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Effectiveness of A Single Immediate Mitomycin C Instillation in Patients with Low Risk Superficial Bladder Cancer: Short and Long-Term Follow-up

SAMIR EL-GHOBASHY, M.D.; TAREK R. EL-LEITHY, M.D.; MAMDOUH M. ROSHDY, M.D. and HOSSAM M. EL-GANZOURY, M.D.

The Department of Urology, Theodor Bilharz Research Institute, Cairo.

ABSTRACT

Purpose: We analyzed the impact of a single Mitomycin C instillation in patients with low risk superficial bladder cancer with short and long-term follow-up.

Patients and Methods: This study was conducted on 63 patients with low risk superficial bladder transitional cell carcinoma (TCC), admitted to the Urology Department, Theodor Bilharz Research Institute (TBRI) during the period from January 2002 to August 2005. All patients had a 2 cm. or less single, papillary, primary or recurrent tumor and were disease-free for more than 1 year. Patients with muscular invasion, G III tumor or bladder carcinoma in situ on pathological examination were excluded from the study. The tumor was completely resected before patients were divided randomly into 2 arms: first group who have received no further treatment (control group) and a second group with a single immediate instillation of 30 mg. Mitomycin C (mitomycin C group). Recurrences were considered early if they occurred within the first 2 years of follow-up.

Results: At 24-months follow-up, the recurrence-free interval was significantly increased and recurrence, recurrence per year and tumor per year rates were decreased in the mitomycin C group compared to the control group. Early recurrence was (16.1%) in the mitomycin C group versus (34.3%) in the control group. It was noted also that early recurrences were concentrated in the first year in the control group (18.7%) versus (3.2%) in the mitomycin C group. However, at long-term follow-up, these differences were not statistically significant (26.9%) in the mitomycin C group versus (28.6%) in the control group, and the recurrence-free interval curves were parallel. A significant relationship between early and late recurrences was found in the mitomycin C, but not in the control group. Shorter hospital stay and catheterization periods were noted in the mitomycin C group compared to the control group, but the differences were not statistically significant.

Conclusion: These data confirm the positive effect of a single immediate mitomycin C instillation in patients with low risk superficial bladder cancer. This benefit is limited to early recurrence and is not maintained with long-term follow-up. Thus, this approach is an alternative to observation or classic long-term intravesical chemotherapy. Our study also suggests that cell implantation as a mechanism of early recurrence can be controlled or minimized with a single mitomycin C instillation.

Key Words: *Bladder cancer – Mitomycin C – Recurrence.*

INTRODUCTION

Intravesical chemotherapy or immunotherapy (Bacillus Chalmette-Guerin BCG) has been demonstrated to be effective in preventing recurrence in patients with superficial bladder TCC after transurethral resection (TUR) **[1]**. Although patients at low risk for recurrence and progression benefit with these therapies, many can be overtreated **[2]**.

Although intravesical chemotherapy delays the time to first recurrence after TUR, there is no consensus whether patients with a single, low risk tumor should receive intravesical chemotherapy or just be followed for recurrence by cystoscopy alone **[3]**.

Nevertheless, recurrence has ranged from 41 to 44% in this low risk group with observation only, which represents an uncomfortable, economical and psychological problem for patients **[4]**. On the other hand, random trials have demonstrated lower recurrence rates with early instillation of intravesical chemotherapy, sug-

Correspondence: Dr Tarek R. El-Leithy, Theodor Bilharz Research Institute, tleithy@thewayout.net

gesting that tumor cells floating free within the bladder can be controlled early with chemotherapeutic agents **[5,6]**. Moreover, the concept of cell implantation during transurethral resection of superficial bladder cancer as a recurrence mechanism has been supported in animal models and clinical trials **[7,8]**.

More recently, in patients with superficial bladder cancer in 2 randomized controlled trials, recurrence was significantly decreased for those who received a single early dose of a different chemotherapeutic agent compared to controls **[9,10]**. However, the results of these trials have mainly been evaluated based on short-term follow-up.

Therefore, whether a single early dose of a chemotherapeutic agent influences late recurrence and progression, and has a positive impact on economic cost, psychological well-being and follow-up schedule, have not been thoroughly analyzed.

Although the European Association of Urology guidelines recommended one immediate instillation after TUR for all superficial bladder tumors, there is still doubt regarding the value of one immediate instillation of chemotherapy after TUR, not only in low risk tumors but also in patients with multiple tumors who are at a higher risk for recurrence **[11]**. We herein analyze the impact of a single mitomycin C instillation in patients with low risk superficial bladder cancer with short and long-term follow-up.

PATIENTS AND METHODS

During the period from January 2002 to August 2005 at the Urology Department of Theodor Bilharz Research Institute, we performed a prospective randomized controlled study of patients with a 2cm. or less, single, papillary, primary or recurrent transitional cell carcinoma (TCC) of the urinary bladder, who were disease free for more than 1 year. In all patients the upper urinary tract was normal on excretory urography. Patients with muscle invasive or G III tumors or bladder carcinoma in situ on pathological examination were excluded from the study. During endoscopic evaluation, urine cytology, random biopsies of normal bladder mucosa and complete transurethral resection of bladder tumor were performed.

Patients were randomly allocated to observation only (control group) or to receive a single dose of 30 mg mitomycin C diluted in 50 mL. saline (mitomycin C group), which was instilled when hematuria ceased, usually within 6 hours of transurethral resection. The instillation was retained for 1 hour with catheter clamping and then the bladder was irrigated with saline if needed.

Patients were evaluated with urine cytology and cystoscopy at 3, 6, 9, 12, 18 and 24 months, and then once yearly postoperatively. At 15 and 21 months, urine cytology and bladder ultrasound were performed and intercalated with endoscopic evaluations once a year.

The end points of the study were: 1-recurrence-free interval (the period between initial transurethral resection and first recurrence), 2-recurrence (the percentage of patients with recurrence during the follow-up period), 3-recurrence per year (the number of positive cystoscopies divided by the total years of follow-up) and 4-tumor per year (the total number of tumors observed during all positive cystoscopies divided by the total years of follow-up).

Recurrences were considered early during the first 2 years of follow-up and late thereafter. The early recurrence period was considered when analyzing the recurrence-free interval, recurrence, recurrence per year and tumor per year rates. A secondary end point of the study was progression, which was the percentage of cases of invasive bladder tumor or metastases.

Complete blood count, serum creatinine, urinalysis and urine culture were performed before and one week after transurethral resection. Allergic reactions, urinary disturbances, catheter duration, hospital stay and psychological reactions were recorded.

Statistical analysis:

Data were expressed as mean ± standard deviation (SD) or number (%). Comparison between numerical data was performed using the unpaired Student *t* test while comparison between categorical data was done using the Chi square test. The SPSS computer program (version 11 windows) was used for data analysis. *p* value less than or equal to 0.05 was considered significant.

RESULTS

Both groups (total of 63 patients), 31 patients in the mitomycin C and 32 in the control group who are eligible for study were comparable as regards clinical and pathological characteristics (Table 1). All cases were not associated with Bilharziasis in any of the histopathological specimens studied.

Recurrence timing was considered using different cut off points when determining the possible impact of single early instillation of mitomycin C on cell implantation as a mechanism of early recurrence. Early recurrence (within the 1st 2 years) occurred in 5 of 31 patients (16.1%) of the mitomycin C group, while it happened in 11 out of 32 patients (34.3%) of the control group (Table 2). It was further noted that recurrence was concentrated in the 1st year in the control group {6 out of 32 patients (18.7%)} versus 1 out of 31 patients (3.2%) of the mitomycin C group (p=0.005).

While a significantly lower early recurrence rate was observed in the mitomycin C compared to the control group, this difference was not significant regarding late recurrences that occurred in 7 of 31 patients (26.9%) in the mitomycin C group versus 6 of 32 patients (28.6%) in the control group.

A significantly longer recurrence-free interval was observed in the mitomycin C compared to the control group at early evaluation. However, at the final evaluation at a median follow-up of 44 months, these differences were not significant (Fig. 1).

Also, the effect in the mitomycin C group as regards early recurrence/year and early tumor/year was better than the control group, but not if we consider overall recurrence/year and overall tumor/year within 4 years of follow-up (Table 3).

Progression to a more advanced stage was not significantly different between the two groups occurring only 2 patients (1 in each group).

Side effects were acceptable in both groups. In the control group, only 1 patient (3.1%) had cystitis with negative urine culture, while in the mitomycin C group, 2 patients (6.4%) had chemical cystitis and slight allergic skin reactions. No hematological changes were recorded in either group (Table 4). Prolonged hospital stay and catheterization periods were observed in the control group compared to the mitomycin C group and the difference was not significant.

Table (1): Patient characteristics.

	Mitomycin C group (n=31)	Control group (n=32)	Significance
Mean age (yrs)	62.2±7.4	59.9±6.7	NS
Mean tumor size (cm)	1.8±0.13	1.9±0.11	NS
No. recurrence (%)	3/31 (9.7%)	4/32 (12.5%)	NS
Pathological stage:			
Ta	15/31 (48.4%)	16/32 (50%)	NS
T1	16/31 (51.6%)	16/32 (50%)	NS
Pathological grade:			
G1	15/31 (48.4%)	17/32 (53.1%)	NS
G2	16/31 (51.6%)	15/32 (46.9%)	NS
Mean follow-up period (months)	44±6.7	43±5.2	NS

Data were expressed as mean ± standard deviation or number (%).
NS= Not significant.

Table (2): Recurrence and progression.

	Mitomycin C group (n=31)	Control group (n=32)	Significance
Early recurrence	5/31 (16.1%)	11/32 (34.3%)	S (p<0.05)
Late recurrence	7/31 (26.9%)	6/32 (28.6%)	NS
Progression	1/31 (3.2%)	1/32 (3.1%)	NS

S= Significant (p≤0.05); NS= Not significant.
Early recurrence: Less than 2 years of follow-up.
Late recurrence: More than 2 years of follow-up.

Table (3): Recurrence and tumor per year rates.

	Mitomycin C group (n=31)	Control group (n=32)	Significance
Early recurrence/Y	$5/2^{Y}$= (2.5%)	$11/2^{Y}$= (5.5%)	S (p<0.05)
Early tumor/Y	$6/2^{Y}$= (3%)	$17/2^{Y}$= (8.5%)	S (p<0.05)
Overall recurrence/Y	$12/4^{Y}$= (3%)	$17/4^{Y}$= (4.25%)	NS
Overall tumor/Y	$14/4^{Y}$= (3%)	$19/4^{Y}$= (4.75%)	NS

S= Significant (p≤0.05); NS= Not significant.
2^{Y}= 2 Years. 4^{Y}= 4 years.

Table (4): Local and systemic adverse reactions.

	Mitomycin C group	Control group
% Local adverse reactions:		
Bacterial cystitis	–	–
Chemical cystitis	3.2	3.1
Hematuria	–	–
% Systemic adverse reactions:		
Fever	–	–
Nausea & vomiting	–	–
Skin rash	3.2	–
Malaise/fatigue	–	–
Hematological changes	–	–

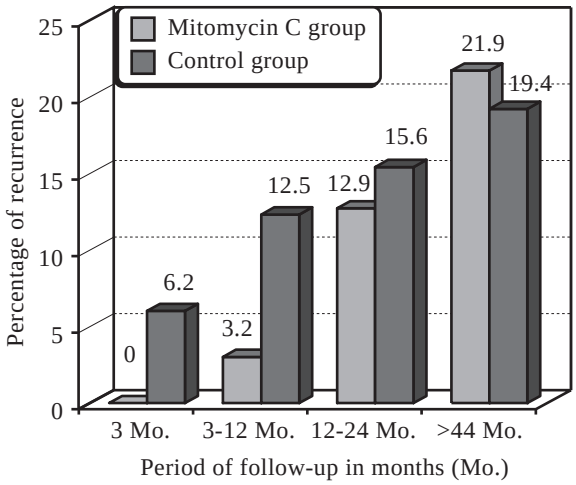

Fig. (1): Time of recurrence.

DISCUSSION

Although intravesical chemotherapy has now been used for more than 40 years, the role of one immediate postoperative instillation has remained unclear **[3]**.

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 with superficial bladder cancer **[12-14]**. Considering these clinical factors, patients with a 2cm. 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 **[15,16]**. Our inclusion criteria were based on these findings, and the low risk status of this group was substantiated, since with a median follow-up of 44 months, only 3.2% had progression.

In our trial during the early period, recurrence, recurrence per year and tumor per year rates were significantly decreased and also, the recurrence-free interval was increased in the mitomycin C compared to the control group (Table 3). Our results are comparable to those obtained in controlled trials of a single instillation of epirubicin or mitomycin C with short-term follow-up **[17-19]**. Clinically, this outcome indicated a significant reduction in the number of transurethral resection times for patients treated with mitomycin C.

In addition, a single mitomycin C instillation is an inexpensive approach with minimal and slight local and systemic side effects.

The effect of one instillation may be explained either by chemoresection of tumor left after incomplete TUR or by destroying circulating tumor cells that could implant at the site of resection. Incomplete TUR may be an issue even in patients with solitary tumors as seen by the large variation between institutions in the recurrence rate at the first follow-up cystoscopy after TUR **[20]**.

The significant reduction in early recurrence with a single instillation of mitomycin C strongly supports the hypothesis of cell implantation as a recurrence mechanism (16.1% Vs. 34.3%). Moreover, early recurrences were concentrated during the first 12 months in the control group (18.7%) compared to the mitomycin C group (3.2%).

Late recurrence was similar in both groups, and with long-term follow-up recurrence and tumor per year rates between both groups were not significantly different. Furthermore, the disease-free intervals were similar, which proves that a single mitomycin C instillation does not have any impact on the biology of low risk bladder cancer.

In the mitomycin C group, only 3.2% had recurrence during the first 12 months compared to 18.7% of the control group; therefore, patients could have been spared cystoscopies at 3, 6 and 9 months or substituted with other noninvasive procedures, such as bladder ultrasonography and urine cytology, in the mitomycin C group which would have provided additional cost savings. However, after 12 months the follow-up schedule should be the same for both groups since overall recurrence was similar.

Kaasinen and associates found a doubling in the risk of recurrence if the first of 5 weekly mitomycin C instillations was not given on the same day of the TUR **[21]**. But in all the other studies in the literature, the instillation was given within 24 hours, generally immediately after TUR or within 6 hours after surgery as we did in our study. So, it is not possible to assess the impact of instillation timing after TUR on recurrence rate or to confirm Kaasinen findings **[3]**.

In conclusion, our analysis confirms the positive effect of a single immediate mitomycin C instillation in patients with low risk superficial bladder cancer.

This benefit is limited to early recurrence and is not maintained with long-term follow-up. Thus, this approach is an alternative to observation or intravesical chemotherapy, sparing patients a significant number of transurethral resections during the first 24 months postoperatively. Our study also suggests that cell implantation as a mechanism of early recurrence can be controlled or minimized with a single mitomycin C instillation.

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