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Outcome of Post-resection Intravesical BCG and Mitomycin C Therapy on Non-muscle Invasive High-Grade Transitional Cell Carcinoma of Urinary Bladder

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Conflicts of interest: None

Abstract

Objective: *This study aimed to compare the outcome of postoperative intravesical BCG and Mitomycin C therapy on non-muscle invasive high grade superficial bladder tumor.*

Methods: *This prospective quasi experimental study was carried out among the patients with non-muscle invasive high grade transitional cell carcinoma (TCC) of urinary bladder, who underwent complete transurethral resection of bladder tumor of primary tumor attended at the urology department of DMCH, during March 2017 to August 2019. After pre-operative evaluation and counselling, 70 patients with histologically documented high grade superficial bladder tumor were included and divided in two groups. We instilled intravesical BCG in one group and Mitomycin C (MMC) therapy in other group. The patients were followed up at 3rd ,6th , 9th , 12th and 18th month.*

Results: *The mean age of BCG group was 55.8 years while 60.2years in MMC group with majority between 45 to 65 years (>80%). Sex distribution in both groups were almost equal (p=0.062). There were equal number of TaG3 and T1G3 disease in each group (p=0.809). Local adverse reactions were significant in BCG group (p= 0.016), among them UTI, between two groups, was statistically significant (p=0.039). Incidence of hematuria (p=0.324), voiding frequency (p=0.163) and local rash (P=0.642) had no statistically significant difference. The incidence of post-instillation systemic adverse reactions between two groups were statistically significant (p=0.034). Fever (p=0.028) was significant among them. Intavesical BCG was significantly more effective than MMC in terms of disease recurrence (p=0.047) and progression (p=0.008).*

Conclusions: *We analysed the efficacy and safety of intravesical BCG and MMC in two groups, showing that BCG was more effective in terms of disease recurrence and progression but local and systemic side effects were higher in BCG group.*

Keywords: Bacillus Calmette-Guerin (BCG), Mitomycin C (MMC), non-muscle invasive bladder Cancer (NMIBC).

Introduction

Urinary bladder cancer accounts 7% of all malignancies and it is a cancer of environment and age; the incidence and prevalence rate increases with advancing age, peaking in 8th decade of life, and there is a strong association between environmental toxins and cancer formation (Jemal et al, 2008).

Most urinary bladder tumor are diagnosed after symptoms has been developed. About 85-90% of patients

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with bladder tumor present with hematuria, 90% of them are transitional cell carcinoma (TCC). About 74% of transitional cell carcinoma at diagnosis are found to be non-muscle invasive bladder tumor (NMIBT); among them a certain percentage (25%) found high grade, 18% of them locally advanced and 8% are metastatic disease (Zengin et al, 2013). Even though most TCCs are non-muscle invasive (Ta & T1) there is a 30-80% risk of recurrence after transurethral resection of bladder tumor (TURBT) alone. In addition to that 10-15% of all patients will progress to muscle invasive disease (Zengin et al, 2013).

To reduce the recurrence and progression of high grade superficial urinary bladder tumor, for the last 4-5 decades BCG and MMC are widely used. Since the early 1980s' to 2013 a large number of randomized clinical trials have been conducted to evaluate the efficacy of BCG and MMC. Some authors have impressive results with BCG, but some authors (Witjes and Hendricksen in 2007) like to say that, chemotherapeutics (like mitomycin-C) should be considered first line therapy for all patients with non-muscle invasive bladder tumor (Witjes and Hendricksen, 2007). However, treatment with BCG carries an inherent toxicity profile that limits the ability to deliver the necessary treatment to some individuals. In addition there are certain risk factors for tumor progression and recurrence despite therapy (Braasch, Bohle and O'Donnell, 2009). In Bangladesh multiple centers are following both the protocols. As per our knowledge very few study was conducted in our country to see the efficacy of post-resection intravesical therapy of NMIBT.

General objective was to evaluate outcome of intravesical instillation of BCG in comparison to mitomycin-C in HGNMIBC. Specific objectives were to see the treatment complications, recurrence and progression of disease.

Materials and Methods

This Quasi Experimental study was done in the Department Of Urology, Dhaka Medical College Hospital, Dhaka during March 2017 to August 2019. Study population included all the patients presented with non-muscle invasive high grade bladder tumor who underwent complete resection of bladder tumor and had instillation of intravesical chemotherapy or immunotherapy. Inclusion criterion was- patient with non-muscle invasive high grade TCC of total < 5cm size, single or multiple, who underwent complete resection of primary lesion .

Exclusion criteria were- concomitant CIS, incomplete resection of bladder tumor, recurrent urinary bladder tumors, urinary bladder perforation during TURBT.

Independent variables were- age and sex of patients, stage of the tumor, number of the tumor. Outcome variables were- complications of treatment (local: cystitis/dysuria, hematuria, UTI, voiding frequency, local rash; systemic: skin rash/ allergic reaction, fever, chills, gastro-intestinal upset, hospitalization due to adverse reactions or severe illness), recurrence of disease (after 6 weeks of resection), time of recurrence, progression of disease (advancement of recurrent disease in grade and/or stage)

Group Allocation Procedure: After final evaluation 70 patients, ages ranging from 35-74 years were selected for this study as per selection criteria. The purposive sampling was done to divide the participants into two groups according to number of and stage of tumor. Every attempt was applied to keep equitable distribution of participants in accordance to number of tumor and stage of tumor. Group-A included 35 cases and subjected to be treated by BCG, after complete TURBT. Group-B included 35 cases and subjected to be treated by MMC after complete TURBT.

Intravesical Instillation Procedure: After transurethral resection of bladder tumors, if there was no hemturia, intravesical adjuvant therapy started as following schedule:

MMC, an alkylating agent, and an anti-tumor antibiotic with a molecular weight of 329 (Stapp et al, 2000), is soluble in water and organic solvent (Iqbal et al, 2007). MMC is usually minimally absorbed on intravesical instillation due to high molecular weight and hydrophobic in nature. Its dose is typically 40mg per instillation; the first dose should be started as soon after complete TURBT, ensuring that there is no hematuria, clot, or bladder injury.Total 40 mg (10mg x 4 vials) of MMC dissolved in 40ml of distilled water then instilled into UB via a Foley catheter (Appx-E,F), keeping it into the bladder (by clamping the catheter) for two hours. Patient was advised for frequent change of position so that all the surfaces of the bladder may come in contact of the agent. Care was taken not to introduce any amount of air. This cycle was repeated weekly for 6 weeks. Urethrocystoscopy was done after 6 cycles of instillation. Maintenance dose are monthly for one year. Side effects includes chemical cystitis and allergic reactions such as palmar rash (Stapp et al, 2000).

Fig.-1: *BCG vial.*

Fig.-1: *MMC vials (10mg x 4 vials)*

BCG is also used for many years to reduce the recurrence rate. It's mode of action is unknown but study suggested that, it introduce a immunologically mediated cytotoxicity. BCG has risk of local and systemic illness and environmental hazards. There are some limitations to use BCG for treatment of superficial bladder tumor, immunosuppressed and immunocompromised patients, immediately after transurethral resection on the basis of the risk of intravasation and septic death, personal history of BCG sepsis, gross hematuria (intravasation risk) traumatic catheterization (intravasation risk), total incontinence (patient will not retain agent), pregnancy and lactation are regarded as absolute contraindications. Poor performance status, advanced age, urinary tract infection (intravasation risk), liver disease (precludes treatment with isoniazid if sepsis occurs), personal history of tuberculosis (risk theorized but unknown) were considered as relative contraindications for BCG instillation (Jones, 2016). Waiting for two weeks for wound healing after TURBT. Then one ample of Tice strain BCG ($1x10^8$ to $8x10^8$ organism) with 50ml of normal saline is instilled via Foley catheter , and retained in bladder (by clamping the catheter) for two hours. Patient was advised for frequent change of position so that all the surfaces of the bladder may come in contract of the agent. Care was taken not to introduce any amount of air. The agent kept in urinary bladder for 1-2 hours than advised to evacuate the bladder in a pot containing 100 ml of chlorine solution or directly into commode and flash with plenty of water. The vial, gloves, catheter and syringes were put in a plastic bag and advised to bury under soil. This procedure was repeated weekly for six weeks. Maintenance dose are weekly instillation for three weeks, three monthly for one year. Surveillance cystoscopy and urinary cytology done every three monthly during treatment. Side effects include bladder irritability such as frequency, urgency, nocturia and haemorrhegic cystitis regards as local adverse effects. Serious systemic side effect is BCG-osis or BCG sepsis with clinical features of high fever, chills, confusion and hypotension. Granulomaous prostatitis and systemic infection are two common side effects. Pulmonary infiltration, abnormal LFT, DIC, organ failure and shock are also major systemic side effects of BCG instillation.

Patients were advised to take antihistamine and/or paracetamol as required. If high fever or prolonged fever or severe systemic illness occurred they are advised to attend in urology or emergency department of DMCH.

All patients were advised to attend at urology department at 6 weeks, 3 months, 6 months, 9 months, 12 months and 18 months after operation. Follow-up protocol includes- history (hematuria, bone pain, voiding symptoms, adverse effects), investigation (Urine RME and CS, USG of whole abdomen special attention to KUB & prostate, urethrocystoscopy, biopsy specimen for histopathology (if suspected lesion seen in cystoscopy), bone scan (if needed).

Data Collection: The clinical history of the patients, physical examination findings and relevant investigations and post instillation follow up results were recorded in a structured questionnaire which addressed all the variables of interest (Appx-C). Data on patient's age and sex, number of tumor, grade of tumor, complications, recurrence and disease progression were recorded and compared between the two groups. The result presented in tables, figures, and diagrams.

Data Processing & Analysis: Data were processed and analysed with the help of computer software SPSS (Statistical Package for Social Sciences) version 22 and net based graph pad. The appropriate test statistics (eg. descriptive statistics, Chi-square (X^2) or Fisher's exact probability test and unpaired studen's t-test) were used

to analyse the data. The data presented on categorical scale were expressed as frequency and corresponding percentages were compared between groups using Chi-square (X^2) or Fisher's exact probability test, while the data presented on continuous scale were expressed as mean and standard deviation (SD) from the mean and were compared between groups with the help of Z-test. Level of significance for all comparative analyses were set at 0.05 and $p<0.05$ was considered as statistically significant.

Results

The present study was conducted to compare the outcome between intravesical instillation of BCG and Mitomycin C for the treatment of high grade non-muscle invasive transitional cell carcinoma of urinary bladder in terms of recurrence and progression of disease following transurethral resection of tumor. A total of 70 subjects were selected for study. Of them 35 were randomly assigned to Group-A (BCG group) and 35 to Group-B (MMC group). The outcome of two groups were evaluated and compared. The findings of the study derived from data analysis are presented in following tables and graphs.

Table I: *Demographic variables of study subjects*

Variables	Group		p-value
	Group-A (n=35)	Group-B (n=35)	
Age (years) Mean ± SD	55.28 ±11.6	60.2±10.5	0.062[a]
Sex			
male	26(74.3)	27(77.1)	0.780[b]
female	09(25.7)	08(22.9)	
Stage & grade			
T1G3	20 (57.1)	19 (54.3)	0.809 [b]
TaG3	15 (42.9)	16 (45.7)	
Tumor number1	13(37.1)	15 (42.9)	0.755 [b]
2 -3	14 (40.0)	11 (31.4)	
>3	08 (22.8)	09 (25.7)	

Group-A=BCG group; Group-B = mitomycin C group,
Figures in the parentheses denote corresponding percentage;
a = p-value reached by **unpaired Student's t-Test**
b = p-value reached by **Chi-square (x^2) test.**
T1G3= Tumor invading lamina propria, high grade
TaG3= Tumor within urothelium, high grade
Level of significance p <0.05.

Table II: *Post instillation complications in study subjects*

Variable	Group		p-value
	Group-A (n=35)	Group-B (n=35)	
Local adverse reactionsUTI	15 (40.0)	07 (20.0)	0.039* c
Cystitis/dysuria	11 (31.4)	04 (11.4)	0.041* c
Hematuria	07(20.0)	04 (11.4)	0.324 c
Voiding frequency	11 (31.4)	06 (17.1)	0.163 c
Local rash	02 (5.7)	03 (8.6)	0.642 c
UTI 15 (40.0)	07 (20.0)	0.039* c	
Cystitis/dysuria	11 (31.4)	04 (11.4)	0.041* c
Pt. with local adverse reactionsYes	21 (60.0)	11 (31.4)	0.016* c
No.	14 (40.0)	24 (68.6)	
Systemic adverse reactions			
Fever	13 (37.1)	05 (14.3)	0.028* c
Chills	07 (20.0)	03 (8.6)	0.171 c
Nausea/vomiting/diarrhea	10 (28.6)	06 (17.1)	0.254 c
Allergy	00 (0.0)	02 (5.7)	0.492G"
Hospitalization	02 (5.7)	01 (2.9)	0.555 c
Pt.with systemic adverse reactions			
Yes	14 (40.0)	06 (17.1)	0.034m c
No.	21 (60.0)	29 (82.9)	

Group-A= BCG group, Group-B = Mitomycin C group,
* -Significant
Figures in the parentheses denote corresponding percentage
a = p-value reached by **Chi-square (X^2)test,**
b **=** p-value reached by **Fisher exact test,**
Level of significance p <0.05

Table III: *Recurrence and progression of disease in study subjects*

Recurrence	Group		p-value
	Group-A (n=35)	Group-B (n=35)	
Recurrence of disease			
At 6 weeks	00 (0.0)	00 (0.0)	
At 3 months	01 (2.86)	03 (8.6)	0.303
At 6 months	05 (14.3)	07 (20.0)	0.525
At 9 months	03 (8.6)	07 (20.0)	0.157
Total	09 (25.7)	17(48.6)	0.047m
Progression to			
T1G3	00 (0.0)	01 (5.9)	
T2G3	02 (22.2)	06(35.3)	
T3G3	01 (11.1)	03 (17.6)	
Total	03 (33.3)	10 (58.8)	0.008m

Group-A = BCG group, Group-B = Mitomycin C group,
Figures in the parentheses denote corresponding percentage
*- significant
p-value reached by **Chi-square (X^2)test,**
Level of significance p<0.05

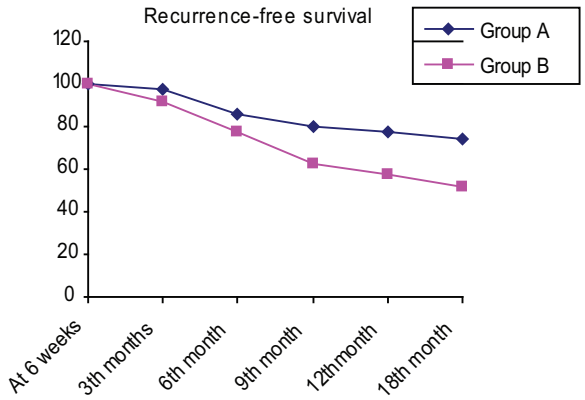

Fig.-3: *Line diagram- recurrence free survival rate*

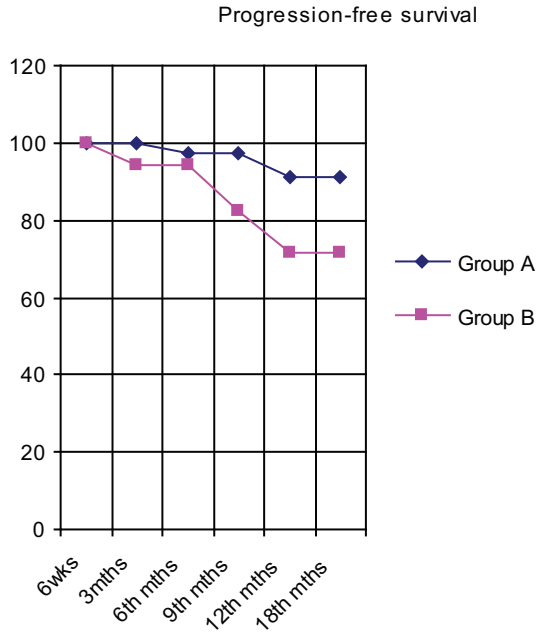

Fig.-4: *Line diagram- progression-free survival rate*

Discussion

This quasi experimental study was carried out prospectively to find out the outcome of intravesical instillation of BCG and MMC after complete resection of high grade non-muscle invasive transitional cell carcinoma of urinary bladder, in the department of urology, Dhaka Medical College Hospital, Dhaka. One patient of group A had to stop BCG treatment temporarily due to severe illness but continued later on. After 9 months of follow up 35 patients in group-A and 35 patients in group-B were available for evaluation of final outcome.

The demographic and baseline characteristics included in this study were almost identical between 2 groups. Age ranges were equal in both the groups (35-74 yrs). The mean age of group-A was 55.28±11.6 yrs and 60.2±10.5 yrs for group B. Most of the patients were between 51-60 years of age (40% in group-A and 48% in group-B). Age distribution was almost homogenously distributed (Table I) in both the groups (p-value 0.984). Zengin et al.(2013) managed a series of 127 patients with NMIBC, of those patients, 41of them had received BCG, and 26 had received MMC instillation. While the age in BCG group ranges between 36 and 85 (mean59.83±10.59 years), in MMC group, it ranges between 35 and 75 years (mean 57.42 ± 9.73 years) which was also similar to this study. However, Rentsch et al, (in 2014) treated 71 patients with BCG and 60 patients with MMC with a mean age 72 years in both groups, and age ranges from 47-92 years, and 46-96 years respectively; which was dissimilar to this study. In another study Wilson et al. (2010) treated 70 patients aged 43 to 94 years with a mean age of 75.8 ± 2.4 years which was also not similar to this study. Oddens et al. (2013) had a multi- centre analysis of 1355 patients with average age was 68 years which was also higher than this study. It may be due to inclusion of recurrent diseases in their studies, and higher mean age of western population.

74.3% of patients of group-A, and 77.1% of group-B were male; while 25.7% and 22.9% of patients were female respectively, sex distribution was homogenous (Table I) between groups (p-value 0.780). This was supported by text books. Males are 3 to 4 times more likely to develop bladder cancer than females, presumably because of an increased prevalence of smoking and exposure to environmental toxins (Wood, 2012 and Shelley et al. 2004). Oddens et al.(2013) in a study of 1355 subjects, male were 81.1% and female were 18.2%, which support this study. Farah et al. (2014) also found similar ratio (83.3%:16.7%) in a similar study.

In this study all subject were high grade TCC as per study protocol. Among them TaG3 were 20 (57.1%) and 19 (54.3%), T1G3 were 15 (42.9%) and 16 (45.7%) in group-A and group-B respectively; p-value was 0.809, which was not statistically significant (Table I).

In this study 37.1% of group-A and 42.9% of group-B subjects had single tumor, 40% and 31.4% had 2-3 tumors respectively (Table I). More than 3 tumors were found in 22.8% of group A and 25.7% of group B cases. Total 40% had single tumor, 35.7% had 2-3 tumors and rest 24.3% had more than 3 tumors during TURBT (p-value 0.755). Solsona et al.(1999) in a study found 44% of people with high grade NMIBT presented with single tumor, 29% with 2-3 tumors and 27% with tumors >3, which supports this study. Oddens et al, (in 2013) in a series of 1355 found 13% were single tumor which not support this findings. Grey et al. (2009) in their study found only 33% of multiple tumor with a 67% of single tumor, which also not support this study. This dissimilarity may be due to purposive group allocation in respect to tumor number.

In comparison over all adverse effect found significantly higher in BCG group, than MMC group. Total 34 (48.6%) patient developed local and/or systemic adverse effects. Among the adverse reactions local reactions were observed in 33 (47.1%) patients. 60% and 31.4% in group-A and group-B respectively (Table II). That was statistically significant (p-value 0.016). UTI was one of the most common adverse complaint by the patients and it was found statistically significant between groups (p-value 0.039). Approximately 28.6% patients developed systemic adverse reactions, 40% of BCG cases and 17.1% of MMC cases developed one or more systemic adverse reactions (Table II), this was statistically significant difference between groups (p-value 0.034). Fever (temperature >38.5^{0}C) was at a higher rate among the patients received BCG therapy. About one third (37.1%) of patients received intravesical BCG developed fever within 1-2 days of instillation, in comparison only 14.3% of MMC group experienced fever, that was statistically significant (p-value 0.028). Gastrointestinal symptoms like nausea, vomiting and diarrhoea were also higher in BCG arm but it was not significant (p-value 0.254). Chills and severe adverse reactions that required hospitalization or withdrawal from treatment were not significant among groups (p-value 0.555). Rentsch et al. (2014) found similar adverse effect of BCG, while they were comparing the BCG strains, they found 68% local & systemic adverse reactions in Connaught strain with a lower (50%) with that of Tice vaccine. We also use Tice strain and their works support the rate of adverse reactions we observed. In that study 30% subjects experienced dysuria, 13.5% frequency, hematuria 7% and fever 13.5%. Solsona et al, in 1999 also found a significantly higher adverse effect with BCG; it was about 67% local side effects like frequency, dysuria, hematuria and UTIs. They found systemic side effects on 26.7 % of cases.

Disease recurrence developed in 26 patients (37.1%) during 18 months (median 12 months) of follow up. The median time to recurrence was 9.0 months for both the BCG group and the MMC group. In 9(25.7%) patients of group-A (BCG) and 17(48.6%) patients of group-B (MMC) disease recurred (Table VIII). There was statistically significant difference between two groups in terms of disease recurrence (p-value 0.047). The period of this study was 24 months and follow up done for only 18 months, at this short period of time actual recurrence and median time of recurrence estimation was so difficult.

Grey et al, (in 2009) done a one arm study with mitomycin-C for early recurrence rate in two different centers, and followed up at 4 months, 6 months, 9 month and up to two years. They found 46.15% recurrence in institution A and 24.14% in institution B at 4th month of treatment. 41.30% in 6th month, 37.50% in 9th months in institution A, while 33.33% and 18.42% were observed in institution B. It shows much higher in institution A, but similar to our study. They also commented, there was no significant difference between the recurrence-free interval for two groups (log rank test p=0.28). Krege et al (in 1996) found 24.5% recurrence in BCG group versus 26.7% in MMC group with no statistical significance at 20 months of follow up. Rintala et al, (in 1991) published their study in 1991 which shows 23.3% recurrence in BCG arm in comparison with only 9.0% recurrence in MMC group. In the same

year Lamm et al, (in 1991) found 65.1% recurrence in immunotheraphy group, 80.9% recurrence in chemotheraphy group, at 5 years follow up with a 36.9% and 17.2% of disease free survival rate in respective groups. Farah et al, (in 2014) in a meta analysis of 11 studies shown BCG instillation was better than MMC instillation in 7 studies, MMC was better in 3 studies than BCG instillation. One study found insignificant data. Ehdaie, Sylvester and Herr (in 2013) in a meta-analysis, found BCG reduced the risk of recurrence compared to MMC by 32% in the studies with BCG maintenance; however there was a 28% increase in the risk of recurrence when BCG maintenance was not used. Vegt et al, (in 1995) found 64% of recurrence in BCG Tice strain, and 43% in MMC group; MMC was significantly better. Due to short period of follow up time our result may not reflect the actual scenario.

After 18 months (median 12) of follow up with maintenance therapy, 33.3% (3 out of 9) of patients in the BCG group and 58.8% (10 out of 17) of patients in the MMC arm, recurrence was accompanied by disease progression (Table IX). There was statistically significant difference in the progression rate at the time of recurrence between the BCG and MMC group (p-value 0.008). In the current study, we compared the outcomes of BCG and MMC treatments in DMCH with primary high grade NMIBC. None of the patients had received previous intravesical therapy. The 18 months recurrence-free rates were 74.3% for the BCG group and 51.4% for the MMC group (Fig 1). There was significant difference in the progression rate at the time of recurrence between the two groups (p-value 0.008). The 18 months progression-free rates were 91.5% for the BCG group and 71.5% for the MMC group (Fig 3). This is an rational finding because it suggests better efficacy of BCG than MMC for high-risk bladder cancer in terms of recurrence and progression of disease. Several authors favour BCG in comparison to MMC in high-risk nonmuscle-invasive bladder cancer. Alvarez-Mugica et al. (2013) analysed 108 patients underwent BCG therapy and found 32.4% recurrence and 19.4% progression. Witjes and Hendrickson (2007), in a meta-anlysis, mentioned that adjuvant BCG more effective than adjuvant chemotherapeutic drugs with regard to progression free survival; after a median follow-up of 2.5 years, progression was seen in 9.8% in the BCG treated group versus 13.8% in the non-BCG group. They found significant difference in disease progression (odds ratio=0.73, p=0.001). Bohle et al. (2003), in a mata-analysis, mentioned that BCG was better than MMC in preventing tumor recurrence and that BCG with maintenance was better for preventing tumor progression. Vegt et al. (1995) reported a significant advantage for BCG regarding tumor recurrence in patients with high-risk bladder, including CIS, pT1G3, and recurrent tumors. These results were confirmed in another study that reported a significantly better recurrence-free survival in patients with recurrent bladder cancer (Lamm et al, 1995). On the basis of these data, BCG has become the treatment of choice for grade 3 and high-risk bladder cancer. It should be pointed out, however, that these data were not homogeneous for high-risk nonmuscle-invasive tumors. Ehdaie, Sylvester and Herr (in 2013) had a meta-analysis of 24 randomized studies (n=4863) concluded that BCG reduced the risk of progression by 4% as compared to the various control groups, but that only patients receiving BCG maintenance were benefited. Progression on which the analysis was based on, the end point was actually worsening-free survival, not progression. The meta-analysis used data from randomized controlled trials to evaluate the impact of BCG compared to intravesical chemotherapy. Despite demonstrating a 59% relative reduction in the odds of recurrence in favor of BCG as compared to chemotherapy, a reduction of 26% in the odds of progression with BCG therapy was not statistically significant, that were observed appeared superior to mitomycin-C for reducing recurrence only in the studies using maintenance BCG (Ehdaie, Sylvester and Herr, 2013).

In the present study, the recurrence rate of high grade NMIBC during the 18 months follow-up was about 37.1% when only patients with a histologically confirmed muscle layer in the TUR specimens were analyzed. At the time of recurrence, about 19.9% (13 out of 70) patients also experienced disease progression. However, in this study, BCG found superior to MMC in term of disease recurrence and progression.

Conclusion

From the present study it can be concluded that outcome of intravesical BCG therapy after complete TURBT is better than MMC therapy, in term of recurrence and progression, in primary high grade non-muscle invasive TCC of urinary bladder. Though local and systemic complications are significantly higher in BCG therapy comparing MMC, post-resection intravesical BCG therapy can be administered as a better option.

Limitations of the study

The limitations of this study were: Small group of patients, non randomized sampling, short study period.

Recommendations

According to the findings of the present study following recommendations are put forward for consideration to relevant authority.

1. Intravesical BCG can be used to treat high grade NMIBC, as a better option than intravesical MMC.
2. Study should be done on large sample size.
3. Study should be done with long period of follow up.

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