A RANDOMIZED PROSPECTIVE STUDY COMPARING THE EFFECTIVENESS OF MITOMYCIN C AND MITOMYCIN/S_2 COMPLEX SEQUENTIAL INTRAVESICAL THERAPY FOR SUPERFICIAL BLADDER CANCER

Ahmad A. Al-Azawi[1] *FICMS*, **Abdul-Wahab R. Hamad**[2] *BSc MSc PhD*, **Mahmood H. Hammash**[3] *BSc, PhD*

Abstract

Objective: Comparison of two protocols regarding efficacy and toxicity of intravesical mitomycin C versus mitomycin C and S_2 complex sequential therapy for superficial transitional carcinoma of urinary bladder.

Methods: A prospective, randomized parallel two lines of treatment groups. Seventy-three patients were evaluated after transurethral resection of superficial bladder cancer with median follow-up of 26 months. In group A, 37 patients received intravesical mitomycin C 30mg on day1 weekly for 6 weak and monthly for 12 month, while group B (36 patient) received in addition to mitomycin C, intravesical S_2 complex 3ml on day 2. Statistical analysis performed by Kaplan-Meier methods.

Result: After follow-up of 26 months, 46% of patient given mitomycin C were disease free compared to 70% for that of group B patient who received mitomycin C and S_2 complex, with no significant difference in incidence of the adverse effects.

Conclusion: The results show that intensive intravesical instillation of sequential mitomycin C and S_2 complex; were highly effective in eradication and/or prophylaxis of superficial transitional bladder cancer.

Key ward: Transurethral resection; bacillus Calmitte-Guerin; complete response; mitomycin C, carcinoma in situ

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Introduction

Bladder cancer is the third most prevalent malignant disease among male patients and the tenth among female patients in the United States[1]. Superficial transitional type constitutes 75-80 percent of bladder cancer and 30-60% recur within 6-18 month after trans-urethral resection[2].

Transurethral resection can effectively control the primary tumor, confirm the superficial nature of the disease, provide cytological and histological tumor, characteristics of prognostic significance; and allows for assessment of extent of mucosal involvement by tumor[1,2]. Tumor recurrence and progression related to stage, grade, number, and size, duration of the disease, positive or negative cytology and aneuploidy[1,3].

There is increasing interest in intravesical instillation of cytotoxic agent or immunotherapy bacillus Calmitte-Guerin (BCG) and become common practice after TUR to cure or prevent recurrence of superficial transitional cell bladder cancer (cis; Ta and Tb) in more than 45% of cases[3-5]. Intravesical trials divided into 2 major categories

1. Therapeutic, designed to treat established disease and
2. Prophylactic/adjuvant, designed to prevent recurrence in patients at high risk for tumor recurrence and progression[1,6].

The most effective intravesical therapy is mitomycin C (can achieve complete

[1] Dept. Medicine-Section of Oncology [2] Dept. Chemistry & Biochemistry [3] Dept. Human Anatomy, College of Medicine, Al-Nahrain University.

Address correspondence to Dr. Ahmad A. Al-Azawi.

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response in 48%) and BCG (60%) after the basic therapy with TUR[5,6]. After TUR, those patients with: transitional cell stage T_1 papillary tumor, multifical stage Ta (grade 1-III), multifocal and/or symptomatic carcinoma in situ (CIS) and persistent positive urine cytology, are require adjuvant intravesical therapy[1,8].

In the present paper, a clinical study of efficacy of therapeutic of cytotoxic and immunotherapy in patient with superficial transitional bladder cancer after TUR and were analyzed for incidence of recurrence, time-free progression according to Japanese Urological Association[7].

We tried in this study to evaluate, investigate the effectiveness and the adverse effects of MMC in comparison with the immunotherpeutic agent S_2 complex in intravesical local therapy of superficial bladder cancer.

MMC selected in our study because of its proved efficacy[8]. S_2 complex (has been developed at Medical Research Center at the Iraqi Medical College), it is a low molecular weight synthetic organs-metalic complex[9]. The high effectiveness of BCG as immunotherapeutic agent encouraged us to use S_2 complex on it base because S_2 complex is a potent immunostimulator and seem to have antitumor activity[9-11].

Patients and methods

Our study included 75 patients with grade 1-III superficial transitional cell bladder (cis, Ta-T1) who had been registered, treated (and then followed-up between 2001-2003 in Al-Kadhymia Teaching Hospital with intravesical installation mitomycin C and S_2 complex, 2 weeks post TUR. We randomized the patients in two groups:

Group A (38 patients) received therapeutic MMC installation (30mg/30ml/1hour) on day 1 weekly for 6 week & then prophylactic regimen, monthly for 12 month. Group B (37 patient) had been receiving additional S_2 complex (3ml, diluted in 30ml normal saline/1hour) on day 2 after each of the eighteen MMC installations.

The response assessed after induction therapy (6 weeks) and after maintenance doses (12 months), complete response defined as no residual carcinoma cystoscopically and negative urine cytological finding, follow-up ranged from 16 to 26 months with median of 18 months.

Statistical analysis was done for recurrence-free rate (disease free-rate), performed by Kaplan-Meier method for both disease group and were tested with the log rank test.

Results

Patient and tumor characteristics:

Seventy-five patients were entered the study between June 2001 to November 2003 with patient and tumor characteristics were equally distributed between 2 arms. Two patients had been lost during the study; one died because of myocardial infarction and the other refused to continue after the second dose. Table 1 Shows 33 patients had grad-II tumor; male to female ratio 7.1:1 and the age range 21-75 years.

Table 1: Clinicopathological profile of 73 patients with superficial bladder cancer

Criteria's of the study group	Number	%
Men	64	87.6
Women	9	12.4
Age ≤ 30	7	10
≤ 50	12	16
≥ 50	54	74
Stage TA	51	70
T1	16	22
cis	6	8
Grade GI	33	45
GII	27	37
GIII	13	18
Multicentericity		
Solitary	49	67
Multiple	15	21
Unknown	9	12

The efficacy of treatment and the time to first recurrence recorded in both groups showed more effective treatment system in the group B who treated with MMC and S_2 complex especially for those with TA and grade-III, (Table 2 and figure 2).

Table 2: Overall results of the study, according to stage and grade of the cancer

Result	MMC Group		MMC+S_2 Complexe group	
	No	**%**	**No**	**%**
Recurrence of tumor	20(37)	54	11(36)	30
Stage				
Cis	1(3)	3	0(3)	0
TI	4(10)	10	3(6)	8
TA	15(24)	41	8(27)	22
Grade				
GI	8(20)	21.5	2(13)	5.5
GII	7(11)	19	6(16)	16.5
GIII	5(6)	13.5	3(7)	8

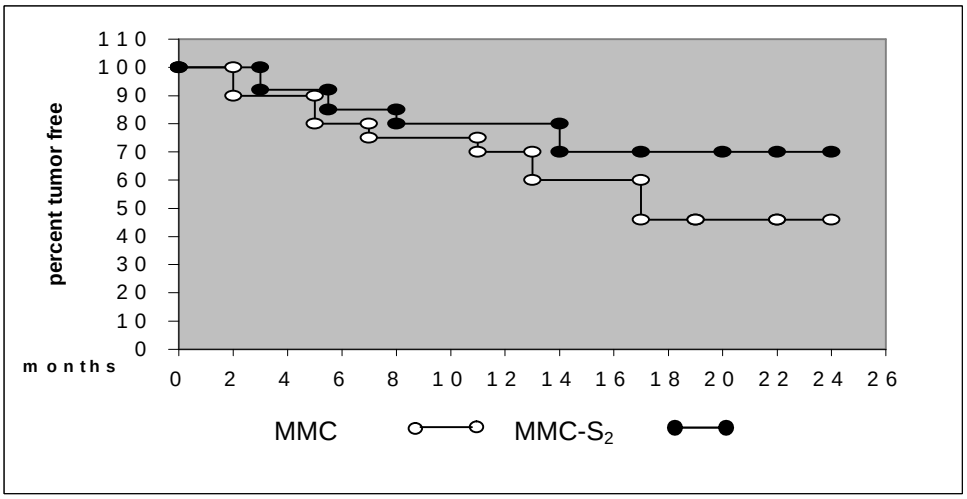

Figure 1: Kaplan Meier curves for time recurrence of patient with papillary tumor cis, pTa, pT1; grade 1 to 3 transitional cell cancer free of tumor after TUR% and adjuvant MMC group and MMC-S2 group.

Figure 2 shows higher percent of patients in group A were remain in remission state after 26 months of follow-up, two patient end with cystectomy and pulmonary metastases in group A while another 3 patients end with total cystectomy and with radiotherapy in group B.

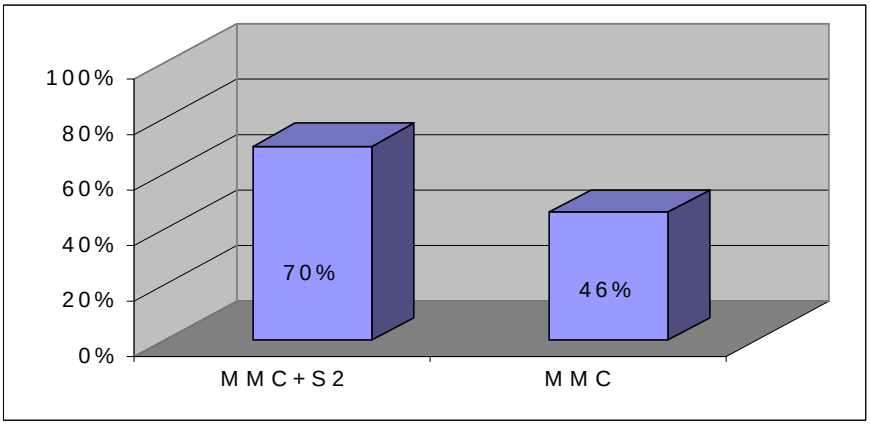

Figure 2: Percentage of patient in remission at the end of the study.

The number and severity of adverse effects were recorded during instillation period are listed in table 3. Mild drug induced cystitis equally reported in both groups.

Table 3: Toxicity

Toxicity	Group A		Group B	
	Number	%	Number	%
Bladder irritation				
Mild	9	24	10	28
Moderate	2	5	3	8
Severe	0	0	0	0
Microscopical hematoria	6	16	7	19
Systemic allergy (mild)	0	0	2	5

Discussion

Administration of adjuvant intravesical chemotherapy after TUR of superficial transitional cell cancer of the urinary bladder (cis: Ta: T1) has become a common practice and confirmed to be effective in reduction of the short and intermediate term incidence of recurrence[12,13].

Intravesical MMC and doxorubicin sequential therapy seemed to be more effective in eradicating carcinoma in situ than single therapy with MMC or doxerubicin and equally affective as BCG[8,15,17].

Topical BCG therapy is now widely accepted as a choice of treatment on base of immunomodulating effect, although systemic adverse and even fatal reaction may occur[7,14,15].

According to those data about the effectiveness of the combination therapy and immunotherapy: The evaluation of sequential MMC and S_2 complex therapy, confirm clearly the efficacy and safety of this regimen in induction (eradication) and maintenance (prophylactic) treatment of transitional cell carcinoma of bladder after TUR, than if those of MMC or BCG is used singly[6,16,17].

Seventy-six clinical studies reviewed, reporting intravesical therapy within last 20 years; their results rate of the net

benefit: thoitepa (8-27%), doxorubicin (12-23%), MMC (13-35%); MMC and doxorubicin sequential therapy (60-65%)[1,7,8], and in comparison to the overall response of MMC and S_2 sequential therapy (70%) and can reduce significantly the number of tumor recurrence within 2 years[1,13].

In addition, S_2 complex is economically available with minimal local and systemic side effect if compared to that of BCG and the majority of patient can tolerate this treatment schedule[7].

Future efforts have to teach us how to select patient for instillation therapy as surprisingly, when patients were separated according to the presence or absence of ABH antigen on the tumor, the more aggressive ABH-negative tumor were found to recur less frequently than ABH positive tumor[14,15].

Many questions remain unanswered in relation to scheme of instillation, when the ideal time to start treatment? What is the optimal duration of treatment? When is the ideal interval between two installations? Those entire questions must be included in longer duration study to evaluate another schedule and real effect of the promising agent S_2 complex[6].

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