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Sequential Chemoimmunotherapy Using Mitomycin Followed by Bacillus Calmette-Guerin (MCC + BCG) Versus Single-Agent Immunotherapy (BCG) for Recurrent Superficial Bladder Tumors

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ABSTRACT

INTRODUCTION: The purpose of the present study was to compare the outcomes of patients receiving sequential chemoimmunotherapy using mitomycin (MMC) and bacillus Calmette-Guerin (BCG) with the outcomes of patients receiving BCG alone for the treatment of recurrent superficial bladder tumors.

METHODS: A total of 56 patients with recurrent Ta or T1 bladder tumors were enrolled in this prospective randomized study. Group 1 (n = 29 patients) received MMC instillation immediately after resection followed by weekly instillation for 4 weeks. Patients then received BCG monthly for 1 year. Group 2 (n = 27) received only BCG, instilled weekly for 6 weeks and then monthly for 1 year.

RESULTS: There was a significant treatment effect for both groups, as indicated by a reduction in mean recurrence rate and recurrence index ($P = .001$). However, the difference in recurrence rate and recurrence index distributions after treatment was significant in favor of group 1. The mean follow-up period was 24 months (range, 3-30 months). Recurrent tumors were found in 9 patients (31%) in group 1 and 16 patients (70%) in group 2 at the end of the follow-up period. Kaplan-Meier estimates were significantly different throughout the follow-up period. MMC followed by monthly BCG was significantly superior to BCG in the time to initial recurrence (log rank $P < .0024$).

CONCLUSIONS: Patients receiving BCG single-agent immunotherapy and patients receiving sequential chemoimmunotherapy using MMC instillations followed by monthly BCG instillation both had significant treatment effects. However, the difference in recurrence rate and recurrence index distributions after treatment was significant in favor of the group receiving the sequential therapy.

INTRODUCTION

The primary treatment of bladder cancer is transurethral resection of the bladder, but up to 70% of superficial tumors recur. Only 5% of tumors that are limited to the mucosa (stage T0), and 30% to 50% of tumors that invade the lamina propria (stage T1) progress within 5 years to a higher tumor stage or metastatic disease [1,2]. Despite conflicting results in recent and relatively large prospective studies, bacillus of Calmette and Guerin (BCG) vaccine is considered the most effective agent for high-grade superficial bladder cancer because of its ability to provide long-term protection from tumor recurrence

KEYWORDS: Sequential chemoimmunotherapy; Bladder cancer; BCG; MMC

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Abbreviations and Acronyms
BCG = bacillus Calmette-Guerin
MMC = mitomycin
TUR = transurethral resection.

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[3]. In contrast, the benefits of chemotherapy apply to more well-differentiated tumors. Mitomycin (MMC), a single chemotherapeutic agent, plays an important role in this respect.

There is a growing perception among urologists that sequential treatment with BCG and MMC might be a more beneficial therapy for some patients with superficial bladder cancer than treatment with either modality alone. It is hypothesized that this regimen would decrease side effects and improve results of prophylaxis. The purpose of the present study was to compare the outcomes of patients receiving sequential chemoimmunotherapy using MMC and BCG with the outcomes of patients receiving BCG alone for the treatment of recurrent superficial bladder tumors.

METHODS

Participants

A total of 56 patients met the eligibility criteria for this prospective study. The study was conducted between 2003 and 2006. It was approved by a special board of the Theodor Bilharz Research Institute and Cairo University Hospitals. All patients were informed of the protocol and provided written consent.

All patients had at least 2 histologically verified recurrent stage Ta or T1 bladder cancers during the preceding 1.5 years. Patients who had previously undergone installation therapy were also included if they had no instillation within the last 6 months. Urography and cytology were used to exclude any patients with tumors of the upper urinary tract. Biopsy of selected sites, including the prostatic urethra, was recommended in cases of malignant cytology. All visible lesions were eliminated by transurethral resection (TUR).

The participants were randomly assigned to one of 2 groups. The demographic characteristics of age, sex, and histopathological tumor stage are contained in Table 1. There were no significant group differences for any of these characteristics ($P > .05$).

Table 1. Demographic Characteristics of Patients in Group 1 and Group 2 (N = 56). doi: 10.3834/uij.1944-5784.2010.06.06t1

Characteristic	Group 1 (n = 29)	Group 2 (n = 27)
Age, mean (years)	47.5	48.1
Sex (n)		
Male	20	18
Female	9	9
Pathology stage (n)		
pTa	15	14
pT1	14	13

Procedure

The patients in group 1 received a combination treatment; the patients in group 2 received a single treatment. The instillation schedule for both groups is shown in Figure 1.

Group 1. Patients in group 1 (n = 29) were given MMC (40 mg in 50 mL saline), which was instilled into the bladder for 2 hours according to the following schedule:

- 1 perioperative instillation (immediately after resection)
- 4 postoperative instillations (1 per week for 4 weeks)
- discontinue MCC after the first month

The patients in group 1 then received 1 ampoule of BCG (or $5x10^8$ bacilli in 50 mL saline), which was instilled into the bladder for 2 hours. The schedule was:

- 11 postoperative instillations (1 per month for postoperative months 2 through 12)

Group 2. The patients in group 2 (n = 27) received 1 ampoule of BCG (or $5x10^8$ bacilli in 50 mL saline), which was instilled into the bladder for 2 hours. The following schedule was used:

- no perioperative instillation
- 6 weekly postoperative instillations (1 per week for the first 6 weeks)
- 10 monthly postoperative instillations (1 per month for postoperative months 3 through 12)

Figure 1. Time Schedule of Therapy Instillations.
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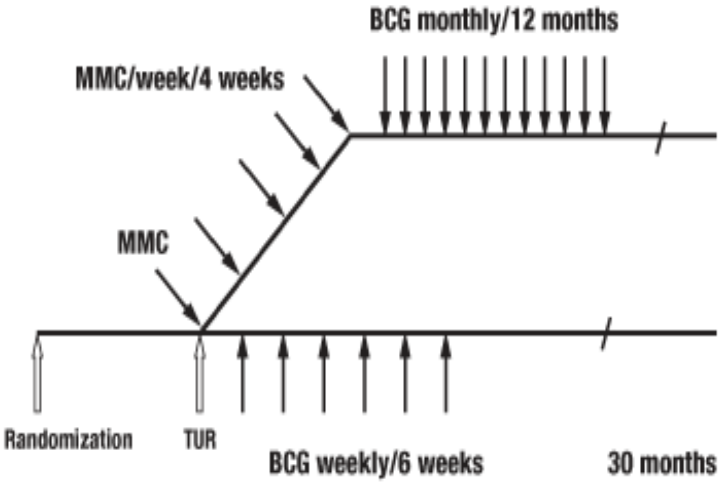

30 months = total follow-up period

Table 2. Means and Standard Deviations (SD) for Recurrence Rate and Recurrence Index Before and After Treatment; Probability of Significant Differences (N = 56).
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Outcome Measure[a]	Before Treatment		After Treatment		Difference		*P*
	Mean	SD	Mean	SD	Mean	SD	
Recurrence Rate							
Group 1	2.40	1.27	0.52	0.62	1.88	1.40	.001
Group 2	2.68	1.91	1.53	1.0	1.16	1.27	.001
Recurrence Index							
Group 1	11.73	8.12	1.24	1.46	10.49	8.48	.001
Group 2	10.33	8.08	3.74	1.51	6.59	8.47	.001

[a]Group 1 received MCC followed by BCG therapy; Group 2 received only BCG therapy

Cytology and cystoscopy were performed every 3 months. Biopsies obtained through TUR were performed in cases of suspected tumor recurrence or malignant cytology.

Data Analysis

The endpoints used to determine the efficacy of the prophylaxis included median time to first recurrence, treatment failure (termination due to tumor progression or severe side effect), recurrence rate ([number of recurrences/number of patients] x 100/months of follow-up), recurrence index (mean number of recurrent tumors per year), and the disease-free interval. Recurrence rate and recurrence index were calculated from the initial reappearance of bladder cancer. The differences between the recurrence rate and recurrence index before and after treatment were used to determine the recurrence-preventive efficacy.

Data were expressed as means and standard deviations or as number and % of N. Pretreatment and posttreatment means for the endpoints were compared using paired *t* tests; group means were compared using unpaired *t* tests. Analysis of covariance was used to compare the mean difference of recurrence rate and recurrence index between the 2 groups. The chi-square test was used to compare categorical data in the 2 groups. Time to initial recurrence in each treatment arm was calculated by the Kaplan-Meier method, and the log rank test was performed to estimate the significance of the difference in the groups. $P < .05$ was used to indicate significant differences in all comparisons. A power analysis was not conducted, so there is a possibility of type II error based on the sample size.

RESULTS

The mean follow-up period was 24 months (range, 3-30 months). Recurrent tumors were found in 9 patients (31%) in group 1 and 16 patients (70%) in group 2 at the end of the follow-up period. One case in group1 had muscle-invasive tumor and 2 cases in group 2 changed from superficial to invasive bladder tumors; radical cystectomy was performed for these 3 cases. The median time to first recurrence was 9 months and 6 months in group 1 and group 2, respectively. These results suggest that treatment efficacy was greater for group 1 than for group 2.

Table 2 contains the means and standard deviations (SD) for the recurrence rate and recurrence index before and after treatment for both groups, and the probability of significant treatment differences. The mean pretreatment recurrence rates of 2.4 in group 1 and 2.7 in group 2 decreased after treatment to 0.5 and 1.5, respectively. There was a significant treatment effect for both groups ($P = .001$). The superiority of MMC+ BCG was evident in the recurrence rate distribution. The difference in recurrence rate distributions after treatment was significant in favor of group 1. There were no side effects that resulted in discontinuation of a single instillation agent or cessation of the remaining instillation in this study.

Similar patterns were noted in the recurrence index. The mean pretreatment index of 11.7 in group 1 and 10.3 in group 2 significantly decreased to 1.2 and 3.7, respectively ($P = .001$). These outcomes indicated a marked treatment effect in both groups. However, the difference in recurrence index distributions after randomization was significant in favor of group 1.

Kaplan-Meier estimates were significantly different throughout the follow-up period (Figure 2a; Figure 2b). MMC followed by monthly BCG was significantly superior to BCG in the time to initial recurrence (log rank $P < .0024$).

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Figure 2a. Number of Recurrent Tumors for Patients in Each Group.
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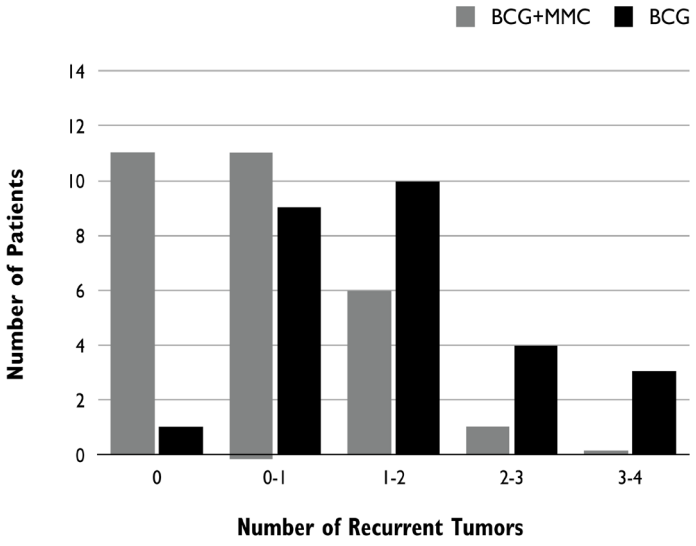

Figure 2b. Kaplan-Meier Estimate of Time to Initial Recurrence at Each Follow-up Interval From 3 to 30 Months.
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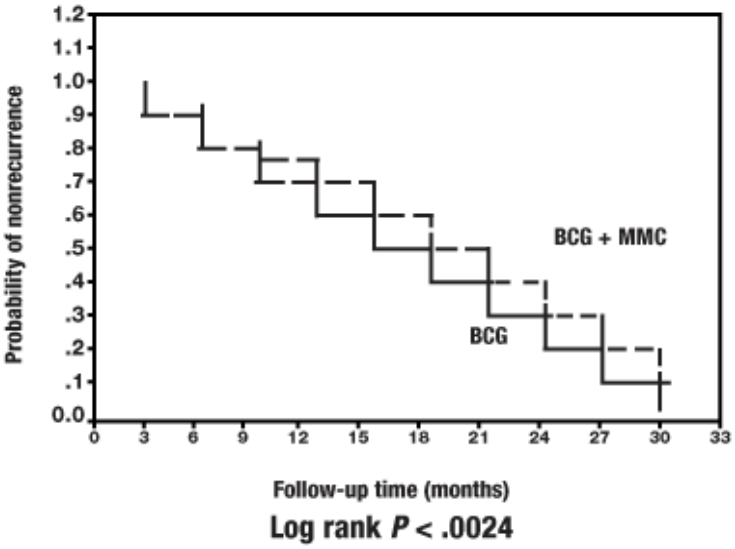

DISCUSSION

Several studies have demonstrated the clinical safety and efficacy of intravesical chemotherapy, especially in the prevention and management of stages Ta and T1 bladder cancer [4-7]. BCG has been shown to be the most effective intravesical agent for superficial bladder carcinoma [8-11]. Rintala et al [12] showed that BCG monotherapy was significantly superior to MMC in the prophylaxis of rapidly recurring Ta and T1 tumors. Other authors have reported that patients with intermediate-risk and high-risk nonmuscle-invasive bladder cancer treated with MMC with hyperthermia (thermochemotherapy) had significantly prolonged recurrence-free survival when compared with patients treated with MMC alone [13,14].

The present authors attempted to determine whether a sequential regimen with 2 effective agents having different mechanisms of action could diminish the harmful effects of BCG and improve the prophylactic effect against recurrent tumors. Another study demonstrated improved recurrence and progression rates in 108 patients with T1 disease treated with sequential BCG and MMC compared with BCG alone [15]. The present study included patients with Ta tumors.

The European Organization for Research and Treatment of Cancer (EORTC) concluded that the use of a cytotoxic agent (which leads to widespread deepithelization of the bladder) followed by BCG was an effective therapy against a marker lesion in the bladder. It was hypothesized that scarification of the urothelium with cytotoxic therapy allows the BCG to combine more successfully with the suburothelial tissues and initiate immunological response [16].

According to Kaplan-Meier analysis in the present study, the probability of remaining free of recurrence at 30 months was significantly better in the group treated with MMC followed by BCG. However, this conclusion should be made with caution because of the small number of patients, different treatment schedules, and short follow-up duration.

The results of most previous prospective studies are difficult to compare because of different randomization criteria and endpoints. Many trials included patients with low-risk tumors with primary papillary cancers, and only a few investigated papillary recurring tumors [9,17,18]. In the current study, patients with tumors of the upper urinary tract were excluded, and there was no significant pretreatment group difference in the number or pathological types of tumors.

The number of side effects leading to discontinuation of a single instillation agent or cessation of the remaining instillation was negligible in the present study. This observation may be attributed to limiting the number of MMC instillations and, more importantly, to the BCG-free induction period.

Although patients receiving both treatment protocols had significant treatment effects, the recurrence rate and

recurrence index distributions showed that the sequential chemoimmunotherapy regimen was more efficacious. Rintala et al [4] showed no significant difference between combination therapy using MMC plus BCG and MMC alone. However, treatment sequences were alternated in the previous study. A sequential regimen may be superior because alternating the treatments may hinder the cumulative effect of BCG.

CONCLUSIONS

Sequential chemoimmunotherapy using perioperative and additional 4 weekly MMC instillations followed by monthly BCG instillation for 1 year is well tolerated and effectively decreases frequently recurring superficial bladder carcinoma. Treatment effects were also significant for patients receiving only BCG. However, recurrence rate and recurrence index distributions were significantly in favor of the group receiving the sequential therapy.

Conflict of Interest: none declared

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