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Intravesical Mitomycin C Instillation to Delay Recurrence of Superficial Bladder Cancer (Long-Term *versus* Short-Term Protocols)

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Abstract

Background Majority of patients with bladder cancer present with superficial tumor, which is of three types: papillary carcinoma confined to the bladder epithelium, tumor invading but confined to the lamina propria, and carcinoma in situ (cis). Transurethral resection represents the effective management of superficial tumors but with high recurrence rate (75%) that can be minimized to 50% by using cytotoxic drug or immunotherapy.

Objective To compare two method lines of treatment in respect to long - term versus short - term therapy of Mitomycin C (MMC)Intravesical instillation after transurethral resection of superficial transitional carcinoma of urinary bladder to detect the duration of disease free interval, recurrence rate and adverse effects.

Methods A prospective, randomized, two parallel and compared lines of treatment study involved 50 patients who were evaluated after transurethral resection of superficial bladder cancer with median follow-up of 30 months. They were informed about the study and their approval to participate in the study was taken. Group A (25 patients) received intravesical MMC 30 mg weekly for 6 weeks, while group B (25 patients) continue to receive further 12 monthly instillations. Statistical analysis was performed by using Kaplan - Meier methods and chi square test.

Results After follow-up of 30 months, 28% of patients who received short course of intravesical MMC were disease free in comparison to those with long – term treatment in group B which shows significantly higher rate of disease free (56%). Regarding the adverse effects, no significant differences in incidence were noted between two groups.

Conclusion The data from the present study confirm both efficacy and safety of using intensive, prolong regimen of intravesical MMC instillation for superficial bladder cancer.

Key words Mitomycin C, superficial transitional carcinoma, and transurethral resection.

Introduction

Bladder cancer is the third most prevalent disease among male patients, the tenth among female patients in United States [(1)]. The majority of patients (75% - 80%) with bladder cancer initially present with superficial tumor [(2)], which comprising three different types: stage Ta- papillary carcinoma confined to the bladder epithelium, stage T1-tumor invading but confined to the lamina propria, and hot, non papillary carcinoma in situ (cis) [(1-3)].

Transurethral resection (TUR) can effectively control the primary tumor and confirm the superficial transitional cellular nature of the disease. Because of high recurrence rate and / or progression of the tumor after TUR (75%), there is increasing interest in intravesical instillation of Cytotoxic drug or immunotherapy - Bacillus Calmette-Guerin (BCG) and become common practice after TUR in order to prevent recurrence in more than 50% of transitional cell carcinoma (cis, Ta, T1) [(4-6)].

Intravesical trials are divided into 2 major categories:

1- Therapeutic trial designed to treat established disease.

2- Prophylactic / adjuvant, designed to prevent recurrence.

Seventy–six clinical studies had been reported on short-term intravesical therapy within the last 20 years, their result rate of the net benefit was: Thiotepa (8-27%),

Doxorubicin (12-23%), Mitomycin C (13-35%) [6,7].

Japanese studies have shown that Mitomycin C is most effective chemotherapeutic agent in influencing superficial bladder carcinoma, when given intravesically[8]. A clinical study has shown that complete disappearance of bladder tumor can be achieved in 44-49 % of patients [7,8].

A prospective follow-up study was designed to compare long term versus short term therapy of Mitomycin C intravesical instillation after transurethral resection of superficial transitional carcinoma of urinary bladder with respect to duration of disease free interval, recurrence rate and adverse effects.

Methods

The study involved 50 patients with superficial transitional cell carcinoma of the bladder (grade I-III, staging as cis, Ta, T1) diagnosed after TUR. They were collected in the period from January 2007 to November 2009 in AL-Kadhimyia Teaching Hospital and were informed about the study. Patients of the study were free of other diseases like diabetes mellitus, hypertension and ischemic heart diseases.

After 15 days (TUR) all patient under went either short (group A) or long (group B) cores of MMC therapy regiment after taking their approval to participate in the study.

All of the 50 patients (group A and B) started their therapy with intravesical installation of 30 mg of MMC in 50 ml of normal saline to be returned for at least one hour, this procedure was repeated weekly for 6 weeks for those patients in group A (short term therapy, while patients in group B (long term therapy) continued to receive the same dose of MMC monthly up to 12 months.

Regarding the follow up and response assessment as well as adverse (toxic) effect. All patients of the study were subjected to cytological urine analysis as well as cytoscopic examination. These procedures started 3 months following the start of protocol and to be repeated every 3 months for the first year and then every 6 months up to the end of the study period (30 months).

The complete response was defined as no residual carcinoma cystoscopically and negative urine cytology for the malignant cells.

Statistical analysis was done for recurrence free rate (disease free rate), performed by Kaplan-Meier method for both groups and were tested with long rank test and chi square test. Excluding criteria were: the presence of another cancer, previous local or systemic chemotherapy or radiotherapy and renal failure.

Results

From January 2007 to November 2009, 50 patients were treated and their response to MMC intravesical therapy was evaluated. They were of age ranging from 23 to 78 years (median is 56 years). The majority of patients were males (84%). Regarding clinicopathological features, 66% of the patients had solitary tumor and 70% were having Ta bladder cancer (Table 1).

Table 1. Clinicopathological profile of 50 patients with superficial transitional cell cancer of the bladder.

Criteria of the study group		Regimen Therapy				Total	
		Group A		Group B			
		GMA		GMB		No.	%
		No.	(%)	No.	(%)		
Sex	Men	20	80	22	84	42	84
	Women	5	23	3	16	8	16
Age	≤ 30	3	12	0	0	3	6
	≤ 50	6	24	6	24	12	24
	≥ 50	16	64	19	76	35	7
Stage	Ta	16	64	19	76	35	70
	T1	6	24	4	16	10	20
	cis	3	12	2	8	5	10
Multicentricity	Solitary	18	72	15	60	33	66
	Multiple	4	16	7	28	11	22
	Unkown	3	12	3	12	6	12

In assessment of the response to treatment, our study revealed that significantly higher percentage rate (56%) in group B in comparison to that of group A (28%) were free of cancer after the end of the study period (30 months) as in table 2 and figures 1 and 2.

Table 2. Crude results of end points after long term follow-up

Results	Group A		Group B		Total		X^2	*P* value
	No.	%	No.	%	No.	%		
* Recurrence of tumor	18/25	72	11/25	44	29	58	4.11	< 0.05
** Stage								
Ta	12/16	48	8/19	32	20/35	40		
T_1	4/6	16	2/4	8	6/10	12	0.2	< 0.05
cis	2/3	8	½	4	3/5	6		
*** Grade								
GI	12/18	48	6/15	24	18/33	36		
GII	3/4	12	3/7	12	6/11	12	1.66	< 0.05
GIII	3/3	12	2/3	8	5/6	10		

*$P < 0.05$ Significant, ** $X^2 = 0.2$ $P > 0.05$ Not Significant, *** $X^2 = 1.66$ $P > 0.05$ Not Significant

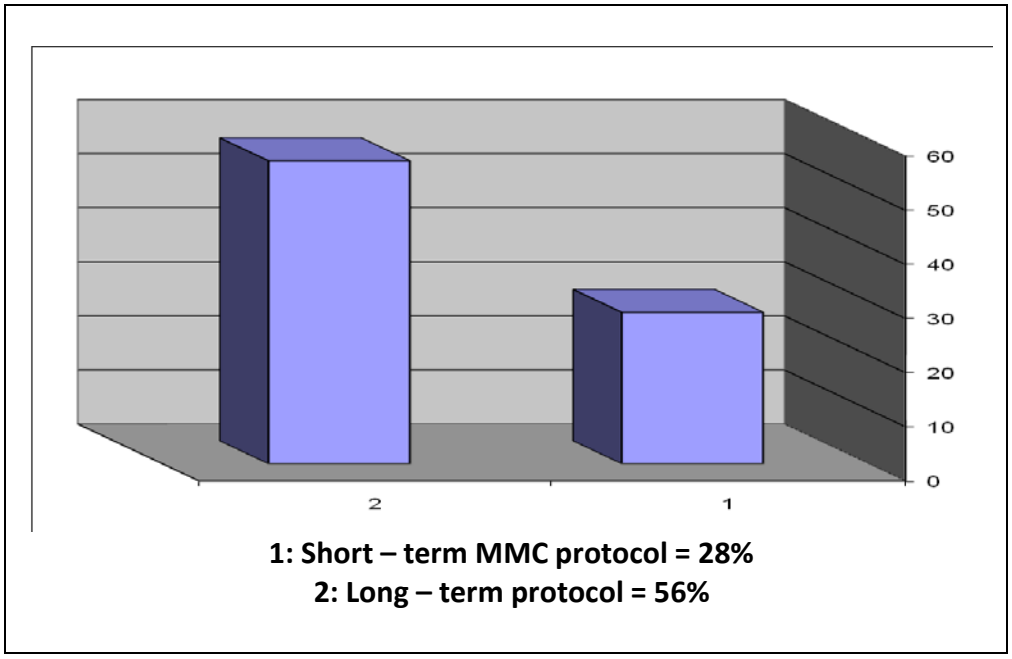

Figure 1. Percentage of disease free patients in short & long – term MMC protocols in both groups of the study

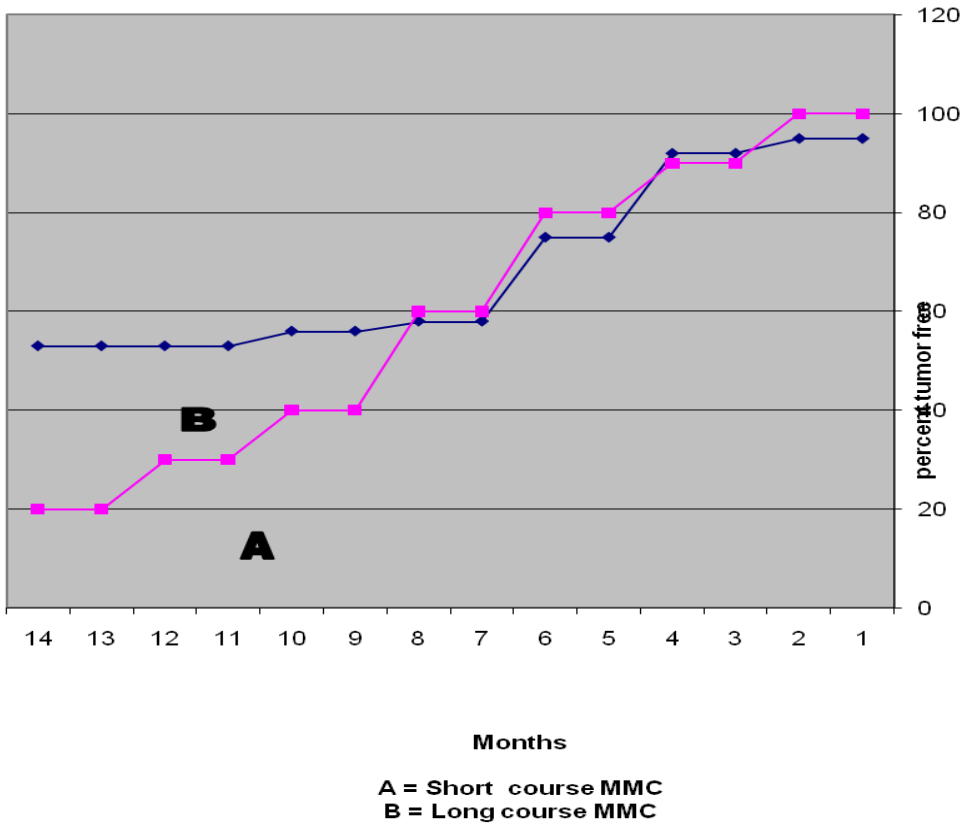

Figure 2. Kaplan- Mieir plot of percentage of patients with papilary tumors cis, Ta, & T1 grades 1 to 3 transitional cell cancer free of tumor after TUR & short MMC protocol versus long term. Long rank test, *p = 0.04.*

In addition to free cancer response assessment, the adverse effects of MMC therapy in both groups were evaluated. Higher percentage of patients in group B affected with bladder irritation (36%) and urinary tract infection (52%). On the contrary, 52% of patients in group A demonstrated positive hematuria. However all these differences were of no statistical significance (x^2=1.07 and *p* value > 0.005) as in table 3.

Table 3. Adverse effects of the short and long term intravesical MMC therapy.

Toxicity		Group A		Group B	
		No.	%	No.	%
Bladder irritation	Mild	5	20	4	16
	Moderate	2	8	3	12
	Severe	1	4	2	8
	Total	8	32	9	36
Microscopical hematuria		13	52	10	40
Urinary tract infection		9	36	13	52
Systemic allergy		1	4	0	0

Discussion

Numerous studies have demonstrated the efficacy of post-TUR intravesical administration of MMC in lowering recurrence rate, at least for 2-3 years of superficial transitional cell carcinoma of the urinary bladder after first observation [8-10].

The results of previous clinical studies showed that the MMC is beneficial in prevention of tumor recurrence in 13-35% of patients in comparison to other chemotherapeutic agents like Thiotepa (8-27%) and Doxorubicin (12-23%) [10,11].

Soloway and Ford reported that recurrence rate was 10 times as great in patients failed to respond to MMC than those showing complete response [12].

The data obtained from our study give an evidence that significantly improve the disease - free survival after the continuation of intravesical MMC for 12 monthly instillations [10] a trend in favor of MMC protocol in group B and Kaplan- Meier curve clear that tendency. Further, the majority of patients tolerate long – term intravesical MMC therapy well [9,12].

Further efforts to select patient were separated according to the presence or absence of ABH (blood group type A, B, and H) antigen on the tumor: the more aggressive ABH- negative tumor were found to recur less frequently than ABH positive tumor [8,10]. Moreover many questions still remain unanswered in relation to scheme of installation, when the ideal time to start treatment? What is the optimal duration of treatment? What is the ideal interval between two installations? All those questions have to be answered in longer duration study.

As a conclusion, the data from the study confirm both efficacy and safety of using intensive; prolong courses of intravesical MMC installation.

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