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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 total of 48 patients with low risk non-invasive bladder cancer were included in a prospective randomized controlled trial. Patients who had a 3 cm or less, single, papillary tumor were included, while patient with muscular invasion, G3 tumor, bladder carcinoma in situ and tumor resection with perforation were excluded. The tumor was completely resected before were randomized patients into 2 arms; Group (A) those who receiving one session mitomycin C instillation of 40 mg (usually within 6 hours) into urinary bladder and (Group B); Receiving six sessions mitomycin C instillation into urinary bladder, Median follow up was 24 months. The events studied were the recurrence free rate, the recurrence rate/ year and the number of new tumors developing/year, progression, duration of hospital stay and catheterization period. **Results:** At 24 months follow up, the recurrence free rate was lower in single session of mitomycin C instillation(group A) was (80.1%) while in six sessions mitomycin C instillation (groupB) was (93.4%). Recurrence rate was (9.1% VS 4.5 %) and recurrence per year rate (9.85% VS 3.3%), were decreased in the six sessions mitomycin C instillation (Group B) compared to the single session mitomycin C instillation (Group A). The new tumor per year rate (16.6% VS 12.5%), were slightly decreased in the six sessions mitomycin C instillation (Group B) compared to the one session mitomycin C instillation, (Group A). No difference in progression between two group, the progression rate was(4.5%), but all the above results were statistically not significant and comparable. A shorter hospital stay, catheterization period, low level of local symptoms and lower cost were noted in one session mitomycin C instillation (Group A) compared to six session's mitomycin C instillation, (Group B). **Conclusions** single session mitomycine C giving immediately after surgery or within 6 hours after resection may be as effective as six session protocol. This regimen may be cost effective and avoid prolong hospitalization and catheterization with six sessions regimen.

KEYWORDS: Intra vesical transuretheral mitomycine sessions regimen.

INTRODUCTION

Bladder cancer is the second most common cancer of the genitourinary tract[1] 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.[2] More than 357,000 new cases are diagnosed worldwide, and more than 145,000 deaths are related to urothelial bladder cancer (UBC) each year.[1] The main risk factor for UBC is tobacco, which is thought to be responsible for at least one third of the cases. Males are three to four times more likely to develop UBC than their female counterparts. This discrepancy has been partially attributed to the higher proportion of smokers among males.[1] At presentation, approximately 30% of patients have muscle-invasive UBC (cT2 or higher) and 70% have non-muscle-invasive UBC, of which 70% is pTa disease, 20% is pT1 disease and 10% is carcinoma in situ (CIS), (table 1).[2]

Both the natural history of non-muscle-invasive UBC and its treatment strategies are highly variable. Although some patients never experience disease recurrence, others experience disease progression and eventually die of their disease.[3] In the absence of intravesical treatment, a patient with non-muscle-invasive UBC has a 47% probability of disease recurrence within 5 years of

diagnosis and a 9% probability of progression to muscle-invasive disease within that period.[4]

There are few evidence and risk-based tools to help with decision-making for patients with non-muscle-invasive UBC. Factors predictive of outcome include clinical and pathologic features and molecular markers such as cytology, NMP22 and FISH. While management of cTa low-grade UBC is relatively non-controversial, the best management of patients with high-grade cTa, CIS, or cT1 UBC has not yet been established. The development and testing of effective intravesical therapies for non-muscle-invasive UBC are still evolving. Indeed, major controversies still exist with regard to the indication, type and regimen of intravesical therapy. Other areas of controversy are the criteria for response/failure of treatment and for decisions regarding secondary intravesical therapy versus radical cystectomy. In this article, we analyze the different intravesical therapeutic strategies and critically compare their oncologic efficacy.[5,6]

Superficial Bladder cancer

Noninvasive bladder cancer are also classified as, well, moderately or poorly differentiated (G1, G2 or G3, respectively)[7], WHO system is collapsed grading system of urothelial cancer of urinary bladder into low grade or high grade.[4] Non-muscle invasive tumors are characterized by their concurrent and sequential presentation at several sites of bladder epithelium and with different histological patterns from the visibleexophyticlesions, mostly of low or intermediate grade, to the invisible generally aggressive CIS.[8] Because the recurrence rate and potential for progression are different among these lesions, the global term of superficial bladder cancer is imprecise and requires greater distinction when considering the natural history or treatment of non-muscle invasive lesions.[9] Gross, painless heamaturia is the primary symptom in (85%) of patients with a newly diagnosed bladder tumor and microscopic hematuria occure in virtually all patients[4], the hematuria is usually intermittent and can be related to valsalva maneuvers, therefor any episode of gross hematuria should be evaluated even if subsequent urinalysis is negative, fifty percent of patients with gross hematuria will have a demonstrable cause, (20%) will have a urologic malignancy and (12%) will have bladder tumor.[4] Some patients complain of urgency, dysuria and frequency, pelvic pain and all symptoms related to urinary tract obstruction are found in more advanced tumors.[10]

Staging system of urothelial carcinoma of urinary bladder.*

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ" flat tumor"
T1	Tumor invades subepithelial connective tissue .
T2	Tumor invades muscularispropria .
PT2a	Tumor invades superficial muscularisproperia (inner half)
PT2b	Tumor invades deep muscularisproperia (outer half)
T3	Tumor invades perivesical tissue
PT3a	Microscopically
PT3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumor invades prostatic stroma, uterus, vagina
T4b	Tumor invades pelvic wall, abdominal wall
Regional lymph nodes include both primary and secondary drainage region. All nodes above the aortic bifurcation are distant lymph nodes.	
NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph nodemetastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph nodes metastasis.

N2	Multiple regional lymph node metastasis, in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph nodes metastasis)
N3	Lymph nodes metastasis to the common iliac lymph nodes
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

**adopted from: Campbell-Walsh, P2320.2012.*

Assessment of patients with bladder cancer

A full hematuria evaluation for bladder cancer includes urine cytology, cystoscopy, upper tract imaging (primarily a CT scan of the abdomen and pelvis) and a prostate specific antigen (PSA) blood test, patient with microscopic hematuria require afull evaluation but low risk patients don't reguired repeated evalusion. High – risk patients include smoking history, occupational exposure, greater than age (40 years), previous urologic surgery, irritating voiding symptoms, history of urinary tract infection, analgesic abuse, history of pelvic radiation and previous cyclophosphamide therapy should be evaluated every (6 months).[4]

White light cytoscopy with random bladder biopsies is the gold standard for tumor detection, but blue light cytoscopy may be an adjunct. There is various urine markers for detection of urothelial cancer like, BTA stat, BTA trak, Nmp22, Telomerase and cytokeratin 20, to date, none of these markers have a high enough sensivity or specificity to replace office cystoscopy.[11]

Only few of these markers have received FDA approval, many of these markers appear to be more sensitive than urine cytology, especially for the detection of low grade Ta tumors, on the other hand, some of these markers are less specific than cytology which implies a higher rate of false – positive results.[11,12]

Management of non muscle invasive bladder cancer

The initial step in the management of non- muscle invasive Bladder cancer is complete transurethral resection of the tumor, despite the initial complete visual ablation of the primary tumor, the recurrence rate is generally high and(40%) to (80%)of patients will develop tumor recurrences within five years.[12]

By analyzing the hazard curve of recurrences after TURBTAkaza et al[13] demonstrated a biphasic recurrence curve with an initial peak within (3-6 months) and a second peak between (1.5 and 2.5 years) (figure 1). These new tumors arise from areas of dysplastic urothelium, from inadequate resection or from implanted tumor cells. The natural course of bladder carcinogenesis after TUR is probably a mixture of all these events.[14]

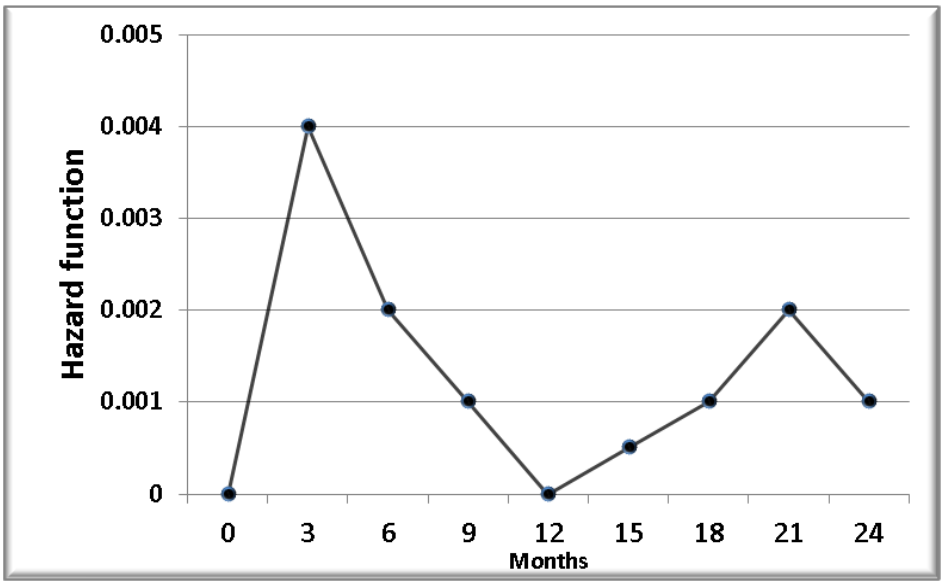

Fig. 1. Time of recurrence- after TUR only

(adapted from Akaza et al., UrolOncol 1998 ; 4:121-9).

The early recurrences are explained mainly by the inadequate resection or implanted tumor cells, while late recurrence related mainly to tumors arise from areas of dysplastic urothelium that's apparently normal at time of first TUR.[15-16]

While low-grade lesions rarely progress, high-grade tumors have a high chance of recurring and progressing to invasive disease.[17-18] Carcinoma in situ is a flat high-grade neoplasm confined to the epithelium. This lesion is significant in that approximately one half of patients with untreated carcinoma in situ develop invasive bladder cancer within 5 years.[19] The concept of field change, and the possibility that tumor cells may be left behind, whether it be from implantation or incomplete resection, have lead many urologists to believe that TUR, though effective, will not alone be sufficient treatment for all cases of non-muscle invasive urothelial carcinoma.

It is in this way that intravesical chemotherapy becomes useful treatment for non-muscle invasive urothelial carcinoma. Thus, surgical resection and medical therapy together allow for more intensive treatment.[20] The fundamental purpose of treatment of non-muscle invasive bladder cancer is three fold:
1. Eradicate existing disease,
2. Prevention of recurrence,
3. Prevention of tumor progression.

Prevention of recurrence is an important goal, Intravesical chemotherapy has been demonstrated to be effective in preventing recurrence in patients with non-muscle invasive bladder cancer.[21] Although patients at low risk for recurrence and progression benefit with these therapies, many can be over treated.[22] Nevertheless, the conclusion that low-grade tumors are devoid of invasive potential is erroneous. Out Of all patients progressing to muscle invasive disease, (25%) initially have grade I, stage Ta orTl disease.[23] In addition to that recurrence has ranged from (4l to 44%) in this low risk group with single session of mitomycin C furthermore The National Bladder Cancer Cooperative Group A (NBCCGA) reported that(36%) of newly diagnosed bladder cancers were Ta stage. There are many factors can affect disease recurrence and progression of these factors is the tumor stage it has been shown that patients with stage Ta tumors have approximately a(4%) chance of progression to invasive disease and almost (50°/o) chance of tumor recurrence after TUR. In contrast those patients with tumors that have invaded the lamina propria (Tl) have approximately a(30%) chance of having invasive disease and a(70%) chance or more, of recurrence within (5 years).[24-25] Likewise, grade has a significant impact on the likelihood of progression : patients with grade 1 cancer have a(3%) chance of progression and (48%) chance of tumor recurrence, while those with grade 2 neoplasms have a(11%) chance, & those with grade 3 tumores have a(44%) chance of disease progression with (59% & 80%) recurrence rate respectively.[25] Multiplicity of lesion is also a potential predictor of recurrence and progression, solitary neoplasms may occur in(22% to 46%) of patients and multifocal in (48% to 75%), with the solitary tumor has less chance of recurrence than patient with multiple lesions.[26] While multiple recurrences increase the chance of progression ,the recurrence rate in patient with primary tumors is approximately half that of subject with previous recurrence. The frequency of recurrence and progression depends further on several simultaneous prognosticators: only (2%) of grade 1, stage Ta neoplasms and (7%) of grade 1,stage Tl tumors progress, but in patient with stage Tl grade 2 or 3 tumors progression occurs in(21% to 48%), respectively as compared to (6%) and (25%) of those at stage Ta, grade 2 and 3, respectively.[26] These rates of recurrence and progression represent an uncomfortable psychological problem for patients as well as dilemma for urologists.[3,7]

Several cytotoxic and immune modifying agents have been used intravesically for therapeutic and prophylactic (adjuvant, either as single or repeated drug administration) purposes.

On the other hand, many trials have demonstrated lower recurrence rates with early instillation of endovesical chemotherapy, suggesting that tumor cells floating free within the bladder can be controlled early with chemotherapy agents.[27-28] Moreover, the concept of cell implantation at transurethral resection of non- muscle invasive bladder cancer as a recurrence mechanism has been supported in animal models and clinical trials.[29-32]

Mitomycin C is an antitumor, antibiotic, alkylating agent that inhibits DNA synthesis. The drug is usually instilled weekly for 6-8 weeks at dose ranges from (20 to 60 mg). Optimization of mitomycin c delivery can result in halving of the recurrence rate in some studies. This can be achieved by eliminating residual urine volume, overnight fasting, using sodium bicarbonate to reduce drug degradation and increasing concentration to (40 mg) in (20 ml). The use of local micro wave therapy in conjunction with mitomycinc, (20 mg/50 ml), reduce recurrence rate from (57.5%) to (17.1%) in amulticenter trial. A study using micro wave with higher doses of (40 to 80 mg) for (6 to 8 weeks) in high grade bladder cancer found a recurrence – free rate of (75%) at 2 years.[33-35]

Electro motive intravesicalmitomycin c appear to improve drug delivery into bladder tissue (4). The main side effect of mitomycin c is transient filling type symptoms (LUTS) in 15% of patients, occasionally, dermatitis of external genitalia or palms of the hand, so treatment must be stopped. Systemic toxicity is rare because of large size of the molecule of (329) dalton(6). Between 39% and 78% of patient with residual tumor experience, a complete response to mitomycin c and recurrence is reduced in (2-33%).[36]

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 included into the study from Baquba teaching hospital between October 2013 and October 2015 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 psychologica disturbances were excluded from study. Bladder tumors were staged and graded accordance with TNM and WHO reference center classifications, respectively. To make a uniform diagnosis of T category and grade all histological examinations were done by the same reference pathologist. After complete transurethral resection of bladder tumor, 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), The instillation was retained for 1 hour with catheter clamping and then the bladder was irrigated 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.[33] A Complete blood count, serum creatinine, urinalysis and urine culture were performed before and 1 week after transurethral resection.

Data Management and Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 21.0 was used for analysis of data (SPSS Inc. 2013). All variables were examined for normality distribution and descriptive statistics presented as frequency (No.), proportions(%), mean ± standard deviation (SD).

A Student's t-test and analysis of variances (ANOVA) tests were used to compare means, chi-square test was used to compare frequencies and proportions and Fisher's exact test was used when the chi square was inapplicable. Level of significance (P.value) was set at ≤0.05 to be considered as significant.

3. 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, (Group A) and 24 in the six sessionsmitomycin C (Group B).

Out of the 48 patients who entered the study (4) 8.5%were women and (44) 91.5% 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 3). 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, (table2).

The recurrence free rates are shown in table 3 and demonstrated in figure 2, 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, figure 2.

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 mitomycinC group, respectively (figure 3).

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.

Recurrence timing was considered using different cutoff points when determining the possible impact of single early instillation of mitomycin C on cell implantation as a mechanism of early 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, (figure 4).

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 sessionsmitomycin C group while no hematological changes were reported.

Table 1. Patient characteristic

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.

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

	Recurrence free rates								**P.value**
Group	**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.

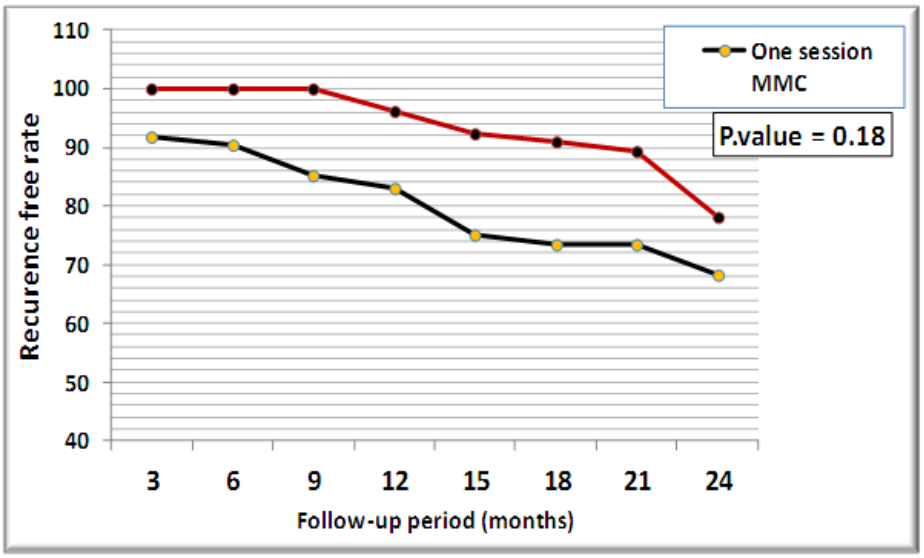

Figure 2. Recurrence-free rates for 24 months follow-up.

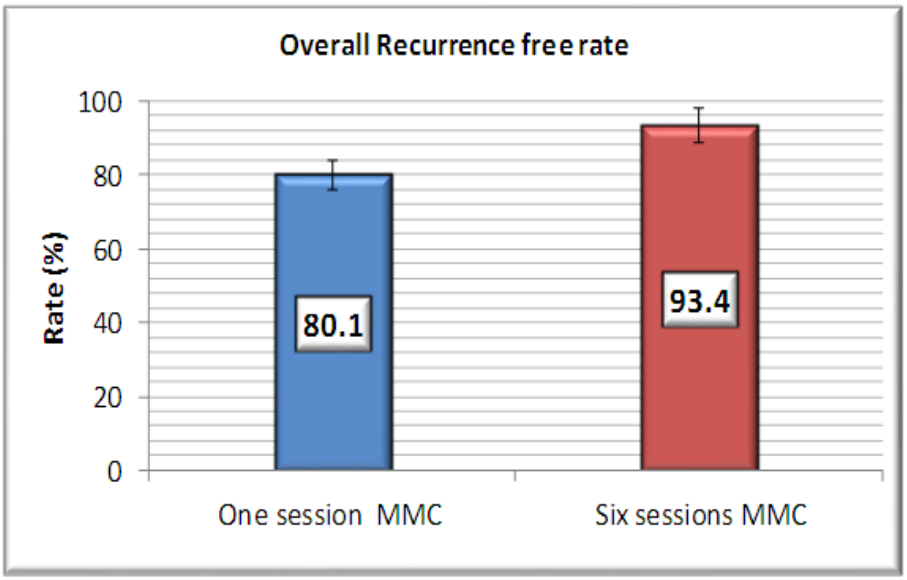

Figure 3. Overall recurrence free rates of both studied groups

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)*

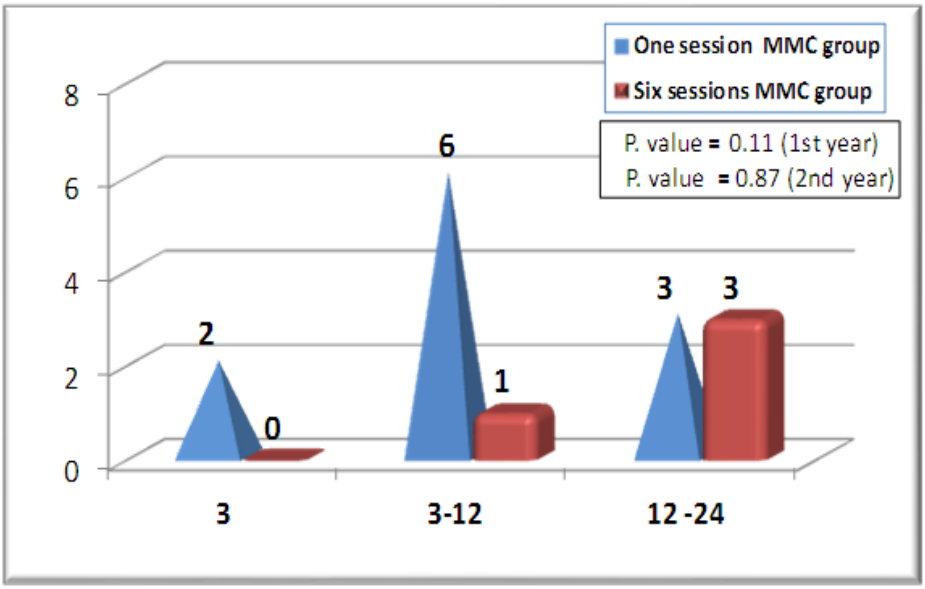

Figure 4. Time of recurrence

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**	

4. DISCUSSION

Several antineoplastic agents have been tested for the treatment of non-muscle-invasive UBC. Mitomycin C (MMC) is the most commonly used intravesical chemotherapy to date. Alternative agents are gemcitabine, doxorubicin and epirubicin. MMC is an anti-tumor antibiotic, which acts by inhibiting DNA synthesis. A review of randomized trials (n = 1,774) revealed a statistically significant benefit in using intravesical MMC after TUR compared to TUR alone. The average recurrence rate was 54% in the TUR alone group versus 32% in the TUR plus MMC group.[37] Dysuria and frequency were the most common side-effects, occurring in 41% of the patients.[38] Response rates have varied widely across studies, due in part to differences in MMC preparation and protocol.

Recently, Gao et al. demonstrated that tumor uptake and consequently oncologic efficacy of intravesical MMC were proportional to the drug concentration.[39]

In an attempt to optimize MMC delivery, a multi-institutional phase III trial was carried-out randomizing patients to the standard regimen versus the optimized regimen (40 mg MMC in 20 mL of sterile water, manipulations to reduce urine production and alkalinization of urine). The recurrence rate at 5 years was decreased from 75% for the standard regiment to 49% for the optimized regimen. Moreover, the median time to recurrence was delayed from 12 to 29 months.[40]

The optimization of intravesical chemotherapy with MMC consists of increasing the urinary pH, reducing the volume of urine production and buffering the intravesical content. This is achieved by restricting fluids for 8 hours before and during the treatment, oral sodium bicarbonate starting 12 hours prior to, until immediately before the instillation, and emptying the bladder with an urethral catheter before instillation.[40]

While MMC has been shown to decrease the risk for disease recurrence (by ~14%), the more important question for the management of patients with non-muscle-invasive UBC is whether MMC reduces tumor progression and mortality. Huncharek et al. performed a meta-analysis of 11 randomized trials comparing patients treated with intravesical chemotherapy after TUR versus TUR alone; the study focused on primary TUR, excluding patients with recurrent disease.[42] The authors reported that addition of chemotherapy to TUR decreased the risk of tumor recurrence at one year by 44%. Patients receiving chemotherapy for two years showed the greatest decrease in recurrence rates. In a follow-up meta-analysis of eight chemotherapy studies focusing on patients with recurrent tumors, Huncharek et al. found a 38% reduction in the risk of disease recurrence at one year; this rate improved with prolonged

treatment beyond 2 years.[43] In these studies, doxorubicin appeared to be less effective than MMC. Although earlier reports suggested that the beneficial effects of adjuvant intravesical chemotherapy are temporary, several studies have since demonstrated durable effects. A trial comparing one and five instillations of MMC after TUR versus TUR alone demonstrated a decrease in the recurrence rate after a median follow-up of seven years.[42]

Similarly, a phase III trial comparing a standard versus an optimized dose of MMC showed a decreased recurrence rate at five years for the optimized dose.[40] The role of maintenance chemotherapy and sequential chemo-immunotherapy, however, remains unclear. The common indications of adjuvant intravesical chemotherapy instillations are directly related to the risk of tumor recurrence and progression. Despite no clear evidence of reducing progression rates with chemotherapy, classifying the patients according to their risk is essential to improve the outcomes. Both intermediate- and high-risk groups, defined by multiple tumors, tumor size > 3 cm, prior recurrence rate, T1(high grade) and CIS (EORTC risk tables), are eligible for intravesical chemotherapy. However, patients at high-risk of progression should certainly consider intravesical immunotherapy, due to the lack of evidence supporting the efficacy of chemotherapy in this setting.[42,43] Although single instillationare the focus of this study, there is some evidence shows that the immediate single post-operative instillation of chemotherapy reduces the recurrence rate when compared to TUR alone. Authors have shown a recurrence risk reduction by half at 2 years of follow-up and over 15% reduction at 5 years, rendering a routine recommendation for single post-operative instillation of MMC in Ta low-risk patients.[44]

The timing of the instillation has previously been evaluated by a large meta-analysis of randomized clinical trials, which showed to be sufficient if performed within the first 24 hours after the TUR. Complications have been rarely reported, except when bladder perforation occurs.[44] The results are best in patients with a single small tumor that was entirely resected.[45] However, this has shown a relatively low acceptance by the urological community to the routine use in clinical practice.[45]

Recently, Dalbagni et al. tested the efficacy of intravesical gemcitabine in patients with BCG-refractory, high-risk non-muscle-invasive bladder cancer in a phase II prospective trial. Results showed that 50% of patients had a complete response and 21% were free of disease at one year.[46] This study try to evaluate the efficacy of single dose instillation versus six doses instillation for the treatment of low grade non-muscle invasive bladder cancer, the study showed that although multiple sessions instillations of mitomycine is effective in reducing recurrence and progression, comparable results also obtained from single dose instillation of mitomycine giving immediately or within 6 hours after TURBT. Multiple instillation of mitomycin C however, are associated with an increased incidence of side effects.[35] Although, side effects and cost of six sessions mitomycin C group incurred by frequent hospital attendance, six sessions mitomycin C or BCG instillations would be preferable for high grade tumors, Several studies have demonstrated that tumor size, multifocality, morphology, disease-free interval, grade, stage and bladder carcinoma in situ are reliable prognostic factors for recurrence and progression in patients withnon-muscleinvasive bladder cancer.[36-39]

Considering these clinical factors; patients with a 3 cm. or less single, papillary, primary or recurrent tumor, who are disease-free for more than 1 year, can be defined as at low risk for progression. Inclusion criteria in this study were based on these findings, and the low risk status of this group was corroborated since with a median follow up of 24 months in both groups receiving one session or six sessionsmitomycine C. The selection of mitomycin-C in this study was made because it avoids the risk of sepsis and myelosuppression associated with BCG and thiotepa.[40] And avoids the tissue destruction from extravasation associated with doxorubicin[40], in addition to that the response rate after intravesicalmitomycin C seems to be relatively higher than those achieved by other chemotherapeutic drugs.[47-48]

In this study during 24 months of follow-up recurrence, and recurrence of tumor per year rates were slightly decreased and the recurrence-free interval was slightly increased in the six sessions mitomycin C group compared tothe one session mitomycin C group, These results are comparable to those obtained in controlled trials of a six sessions instillation of epirubicin or mitomycin C with short-term followup.[38,41,42] Clinically, this outcome indicated a reduction in transurethral resection for patients treated with six sessions Mitomycin C. At 24-month follow-up a prolonged hospital stay and catheterization period were observed in the six sessions Mitomycin C group **c**ompared to One session mitomycin C group. The incidence of side effect in this study was extremely low. On the other hand, a six sessions mitomycin C instillation is anexpensive approach with local and systemic side effects.[49]

The other advantage of one session instillation of mitomycine C is that nearly all patients already have a catheter after TUR and if local regional anesthesia is used, patients will not suffer from any additional discomfort. However in case of a perforated bladder or extended TURan immediate instillation should not be given. This approach also provided an important psychological benefit since many patients were preoccupied with early recurrence, despite being previously informed that they were at low risk. The significant reduction in early recurrence with one immediate session of mitomycine instillation strongly supports the hypothesis of cell implantation as a recurrence mechanism. This finding suggests that in

controls early recurrences mostly correspond to a cell implantation process, which would not be related to the natural history of the tumors.[36] In one study comparing immediate mitomycine instillation before BCG instillations for high grade tumors showed that immediate post-TUR MMC instillation significantly reduced recurrence in high risk non-muscle-invasive bladder cancer patients treated by BCG. But it did not influence the stage and grade at recurrence.[50] Some studies investigate the effect of combined local hyperthermia and intravesicalmitomycin-C (MMC) and microwave-induced local hyperthermia combined with MMC appears to be a safe and efficient treatment modality for both prophylactic and ablative patients. The technology has a potential additional value for the prevention of recurrence of superficial bladder cancer, particularly when other treatments have failed.[51]

CONCLUSIONS AND RECOMMENDATIONS

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.

This safe approach spares a significant number of transurethral resections in these patients, decrease hospitalization and prolong catheterization with minimal or no associated symptoms associated with multiple mitomycine instillations. Consequently, this approach can be considered an alternative for observation only or to six sessionsmitomycin C instillations in patients with low risk non-muscle invasive bladder cancer.

Recommendation

At the end of our research we recommended to

1. Use one session mitomycin C instillation in to urinary bladder after complete non-complicated T.U.R. of bladder tumor in patients with low risk non- muscle-invasive bladder cancer.
2. Optimization of mitomycin C delivery achived by eliminating residual urine volume, overnight fasting, using sodium bicarbonate to reduce drug degradation and increase concentration to (40 mg) in (20 mL).
3. To perform further studies comparing immediate instillation of mitomycin before BCG instillation program.

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