immediately after TURBT is based on its antitumor effect in the resection site, in destroying floating cells that can implant further on, and in destroying small tumours that have gone unnoticed [9,10].

Despite previous growing evidence that an intravesical chemotherapy instillation immediately after TURBT reduces recurrences of NMIBC, many urologists worldwide still do not use it in their daily practise, because in a significant number of patients, the presence of post-operative hematuria or the extent and/or depth of the resection precludes this practice [11-13].
MMC, hydrophobic in nature, is an antitumor antibiotic which by local instillation, works as an immediate chemotherapy measure to provide alonger recurrence-free period. It is minimally absorbed in a dose of 40 mg in saline or water and thus carries minimal side effects [14-15]. Unlike BCG multi-dosage regime, MMC shows no superiority in efficacy by multi-dosage in comparison to single immediate instillation. Thus unanimously, a single dose of 40 mg within 1 h of TUR has been accepted [16].

With the ongoing medical advancements, combinations of therapies have been tried against monotherapy. However, no consensus was found as to combination therapies are safe and efficacious compared to monotherapy. Some studies showed that BCG in combination with MMC is far better in achieving tumor-free interval and lowering disease progression [17-18], whereas some studies fail to see any significant difference with the combination therapy [19-20].

Therefore, the present study was conducted to determine the benefits of a combination of BCG and MMC compared to BCG alone in the treatment of patients with NMI bladder cancer.

PATIENTS AND METHODS

This randomized comparative study was conducted in the department of urologic oncology at the National Cancer Institute, Cairo University. Minimum follow-up period was 18 months. The institutional ethical committee approved the study (IRB Review No. 201920045.3). All patients aged 18 years or older with freshly diagnosed and histologically proven non muscle invasive bladder cancer, stage pTa, pCIS, pT1, whether papillary or solid, were included in the study. Any patient with muscle invasion, non-urothelial bladder carcinomas, cardiac disease, pregnancy, immunocompromised or receiving concurrent corticosteroid therapy, bleeding tendencies, coagulopathies or receiving anticoagulant therapy, other malignancies, psychiatric or neurological disorder, contraindications to spinal or general anesthesia as required for a TURBT, and known hypersensitivity to BCG or MMC were excluded from the study.

Informed written consent was obtained from all patients before enrolling them into the study. The sample size calculation of the study was based on the research of Di Stasi et al**.** (21), who observed that significant

results after studying EMDA mitomycin before TURBT versus PD mitomycin after TURBT versus TURBT followed by BCG alone. Taking the values of Di Stasi et al. study as a reference, the minimum required sample size with 80% power of study and 5% level of significance is 25 patients in each study group. The total sample size taken is 50 patients (25 patients in each study group) to reduce the margin of error.

The patients who were enrolled experienced an investigational protocol that included radiological imaging ultrasonography or CT urinary tract, cystoscopy, and biopsy. Cystoscopy was used to conduct transurethral resection of bladder tumours (TURBT) on all visible tumours.

Using a sealed envelope method, patients were randomly divided into two groups. In this study, ten sealed opaque envelopes were made, with group I and group II assigned in 5 envelopes each, with group I represented by passive intravesical instillation of mitomycin C and BCG and group II represented by BCG alone. When a patient agreed to participate in the study, an envelope was opened, and the patient was given the assigned group. Patients were randomly assigned to one of ten blocks in this method. After assigning 25 patients to each group, we used four sealed opaque envelopes to designate group I and group II in two envelopes each. Before the operation, both the patient and the treating physician were aware of the planned intervention. However, the final analysis was performed by a statistician who was not aware of the changes.

Group I (n=25) included patients who received single passive intravesical instillation of 40mg mitomycin C dissolved in 50ml sterile water infused intravesical for 60 min within 6 hours after complete trans-urethral resection of bladder tumors then intravesical BCG at 120mg mg per week for 6 weeks. BCG therapy was begun 2-4 weeks after the tumor resection as recommended by guidelines.

Group II (n=25) included patients who received intravesical BCG at 120mg mg after complete TURBT per week for 6 weeks. BCG therapy was begun 2-4 weeks after the tumor resection as recommended by guidelines. The procedural flow is shown in Figure 1.

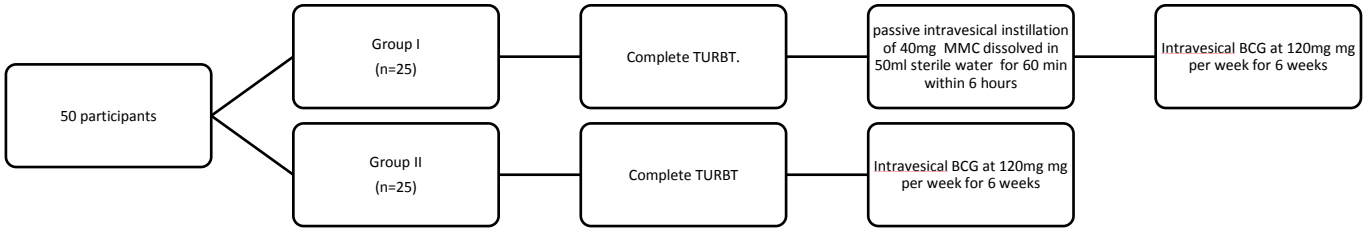

Figure 1. The procedural flow

MMC: Mitomycin C, BCG: Bacillus Calmette-Guérin, TURBT: Trans urethral resection of bladder tumors

Second look cystoscopy was done for cases with multifocal, large sized lesions to ensure complete resection of tumor. Patients with pathologically confirmed intermediate and high risk non-invasive muscle disease received intravesical 120mg BCG dissolved in 50ml sterile water retained in bladder for 120min weekly for 6 weeks starting 2-4 weeks after TURBT according to EAU guidelines. All patients were properly followed for at least 18 months to fulfill the objectives of the study. Adverse events were recorded according to the

World Health Organization toxicity grading after each instillation and a week after the 6th dose. Histopathological types and grades were recorded for each recurrence.

The outcome measures were disease free interval, time to recurrence, recurrence rate, progression to muscle invasive disease and treatment-related side effects. Recurrence was defined as biopsy confirmed non muscle invasive disease (Ta, CIS, and T1) and progression defined as upstaging to muscle invasive disease (pT2 tumor or more advanced stage).

Statistical Analysis

The categorical variables were shown as percentages (%) and numbers. The continuous variables, on the other hand, were shown as mean, standard deviation, and median values. The chi-square test and Fisher's exact test were used to compare qualitative variables, while the Mann-Whitney U test was used to compare quantitative variables. The final analysis was performed using the Statistical Package for Social Sciences software version 21.0 after the data had been entered into a Microsoft Excel sheet. A p-value of less than 0.05 was regarded as statistically significant.

RESULTS

Fifty NMIBC patients were treated at national cancer institute, Cairo University. Patients were randomly assigned into 2 groups, Group (I): 25 patients who received complete trans-urethral resection of bladder tumors followed by passive intravesical instillation of 40 mg mitomycin dissolved in 50ml sterile water for 60 min within 6 hours After TURBT then weekly for 6 weeks induction intravesical BCG. While Group (II): 25 patients who received TURBT followed by weekly for 6 weeks induction intravesical BCG alone.

50 patients diagnosed with NMIBC who participated in this study, have been matched in terms of patient and tumor characteristics; age, gender, pathological stage and risk group. 54% of patients had multifocal disease, 62% of patients had high grade and 68% of patient had invasion of lamina propria (pT1). The majority of our patients at intermediate and high risk groups. Patient and tumor characteristics are given in Table 1.

Table 1: Patient and tumor characteristics

	Group (I) (n=25)	**Group (II) (n=25)**	**P Value**
Age			
Mean ± S.D	57.16±15.737	61.80±14.015	0.228
Male	23(92%)	22 (88%)	1.000
Female	2 (8%)	3 (12%)	
Lesion			
Multifocal	17 (68%)	10 (40%)	0.088
Unifocal	8 (32%)	15 (60%)	
Grade			
Low	12 (48%)	7 (28%)	0.244
High	13 (52%)	18 (72%)	
Pathological T stage			
T1	20(80%)	14 (56%)	0.128
Ta	5 (20%)	11 (44%)	
Risk group			
Low	4 (16%)	4 (16%)	0.952
Intermediate	9 (36%)	8 (32%)	
High	12 (48%)	13 (52%)	

p: p value for comparing between the studied groups
*: Statistically significant at P <0.05

During follow up, no cases of recurrence after 3 months in both group. One case of recurrence after 6 months, 4 patients had recurrence after 12 months and 4 cases of recurrence after 18 months in group I who treated with combined therapy passive MMC and BCG after TURBT. While group II who treated with BCG alone after TURBT, 3 patients had recurrence after 6 months, 6 patients had recurrence after 12 months and 3 cases of recurrence after 18 months. Recurrence rate was higher in BCG alone group in comparison to combined therapy passive MMC and BCG group. Longer disease free interval for combined therapy passive MMC and BCG group. Regarding time to recurrence was 12 months in both groups. Table 2 show follow up period, recurrence rate and disease free interval.

Table 2: Follow up period, recurrence rate and disease free interval.

	Group (I)	**Group (II)**		**P Value**
Follow up after 6 months				
Free	24 (96%)	22 (80%)		0.609
Recurrence	1 (4%)	3 (12%)		
Total	25 (100%)	25 (100%)		
Follow up after 12 months				
Free	20(83.3%)	16(72.7%)		0.398
Recurrence	4 (16.7%)	6(27.3%)		
Total	24 (100%)	22 (100%)		
Follow up after 18 months				
Free	16(80%)	13(81.3%)	0.450	
Recurrence	4(20%)	3(18.7%)		
Total	20 (100%)	16(100%)		
Recurrence rate				
No	16 (64%)	13 (52%)		0.567
Yes	9 (36%)	12 (48%)		
Total	25 (100%)	25 (100%)		
Disease free interval				
No	9 (36%)	12 (48%)		0.567
Yes	16 (64%)	13 (52%)		
Total	25 (100%)	25 (100%)		
Time to Recurrence				

Median	12	12	0.286
IQR	10-18	8.40-15.60	

p: p value for comparing between the studied groups
*: Statistically significant at P <0.05

Most of recurrence were multifocal, 7 patients in combined therapy passive MMC and BCG group while 9 patients in BCG alone group and 6 patients had high grade disease in combined therapy passive MMC and BCG group while 8 patients had high grade recurrence in BCG alone group. Four patients were upstaged to muscle invasive bladder cancer in BCG alone group versus 3 patients in combined therapy passive MMC and BCG group. Table 3 show clinical and pathological characteristics of recurrence and progression.

Table 3: Clinical and pathological characteristics of recurrence and progression

Recurrence	**Group (I)**	**Group (II)**	**P Value**
Lesion			
Multifocal	7 (77.8%)	9 (75%)	1.000
Unifocal	2 (22.2%)	3 (25%)	
Total	9	12	
Grade			
Low	3 (33.3%)	4 (33.3%)	1.000
High	6 (66.7%)	8 (66.7%)	
Total	9	12	
Pathological T stage			
T1	3 (33.3%)	3 (25.0%)	0.896
T2	3 (33.3%)	4 (33.3%)	
Ta	3 (33.3%)	5 (41.7%)	
Total	9	12	
Progression			
Yes	3 (12%)	4 (16%)	1.000
Total	25	25	

In our study, the side effects was comparable in both the study groups. We observed 9 patients with local side effect in combined therapy passive MMC and BCG group, 4 patients had gross hematuria and 5 patients had irritative bladder symptoms and no perforation cases were recorded in both group. Table 4 show complications in both group.

Table 4: Complications in both group.

Complications	**Group (I) (n=25)**	**Group (II) (n=25)**	**P value**
Gross hematuria	4 (16%)	3 (12%)	1.000
Irritative bladder symptoms	5 (20%)	4 (16%)	1.000

DISCUSSION

The present study was a randomized trial on 50 patients (25 patients in each group), where we determined the benefits of combination of MMC with BCG in comparison to BCG alone in the treatment of patients with NMIBC by comparing recurrence and progression rate and disease free interval.

The randomization guaranteed that age, gender, and cancer stage were comparable between groups and that any difference in outcome was due to differential intervention rather than chance bias [22].

A high recurrence incidence in bladder cancers is documented, despite advancements in detection and treatment methods. The progression of non-muscle invasive to muscle-invasive urinary bladder cancer typically causes metastases and is regarded as having a poor prognosis. A subset of high-risk lesions that typically proceed to invasive forms and include between 70 and 80 percent of NMIBC, which typically recur without aggressive histologic characteristics (MIBC). Urinary bladder cancer becomes challenging to treat from the time of diagnosis until death due to recurrent relapses, disease progression, and chemoresistance [23].

Our study revealed a low recurrence rate in passive instillation MMC with BCG compared to BCG alone (36% vs 48%, p=0.567). Among the previous studies that compared the combination therapy with BCG alone, similar findings were reported by **Di Stasi et al.** [21] study, EMDA mitomycin before TURBT patients had a lower risk of recurrence (38%) than passive diffusion (PD) mitomycin after TURBT patients (59%) and TURBT followed with BCG alone patients (64%) (p<00001). Also **Agrawal et al.** [24] found that perioperative MMC in combination with BCG compared to BCG alone reduce recurrence rate (14.81% vs. 33.33%, p=0.202). Even **Oosterlinck et al.** [25] reported that alternating chemoimmunotherapy schedules with MMC and BCG demonstrated comparable efficacy compared to BCG alone in reducing the rate of Recurrence (47.9% vs 54.2%).

Disease-free interval is an important landmark in cancer treatment. Our study revealed a comparable disease-free interval in passive instillation MMC with BCG compared to BCG alone (64% vs 52%, p=0.567) and time to recurrence for both groups were12 months.

Similarly, after a median follow-up of 86 months, 42 (36%) of 116 patients treated with TURBT alone, 49 (41%) of 119 patients treated with PD mitomycin after TURBT, and 73 (62%) of 117 patients treated with EMDA mitomycin before TURBT were disease-free (p<0.0001). Patients randomised to receive EMDA mitomycin before TURBT had a significant longer time to recurrence (52 months) than those assigned to receive PD mitomycin after TURBT (16 months) or TURBT alone (12 months) in ***Di Stasi et al., (2011)*** [21] study. ***Di Stasis et al., (2003)*** [26] reported that during a median follow up of 43 months of high risk patients, median time to first recurrence was 35 months for the electromotive MMC group, which was significantly longer than 19.5 months for the passive MMC group and 26 months for the BCG group.

Also, **Agrawal et al., (2021)** [24] reported that a comparable disease-free survival in perioperative MMC in combination with BCG compared to BCG alone (85.18% vs. 66.66%, p=0.202). **Solsona et al.** [27] also reported similar findings as a combination of sequential BCG with MMC significantly reduced the disease relapse at 5 years compared to BCG alone (20.6% vs. 33.9%, p<0.05).

No statistically significant differences were found between groups regarding progression to muscle invasive disease in our study (p=0.896). The progression rate results reported 3 patients in passive MMC with BCG and 4 patients in BCG alone. According to ***Di Stasi et al.,*** **(2011)** [21] 24 (21%) of 116 patients treated with TURBT alone, 23 (19%) of 119 treated with PD mitomycin after TURBT, and 19 (16%) of 117 treated with EMDA mitomycin before TURBT progressed to muscle-invasive disease (p=0·55). Also **Agrawal et al., (2021)** [24] reported progression rate in perioperative MMC in combination with BCG compared to BCG

alone (11.1% vs. 25.9%, p=0.293). **Solsona et al.** [27], who found no statistically significant difference between MMC + BCG and BCG alone in terms of 5-year PFI (12.3% vs. 12.2%; hazard ratio: 1.05; 95% confidence interval, 0.61 1.83; p=0.852).

Our findings in this study reported that no statistically significant difference between groups regarding side effects. 4 (16.0%) patients had gross hematuria and 5 (20.0%) patients had irritative bladder symptoms in passive MMC+BCG group while in BCG alone group 3 (12.0%) patients had gross hematuria and 4 (16.0%) patients had irritative bladder symptoms. There were no cases of perforation or systemic side effect related to mitomycin or BCG between groups of the study.
Similarly ***Di Stasi et al.,*** [21] study; reported that persistent bladder symptoms in 18 (16%) patients in the TURBT-alone group, 37 (31%) patients in the PD mitomycin post-TURBT group, and 24 (21%) patients in the EMDA mitomycin pre-TURBT group. Hematuria after TURBT in 8 (7%) patients in the TURBT-alone group, 16 (13%) patients in the passive mitomycin post-TURBT group, and 11 (9%) patients in the EMDA mitomycin pre-TURBT group; and bladder perforation after TURBT in 5 (4%) patients in the TURBT-alone group, 9 (8%) patients in the PD mitomycin post-TURBT group, and 7 (6%) patients in the EMDA mitomycin pre-TURBT group. Side effects were minor and comparable between the study groups in **Agrawal et al., (2021)** [24] study, which included dysuria, bacterial cystitis, drug-induced cystitis, macroscopic hematuria prostatitis epididymitis, fever, influenza-like symptoms, and fatigue. Contrarily, **Solsona et al.** [27] found that the MMC + BCG had significantly more local toxicity compared to BCG alone (80.4% vs. 69.7%, p<0.05). Even after reducing the dose of MMC to 10mg, toxicity was still higher compared to BCG alone, specifically in local side effects grade 3 (28.4% vs. 10.9%; p<0.001).
Overall, we found that both protocols were comparable in safety and efficacy in reducing the recurrence rate and improving the disease free interval of NMI bladder cancers. Our findings were in line with the studies by **Di Stasi et al.** [21] and **Oosterlinck et al.** [25] who showed that combination is a better protocol compared to BCG alone in terms of recurrence, progression, and disease-free survival. In contrast to **Agrawal et al.** [24] who found no significant superiority of MMC in combination with BCG compared to BCG alone.

Study Limitations
One of the limitations of the study was that this study was conducted at a single center; thus, results cannot be generalized. The number of patients who could be included and monitored is still limited, so an extended period of ongoing follow-up is required to evaluate the treatment's long-term effectiveness. Additionally, a clearer definition of the optimal therapeutic protocol in terms of timing, dosage, and induction and maintenance times is required. However, according to our results and previous evidence mentioned above, immediate instillation of mitomycin C within 6 to 24 hours following TURBT seems to be effective and decreases the short-term recurrence rate and improve disease-free interval.

CONCLUSION
Immediate single instillation of mitomycin C after TURBT in combination with BCG seems to be effective in decrease recurrence rates and enhances the disease free interval compared with TURBT followed by BCG alone at least in short term.
However, more research with large samples and a longer follow-up time is needed.

Ethical Committee Approval: This study was approved by Institutional Review Board of the National Cancer Institute, IRB Review No. 201920045.3.
Informed Consent: Informed written consent was obtained from all patients before enrolling them into the study.
Author contributions: All authors contributed equally to study design, data collection and preparation of the manuscript.

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