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Research Article

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A comparative Study Between single session versus Six Sessions Mitomycin C instillation In Patients With Low Risk Non-Muscle Invasive Bladder Cancer

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Abstract

Background:
Intra vesical instillation following transuretheral resection of low grade and low stage bladder cancer proved its efficacy in reducing recurrence and progression of bladder cancer.

Aim of the study:
To compare the efficacy of single session of mitomycine C versus six sessions mitomycine C following TURBT on recurrence and progression rates in patient with low risk non-muscle invasive bladder cancer.

Patients and Methods
A prospective randomized controlled study of patients with newly diagnosed Ta or Tl non- muscle invasive urothelial carcinoma of the bladder with a 3 cm. or less ,single, papillary, primary tumor ,65 patients were entered into the study from Baquba teaching hospital between October 2016 and October 2019 In all patients the upper urinary tract was normal on excretory urography.
Patients with muscle invasive or G3 tumors or bladder carcinoma in situ on pathological examination, age older than 80 years, uncontrolled urinary infections or psychological disturbances were excluded from study
Patients were randomly allocated to receive a single session of 40 mg. mitomycin C diluted in 50 ml saline , (Group A) which was instilled when hematuria ceased, usually was within 6 hours of transurethral resection or a six weekly sessions of 40mg mitoaycin C, (Group B)

Results
Out of the (65)patients initially included in the study (17)were excluded because pathological examination revealed muscle invasive tumor in (5) patients, G3 tumor in (4), bladder CIS in (1), no histological evidence of tumor in (l) and (6)were lost during follow-up.
Therefore , 24 patients were eligible in the one sessionmitomyicn C, and 24 in the six sessionsmitomycin C (Group B).
Out of the (24) patients in the one session mitomycin C, 2 patients (9.1%) experienced at least one recurrent tumor compared to only one patient (4.5%) in group B. A lower recurrence rate was observed in the six sessions mitomycin C compared to the one session mitomycin C .

Conclusions
In patients with low risk non-muscle invasive bladder cancer an immediate one session mitomycin C instillation as comparable to six sessions mitomycin C instillations in increasing the disease free interval and significantly decreased recurrence, progression and recurrence tumor per year rates.

Keywords: Low risk non muscle invasive bladder cancer and mitomycin intravesical instillation.

Introduction

Vesical tumor is the second most common tumor of the urinary system, and it is the fourth most common cancer in men after prostate, lung , and colorectal cancers , accounting for (6.6%) of all cancer cases. In woman, it is the ninth most common cancer, accounting for (2.4%) of all cancer. Annually incidence of bladder cancer is about 400 000 cases with about 150 000 mortality rate .The most important etiological factor is cigarette smoking. Regarding gender preponderance men are more affected than women. This may be related to smoking habit difference. When first seen about one third of patient have involvement of bladder muscularis layer. While about three quarters of them have no muscle involvement.

Patients and Methods

A pprospective randomized controlled study of patients with newly diagnosed Ta or Tl non- muscle invasive bladder tumor with a 3 cm. or less ,single, papillary, primary tumor ,65 patients were entered into the study from Baquba teaching hospital between October 2016 and October 2019 .All patients have no dilatation of upper tract as seen by ultrasound.

Exclusion criteria are: high grade 3 tumor , stage 2 tumor, CIS and patient age over 90 years.. After visually seen total cystoscopic resection of vesical tumor, Patients were randomly distributed to have one session of 40 mg. mitomycin C diluted in 50 ml saline , (Group A) which was given when urine become clear, usually given in the first 6 hour post resection or weekly for 6 sessions of 40mg mitoaycin C, (Group B), The mitomycin was kept for 1 hour with catheter closed and then the bladder was flushed with saline. Patients were evaluated with urinary cytology, ultrasound and cystoscopy at 3, 6, 9, 12,15, 18, 21 and 24 months, and then once a year post operatively .

At each cystoscopy any tumor or abnormal looking urothelium was resected and tissue sent to reference pathologist to confirm recurrence. Recurrence-free interval which is the period between initial transurethral resection and first recurrence. Recurrence was defined histologically as biopsy confirmed carcinoma. Statistically recurrence represent the percentage of patients with recurrence during the follow up period, recurrence per year represent the number of positive cystoscopies divided by the total years of follow-up.

Tumor per year represent the total number of tumors observed during all positive cystoscopies divided by the total years of followup, progression which was the percentage of cases of invasive bladder tumor or metastases. Recurrence free rate were calculated according to the Kaplan-Meier method and compared by the log-rank test. A Complete blood count, serum creatinine, urinalysis and urine culture were performed before and 1 week after transurethral resection.

Results

Out of the (65) patients initially included in the study (17)were excluded because pathological examination revealed muscle invasive tumor in (5) patients, G3 tumor in (4), bladder CIS in (1), no histological evidence of tumor in (l) and (6)were lost during follow-up.

Therefore, 24 patients were eligible in the one session mitomyicn C, (Group A) and 24 in the six sessions mitomycin C (Group B).

Out of the 48 patients who entered the study (4)were women and(44) were men, with a mean age of (57.5 ± 8.1) years. Both groups were comparable in regard to clinical and pathological characteristics, the follow-up period was (24) months in both studied group, (table 1).

Out of the (24) patients in the one session mitomycin C, (Group A), 2 patients (9.1%) experienced at least one recurrent tumor compared to only one patient (4.5%) in group B. A lower recurrence rate was observed in the six sessions mitomycin C compared to the one session mitomycin C group, however, the difference was statistically insignificant, P=0.67, (table 2). From other point of view, only (2) patients in both group (1 (4.5%) in each group) had progression with no statistically significance, P=0.98, (table 2).

The recurrence free rates are shown in table 3,these findings revealed that the recurrence free rates were reduced with the advancing time of the follow up in both group with a longer recurrence-free interval observed in the six sessions mitomycin C compared to the one session mitomycin C group , nonetheless, the difference between both groups was statistically insignificant, P= 0.18,

Table1. Patient characteristics

Variable		0ne session MMC Group A	six sessions MMC Group B	Overall
Patients number		24	24	48
Age (year) mean ± SD		56.3 ± 9.7	58.6 ± 10.1	57.5 ± 8.1
Gender	Male	22 (91.7%)	22 (91.7%)	44 (91.7%)
	Female	2 (8.3%)	2 (8.3%)	4 (8.3%)
Mean tumor size (cm)		2.0	2.2	2.1
Pathological stage (%)	Ta	10 (41.7%)	9 (37.5%)	19 (39.6%)
	T1	14 (58.3%)	15 (62.5%)	29 (60.4%)
	G1	15 (62.5%)	16 (66.7%)	31 (64.6%)
	G2	9 (37.5%)	8 (33.3%)	17 (35.4%)
Follow up (month)		24	24	24

Table 2. Recurrence &progression

Variable	**One session MMC (Group A) N = 24**	**Six sessions MMC (Group B) N = 24**	**P value**
Recurrence	**2 (9.1%)**	**1 (4.5%)**	**0.67** ***(NS)***
Progression	**1 (4.5%)**	**1 (4.5%)**	**0.98** ***(NS)***

NS: not significant.

Furthermore, the overall the recurrence free rate for the two years were (80.1%) and (93.4%) for the one session mitomycin C group and six sessions of mitomycin C group , respectively .

A lower recurrence and tumor per year rates were noted in the six sessionsmitomycins C compared to one session mitomycin C group (table 3) , the recurrence rate per year in group B was only 3.3% in six sessions mitomycin C compared to 9.85% in group A, P = 0.08.

Regarding the new tumor per year reported among the studied groups, the new tumor per year was 16.6% in group A and 12.5% in group B, P=0.63, (table 4). Furthermore, one patient in group B, and 5 patients in group A, presented with multiple tumors recurrence.

Early recurrence developed during the first 12 months in 8 patients (33.3%) of the one session mitomycin C group but only one patient of the six sessions mitomycin C group with no statistically significant difference between both groups (p = 0.11) , in the second year, recurrence was found in 3 patients in each group with no significant difference, (P=0.87) , in the second year.

At 24-month follow-up a prolonged hospital stay and catheterization period were observed in the six sessions mitomycin C group compared to one session mitomycin C, however, the differences were statistically insignificant, in both comparison, P> 0.05, (table 5).

Side effects were not severe problem, chemical cystitis and slight allergic skin reactions had been developed in only 3 patients of the six sessions mitomycin C group while no hematological changes were reported.

Table 3. Recurrence-free rates for 24 months follow-up

Group	Recurrence free rates								P.value
	3 Month	6 Month	9 Month	12 Month	15 month	18 month	21 Month	24 month	
One session MMC(Group A)	91.7	90.3	85.1	82.9	75.1	73.4	73.5	68.3	0.39 *(NS)*
Six sessions MMC(Group B)	100.0	100.0	100.0	96.20	92.30	91.1	89.3	78.1	0.57 *(NS)*

NS; not significant

Table 4. Recurrence and tumor per Year rates

•	**One session MMC (Group A) N = 24**	**Six sessions MMC (Group B) N = 24**	P. value
Recurrence per year	9.85%	3.30%	0.08 *(NS)*
New tumor per year	16.60%	12.5%	0.63 *(NS)*

NS; not significant

Table 5. Hospital stay and catheterization period during the 24 months

Variable		**One session MMC (Group A) N = 24**	**Six sessions MMC (Group B) N = 24**	**P value**
Hospital stay:	Total hours	**1231**	**1452**	**0.67 *(NS)***
	Hours/patient	**51.3**	**60.5**	
Catheterization period	Total hours	**696**	**872**	**0.98 *(NS)***
	Hours/patient	**29**	**36.3**	

NS; not significant

Discussion

The standard intravesical therapy for non muscle invasive bladder cancer are BCG and mitomycin c. BCG produces its effect as an immunotherapy.

While mitomycin and other alternative are considered to be chemotherapeutic agents.

Other alternatives include varubicin, gemfitabine, docetaxel, plaxitaxel and combination treatment of mitomycin with gemcitabine.

The general principles that might optimize the effect of intravesical agent instillation include :

Patient is advised to stop drinking 3 hours before instillation to avoid over dilution by urine, avoid any diuretics for the same reason.

Instillation time between 1 hour to 2 hours ,and drink a lot of water after completing the instillation.

High drug concentration and controlling urine PH at higher level give better result.

It is well known now that the mitomycin is clearly effective in reducing the bladder tumor recurrence by about 15 % but stii the answer is not clear whether it reduce the risk of disease progression and fatality.

According to this study and other several studies the immediate post resection instillation is the most important chemotherapy seesion of non muscle invasive vesicle tumor regardless of the stage or the grade.

Furthermore single dose instillation of mitomycin is safe and cost effective in low risk non muscle invasive vesical cancer.

Conclusions

In patients with low risk non-muscle invasive vesicaltumor an immediate one session mitomycin C instillation as comparable to six sessions mitomycin C instillations in increasing the disease free survival and has shown significant reduction in recurrence and progression and recurrence rates.

This approach is considered to be safe and itsaves time and number of cystoscopic resections,as well as, decrease hospitalization and prolong catheterization with minimal or no associated symptoms associated with multiple mitomycine instillations. So single mitomycin instillation is a good alternative for observation only or to six sessions mitomycin C instillations in patients with low risk non-muscle invasive vesicaltumor.

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