
The Use of Intravesical Mitomycin C for Superficial Bladder Cancer

Taha Kareem Kadhum
MBChB, FICMS (Urol.)

Ala'a Al-Deen Al-Dabbagh
MBChB, FICMS (Urol.)

Abstract:

Background: Mitomycin C (MMC) is an antibiotic-alkylating agent isolated from *streptomyces caespitosus*. MMC acts by inhibiting DNA synthesis and inducing apoptosis in tumor cells. It has a higher molecular weight than thiotepa, so its absorption is low when used for treatment of superficial bladder cancer after transurethral resection.

Purpose: We attempted to evaluate our experience with the intravesical Mitomycin C (MMC), the available cytotoxic drug, and to identify its effect on the recurrence and progression of superficial bladder cancer after transurethral resection (TUR).

Patients & Methods: A total of 58 males, 46 to 72 years old, who had superficial bladder cancer (Ta, T1) were evaluated. However, patients with carcinoma in situ (Cis) were excluded from this study. Thirty patients were treated by TUR alone, while the remaining 28 patients were treated by TUR plus intravesical MMC.

Results: The recurrence rate after TUR alone was 43.3%, and it was 17.8% after TUR plus intravesical MMC. The progression rate was 20% and 7.1% after TUR alone and TUR plus intravesical MMC, respectively.

Conclusion: superficial bladder cancers were subdivided into low, intermediate and high-risk group for cancer recurrence. MMC showed benefit in reducing the recurrence rate in intermediate and high-risk group.

Keywords: Mitomycin C, Bladder cancer, intravesical chemotherapy.

Introduction:

At the time of diagnosis, the majority of bladder cancers (80%) are superficial, with only 15% are invasive, and 5% are metastatic^[1]. Recurrence rate in superficial bladder cancer is high (30-80%), and (4-30%) of superficial bladder cancer will subsequently progress to muscle invasive disease^[1, 2]. Superficial bladder cancers are staged into 3 groups (Ta, T1, Carcinoma in situ), as in table 1.^[3, 4, 5]

When the presence of transitional cell carcinoma is suspected, a full urological evaluation is mandatory (urinalysis, urine cytology, U/S, IVU, and cystoscopy). When a lesion is noted on cystoscopy, the configuration (flat, sessile, or papillary), location (trigone, base, right lateral wall, left lateral wall, or dome), size (in centimeter) and number should be noted.

Any visible, resectable lesion should undergo complete TUR. An examination under anesthesia is performed before and after resection for clinical staging.^[5, 6, 7, 8]

Patients with superficial bladder cancer have been divided into low, intermediate and high risk groups. Low risk patients are those with single, grade I, stage Ta tumor. Intermediate risk patients are those with multiple or recurrent, grade I, stage Ta tumor or grade II, stage Ta tumor (single or multiple). High risk patients are those with grade III, T1, Cis or recurrent at 3 months.^[9, 10, 11, 12]

Low risk patients can be treated by TUR followed by a single instillation of intravesical chemotherapy. While intermediate and high risk patients required the addition of Bacillus Calmette Guerin (BCG) because of risk of disease progression. BCG and BCG plus

interferon Alfa can significantly decrease the risk of progression.^[13, 14]

Patients of the low risk group are followed with periodic urine cytology, Sonography, cystoscopic examinations every 6 months for 3-5 years^[15]. While in those of intermediate and high-risk group, these examinations are performed every 3 months for one year, every 6 months to 5 years and every 12 months to 10 years.^[16, 17]

Mitomycin C (MMC) is an antibiotic-alkylating agent isolated from *streptomyces caespitosus*. MMC acts by inhibiting Deoxyribonucleic acid (DNA) synthesis and inducing apoptosis in superficial bladder cancer^[18, 19]. It has a higher molecular weight (334 Da) than thiotepa and ethoglucid, so its absorption is low.^(20, 21) The dose of MMC for intravesical treatment varies between 20-60 mg per instillation (usually 40 mg in 40 ml of normal saline). It is given weekly for 6-8 weeks and then once monthly for 1-year^[22, 23].

In case of recurrence, second TUR is done, and in case of progression to muscle infiltrating tumor, cystectomy is the next therapeutic step.^[24]

MMC also appears to be effective in treating patients who have failed thiotepa treatment. Response rates after intravesical MMC seem to be relatively higher than those achieved by other chemotherapeutic drugs^[25].

Two hundreds micrograms of desmopressin may be given orally 1 hour before instillation to reduce the urine output. Sodium bicarbonate is given so that the urine remaining in the bladder will have a neutral pH.^[14]

The most frequent adverse effects of MMC are chemical cystitis, bladder contraction and allergic reaction, mainly palmer and genital skin rash.^[26, 27]

Table (1). Substages of superficial bladder cancer.

Ta	Papillary tumor confined to the urothelium.
T1	Papillary tumor invading the underlying lamina propria
Tis	Flat, reddened lesion on cystoscopic appearance; high grade histologic features confined to the urothelium

Patients & Methods:

A total of 58 male patients with superficial bladder cancer aged between 46-72 years (mean = 59 years) were evaluated at Al- Rasheed military hospital from April 2000 to March 2002 (23 months).

For all patients we do urine cytology, Sonography, (urography in some patients) and cystoscopy were performed. On cystoscopy, complete TUR of any visible lesion, and selected biopsy were performed. Examination under anesthesia (EUA) was performed prior to and after the TUR.

Fifty eight patients were randomly divided into two groups, 30 (51.7%) were treated by TUR alone and 28 (48.2%) were treated with TUR plus intravesical MMC. MMC was administered weekly for 8 weeks, then monthly for one year. The night before giving MMC, the patients restricted their fluid intake; sodium bicarbonate was administered to get neutral PH urine. Patients should empty their bladder prior to administration of MMC, then urethral catheterization was performed, 40 mg of MMC was diluted in 40 ml of normal saline and introduced into the bladder via the catheter. Then, the patients were asked to lie down in bed with frequent changing of position and to avoid voiding for 2 hours. After that, the catheter was removed and the patients were allowed to void.

This procedure was repeated weekly for 8 weeks. One month later, patients were checked by urine cytology, Sonography, cystoscopic examination, and biopsy. Then, monthly dose of MMC was given to the patients for 12 months. Urine cytology, Sonography, cystoscopy and biopsy were repeated every 3 months.

Results:

Thirty patients underwent TUR alone, thirteen (43.3%) of them showed recurrence. While Twenty-eight patients received intravesical MMC after TUR, five patients (17.8%) showed recurrence during the follow up. The difference of recurrence (the benefit) was 25.5% and P value was significant ($0.05 > P > 0.02$), as in [table \(2\)](#).

The superficial bladder cancer in six patients (20%) of those patients who underwent TUR alone progressed to muscle invasive disease. While two patients (7.1%) of those who received adjuvant intravesical MMC progressed to muscle invasive disease, and P value was insignificant ($0.5 > P > 0.10$), as in [table \(3\)](#). After using intravesical MMC, chemical cystitis was noticed in 6 patients (21.4%), as frequency, urgency, and dysuria, and genital skin rash in 2 patients (7.1%), as in [table \(4\)](#).

Table (2). The effect of intravesical MMC on recurrence:

Total number	TUR alone		TUR plus MMC		Difference %	P value
	Total	Recurrence	Total	Recurrence		
58	30	13(43.3%)	28	5 (17.8 %)	25.5	<0.05

Table (3). The effect of MMC on progression:

	TUR alone	TUR plus MMC	P value
Progression rate	6 (20%)	2 (7.1%)	NS

NS: Not significant.

Table (4). Complications of intravesical MMC.

The complications	Incidence no. (%)
Chemical cystitis	6 (21.4%)
Palmer and genital skin rash	2 (7.1%)
Systemic Allergic reaction	0
Bladder contracture	0

Discussion:

We used MMC as intravesical chemotherapy because it was available in our hospital and because it's the first line of intravesical chemotherapy as shown by Melekos & MOUTZOURIS ⁽²³⁾, Pow-sang et al ⁽²¹⁾, and Baselli et al ⁽³¹⁾.

The first dose of MMC was given within 24 hours after TUR to get optimal results as shown by Kurth et al ⁽²⁶⁾. Some authors give MMC as single dose after TUR such as Malkowicz et al ⁽²⁷⁾ and Solsona et al ⁽²⁴⁾, while others give it as maintenance as shown in our study, Baselli et al ⁽³¹⁾.

We used MMC in 40 mg/40 ml of normal saline / instillation as used by Melekos et al ⁽²³⁾.

The result of our study was comparable with the result of other studies. The recurrence rate was 43.3% after TUR alone and 17.8% after TUR plus intravesical MMC with benefit of 25.5%. These results were statistically significant ($0.05 > P > 0.02$). Altay et al reported a recurrence after MMC of 23.8%⁽⁶⁾, and Melekos et al study revealed a recurrence rate of 30% with benefit of 12% of MMC over that of TUR alone ⁽²³⁾.

Malkowicz and many other studies reported that the intravesical chemotherapy could decrease tumor recurrence ⁽²⁷⁾.

In our study, the effect of MMC on the progression rate was statistically insignificant ($0.5 > P > 0.10$).

In our study, the most common side effects of intravesical MMC was chemical cystitis (21.4%) and genital skin rash (7.1%). No one developed systemic

allergic reaction or bladder contracture. Melekos and Moutzouris reported that the most frequent side effects of MMC are chemical cystitis (40%) of cases and genital skin rash in (10%) and rarely bladder contracture ⁽²³⁾.

Conclusion:

The findings of cystoscopic and histopathological examination of patients with superficial bladder cancer are important for classification of patients into high risk and low risk group for recurrence and progression.

Patients in high-risk group need adjuvant intravesical chemotherapy in addition to TUR. The use of MMC is seen to be beneficial in reducing recurrence with few local and rare systemic side effects.

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Al-Yarmouk Teaching Hospital

Al- Mustansiriya University College of Medicine