

# INTRAVESICAL GEMCITABINE AND MITOMYCIN C CHEMOTHERAPY IN THE TREATMENT OF NON MUSCLE INVASIVE TRANSITIONAL CELL CARCINOMA OF URINARY BLADDER - A RANDOMIZED CLINICAL TRIAL

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## Abstract :

**Objective:** To compare the efficacy of Gemcitabine and Mitomycin C in the treatment of non muscle invasive transitional cell carcinoma of urinary bladder.

**Methods:** This study was a randomized clinical trial conducted between the periods of November 2013 to October 2014 in the Department of Urology, Bangabandhu Sheikh Mujib Medical University (BSMMU). The patients with histopathologically diagnosed as non muscle invasive transitional cell carcinoma of urinary bladder after complete TURBT were included in the study. Total 54 patients were included in this study (27 patients in each group). Those treated with intravesical Gemcitabine were considered as experimental group and those treated with intravesical Mitomycin C (MMC) considered as control group. Intravesical Inj. Gemcitabine and Mitomycin C mg dissolved in 50 ml of normal saline and instilled into the urinary bladder through Foley urethral catheter in the considered group and kept for two hour after getting the histopathology report. Same schedule was maintained weekly for 6 weeks. All patients were followed up at 6 weeks after 1<sup>st</sup> cycle of intravesical instillation then 3 monthly for 1 year.

**Result :** Presence of recurrence of tumour was found non-significant in Gemcitabine and Mitomycin C group (18.5% vs. 40.7%,  $p=0.074$ ). Recurrence free survival was found 81.5% patients in Gemcitabine group and that of 59.3% patients in Mitomycin group. Though there was more recurrence free survival in gemcitabine group than mitomycin group, there was no statistically significant difference. Tumour grade progression was found in 20% and 27.3% cases in Gemcitabine and Mitomycin C group respectively. On the other hand, tumour stage progression was found 40.0% and 27.3% patients in Gemcitabine and Mitomycin C group respectively. No statistically significant difference was observed between Groups ( $P>0.05$ ). Haematuria, dysuria, urinary frequency, urgency and contact dermatitis were found non-statistically significant in both groups.

**Conclusion :** Gemcitabine and Mitomycin C both drugs are effective as intravesical chemotherapy in the treatment of non muscle invasive transitional cell carcinoma of urinary bladder and have a better recurrence free survival. But, accounting statistical significance on chemopreventive activity, neither Gemcitabine nor Mitomycin C therapy showed superiority over each other.

Bangladesh J. Urol. 2019; 22(1): 25-29

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Received: 05 August 2018 Accepted: 15 November 2018

## Introduction:

Bladder cancer is the second most common cancer of the genitourinary tract [1]. At presentation 80% of bladder tumours are classified as non-muscle invasive bladder cancer (NMIBC) confined to the inner lining of

the bladder with stage pTa or pT1. The risk of disease recurrence and progression is highly variable, and risk-stratification based on pathologic and clinical variables is commonly utilized for more accurate prediction. Depending on tumour stage and grade, the number and size of lesions, and preceding recurrences, the probability of recurrence may be as high as 60% within 1 year and 80% within 5 year. Up to 17% of tumours progress to muscle-invasive disease within 1 year, and up to 45% of tumours progress to muscle-invasive disease within 5 year [2].

While observation after complete endoscopic eradication has been advocated, several intravesical drugs have been proposed for non muscle invasive transitional cell carcinoma of urinary bladder in an attempt to reduce or delay both recurrence and progression [3]. Significant limitations in efficacy and tolerability for the most widely used intravesical agents across all categories of non muscle invasive transitional cell carcinoma of urinary bladder have favoured the search for new treatment alternatives and intravesical Gemcitabine is a novel chemotherapeutic agent for non muscle invasive transitional cell carcinoma of urinary bladder [4]. Gemcitabine is a deoxycytidine analogue that inhibits DNA synthesis [5]. Gemcitabine can easily penetrate the bladder mucosa with beneficial effects on non muscle invasive transitional cell carcinoma of urinary bladder [6]. At the same time, its molecular weight is high enough to prevent significant systemic absorption in an intact bladder. Gemcitabine has been proved effective as intravesical therapy and well tolerated as single agent therapy for non muscle invasive transitional cell carcinoma of urinary bladder [7].

There are limitations in efficacy of intravesical treatments for non muscle invasive transitional cell carcinoma of urinary bladder; conventional intravesical chemotherapy (i.e. Mitomycin C) is used to prevent recurrence and progression after complete tumour resection. Early recurrence can be decreased by half after mitomycin C, while long-term recurrence rates seem to be reduced to a lesser extent (54% vs 41%) [8]. Mitomycin C is a cross-linking agent that inhibits DNA synthesis. According to Lamm [4] the short-term recurrence rate cannot be reduced by more than 15–20%, and the long-term risk of recurrence by 6%.

A comparison study between intravesical Gemcitabine with Mitomycin C (MMC) reported that the rate of recurrence and progression were lower with Gemcitabine but did not reach statistical significance

[9]. A further comparison study between intravesical Gemcitabine with Mitomycin C (MMC) reported that Gemcitabine is better than Mitomycin C (MMC) to prevent recurrence and progression in non muscle invasive transitional cell carcinoma of urinary bladder [10]. So various study showed various results. Though Gemcitabine is costly but its side effects are fewer than Mitomycin C. The study was done to see the effects of intravesical Gemcitabine and Mitomycin C (MMC) in the treatment of non muscle invasive transitional cell carcinoma of urinary bladder.

#### Materials and Methods:

The study was a Randomized Clinical Trial which was conducted in the department of Urology, Bangabandhu Sheikh Mujib Medical University (BSMMU) between the periods of November'2013 to October'2014. The patients with histopathologically diagnosed as non muscle invasive transitional cell carcinoma of urinary bladder after complete TURBT in urology units of BSMMU were included. In this prospective study sixty consecutive patients were selected by inclusion and exclusion criteria. These sixty patients were divided into two groups randomly by lottery. Half of the patients were enrolled in each group. The patients were selected according to selection criteria. All patients were counseled about techniques of intravesical chemotherapy and possibility of using one of them. Patients were divided in Gemcitabine group and Mitomycin C groups randomly by lottery. Gemcitabine group was experimental group and Mitomycin C group was control group. Multiplicity of tumour was evaluated by checking the preoperative ultrasonography of kidney ureter and urinary bladder region (KUB) and operation note, tumour stage, grade and muscle invasiveness were evaluated by postoperative histopathology of resected urinary bladder tumour. Urine routine examination, Urine culture and sensitivity and complete blood count (CBC) were done before intravesical chemotherapy. Patients with documented UTI were treated with appropriate antibiotic before the procedure. Informed consent were signed by all patients after being informed about the study, different management options, the possibility of response, the side-effects of the drug and the treatment of complications. Inj. Gemcitabine 1000 mg dissolved in 50 ml of normal saline and Inj. Mitomycin C 40 mg dissolved in 50 ml of normal saline. They were instilled into the urinary bladder through Foley urethral catheter and kept for two hour after getting the histopathology report of transurethral resection of urinary bladder tumour (in

their respective group). All patients of each group were advised to change their position (supine, prone, right and left lateral) in bed for 30 minutes from time to time. Complete emptying of bladder was done routinely prior to therapy in order to improve therapeutic efficacy. Patients were asked to restrict fluid intake 12 hours before therapy for better absorption of intravesical therapy. Same schedule was maintained weekly for 6 weeks. All patients were followed up at 6 weeks after 1<sup>st</sup> cycle of intravesical instillation then 3 monthly for 1 year. In each follow up they were evaluated by history, physical examination and investigations. Investigations include urine routine examination, urine culture and sensitivity, serum creatinine, complete blood count and ultrasonography of KUB region. In each follow up urethroscopy were done for evaluation of recurrence of bladder tumour. If recurrence of tumour was found then transurethral resection of tumour and histopathology were done for evaluation of tumor stage and grade progression. Statistical analyses of the results were done by using computer based statistical software, version 16. Ethical clearance for the study was taken from the Institutional Review Board (I.R.B) of BSMMU prior to the commencement of this study.

## Results

A total of 60 patients (38 male and 22 female) with non muscle invasive transitional cell carcinoma of urinary bladder were enrolled initially in this study according to the selection criteria and randomized into two groups, 30 in Gemcitabine group and 30 in Mitomycin C group by lottery. But 6 patients were lost during follow up. Then ultimately 27 patients of Gemcitabine group and 27 patients of Mitomycin C group were included in this study. In this study, 35 were male and 19 were female. In Gemcitabine group male was 19 and female was 8 whereas in Mitomycin C group it was 16 and 11 respectively.

**Table I**

*Distribution of patients by tumour stage in groups*

Tumour stage	Chemotherapy Agent		p value
	Gemcitabine (%)	Mitomycin C n (%)	
Ta	13 (48.1)	15 (55.6)	0.586
T1	14 (51.9)	12 (44.4)	
Total	27 (100.0)	27 (100.0)	

**Table II**

*Distribution of patients by tumour grade in groups*

Tumour stage	Chemotherapy Agent		p value
	Gemcitabine n (%)	Mitomycin Cn (%)	
Low grade	9 (33.3)	16 (59.3)	0.056
High grade	18 (66.7)	11 (40.7)	
Total	27 (100.0)	27 (100.0)	

**Table III**

*Distribution of patients by multiplicity of tumour in groups*

Tumour stage	Chemotherapy Agent		p value
	Gemcitabine n (%)	Mitomycin C n (%)	
Single	7 (25.9)	14 (51.9)	0.051
Two or more	20 (74.1)	13 (48.1)	
Total	27 (100.0)	27 (100.0)	

**Table IV**

*Distribution of patients by recurrence of tumour in groups*

Recurrence of tumour	Chemotherapy Agent		p value
	Gemcitabine n (%)	Mitomycin C n (%)	
Yes	5 (18.5)	11 (40.7)	0.074
No	22 (81.5)	16 (59.3)	
Total	27 (100.0)	27 (100.0)	

**Table V**

*Distribution of patients by progression of tumour in groups*

Histopathology findings	Chemotherapy Agent		p value
	Gemcitabine (n=5)	Mitomycin (n=11)	
Tumour grade progression n (%)	1 (20.0)	3 (27.3)	0.755
Tumour stage progression n (%)	2 (40.0)	3 (27.3)	0.611

**Table VI**  
*Distribution of patients by Hematuria in groups*

Hematuria	Chemotherapy Agent		p value
	Gemcitabine	Mitomycin	
	n (%)	n (%)	
1 <sup>st</sup> follow up	1 (3.7)	0 (0.0)	0.313
2 <sup>nd</sup> follow up	2 (7.4)	7 (25.9)	0.068
3 <sup>rd</sup> follow up	0 (0.0)	1 (3.7)	0.313
4 <sup>th</sup> follow up	2 (7.4)	1 (3.7)	0.552

**Discussion:**

Regarding management of non-muscle invasive bladder cancer (NMIBC), the primary approach is transurethral resection of the bladder tumour (TURBT) followed by intravesical therapy. The instillation of a chemotherapeutic drug immediately after TURBT was originally proposed in the 1970s and was based on the assumption that chemotherapy could destroy floating tumour cells and prevent reimplantation in the bladder[11].

In an attempt to reduce the recurrence and progression of non muscle invasive transitional cell carcinoma of urinary bladder many new chemotherapeutic drugs have been invented. Mitomycin C chemotherapy is well established drug with reasonable success rate and some side effects. Gemcitabine is newer one and effective as single agent intravesical chemotherapy for non muscle invasive transitional cell carcinoma of urinary bladder.

There are substantial numbers of publications demonstrating the intravesical instillation of Gemcitabine and Mitomycin C in the treatment of NMIBC [12,13,14,15]. It was one of the former clinical trials of NMIBC to compare Gemcitabine and Mitomycin in Bangladesh context. The study compared the findings with result of some other published articles elsewhere in the world.

Analysis of age distribution showed that in a total of 54 patients, the mean age was found 55.00 (8.62) years and range were (40-69) years in gemcitabine group and mean age were 54.07 (8.18) years and range were (43-70) years in Mitomycin group.

Out of all patients in Gemcitabine group 29.6% were female and 70.4 % male. In Mitomycin group 40.7% was female and 59.3% male. No statistically significant difference was observed between Groups in terms of gender (P>0.05). In Bohle et al. (2002) study [12], there was 76.6% male in gemcitabine group and in comparing placebo group 83.1% male.

According to tumor staging of NMIBC, 48.1% patients were presented as Ta stage and the rest 51.9% in T1 stage in Gemcitabine group. As well in Mitomycin group, 55.6% patients were remained in Ta stage and 44.4% in T1 stage. There was no significant difference in the context of tumour stage in Gemcitabine and Mitomycin group (p= 0.586). Nonetheless, regarding tumor grading in Gemcitabine group, low grade tumor was found in 33.3% patients and 66.7% of high grade. In Mitomycin group, 59.3% patients had low grade and 40.7% high grade.

In the context of tumor lesion, single tumour was found in 25.9% patients and 74.1% patients two or more tumour in Gemcitabine group. In Mitomycin group, 51.9 % patients had single tumour and 48.1% two or more tumours. There was no statistically significant difference in tumour grading (p>0.05). A similar frequency of multiple lesions was also observed by Bohle et al (2002)[12] accounting 47.6% in gemcitabine group and 38.7% in placebo group.

In the study, recurrence free survival was found 81.5% patients in gemcitabine group and that of 59.3% patients in Mitomycin group. On the other hand, presence of recurrence of tumour was found non-significant in Gemcitabine and Mitomycin group (18.5% vs. 40.7%, p= 0.074). Though there was more recurrence free survival in gemcitabine group than mitomycin group but there was no statistically significant difference.

Progression-free survival rates at final follow up of 1 year was found 80% in gemcitabine group and 73.7% in mitomycin group. On the other hand, tumour stage progression was found 40.0% and 27.3% patients in Gemcitabine and Mitomycin group respectively. No statistically significant difference was observed between Groups (P>0.05).

Local toxicity in both treatment groups was acceptable. Haematuria was noted in 1<sup>st</sup>, 2<sup>nd</sup>, 3<sup>rd</sup> and 4<sup>th</sup> follow-ups. It was mostly found in 2<sup>nd</sup> follow-up in both Gemcitabine and Mitomycin groups (7.4% vs. 25.9%) but statistically non-significant. Dysuria was found in decreasing trend in both Gemcitabine and Mitomycin groups. In 1<sup>st</sup> and 2<sup>nd</sup> follow-ups, dysuria was presented in both groups (18.5% vs. 11.1%). In consecutive other follow-ups, there was no statistically significant difference between Gemcitabine and Mitomycin groups (3<sup>rd</sup> FU 14.8% vs. 18.5%, p=0.715; 4<sup>th</sup> FU 7.4% vs. 7.4% p=1.000 ;).

There was no statistically significant difference in both Gemcitabine and Mitomycin C groups but in both groups complaining of urinary frequency was observed at follow-up (1<sup>st</sup> FU 0.0% vs. 3.7%; 2<sup>nd</sup> FU 14.8% vs. 18.5%; 3<sup>rd</sup>

FU 14.8% vs. 22.2% and 4<sup>th</sup> FU 7.4% vs. 7.4 %). Urgency was reported in both Gemcitabine and Mitomycin C groups of patients (1<sup>st</sup> FU 0.0% vs. 3.7%; 2<sup>nd</sup> 7.4% vs. 7.4%; 3<sup>rd</sup> FU 3.7% vs. 0.0% and 4<sup>th</sup> FU 7.4% vs. 3.7%). But no statistically significant difference was found in two groups in terms of urgency complain.

### Conclusion

Gemcitabine and Mitomycin C both drugs are effective as intravesical chemotherapy in the treatment of non muscle invasive transitional cell carcinoma of urinary bladder and have a better recurrence free survival. But, accounting statistical significance on chemopreventive activity, neither Gemcitabine nor Mitomycin C therapy showed superiority over each other.

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