Single instillation of mitomycin C plus bacillus Calmette-Guérin (BCG) versus BCG alone in high grade non-muscle invasive bladder cancer

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Introduction: *This study sought to determine if the addition of perioperative mitomycin C (MMC) to treatment with bacillus Calmette-Guérin (BCG) after transurethral resection (TURBT) is superior to TURBT plus BCG alone in high grade non-muscle invasive bladder cancer (NMIBC).*

Materials and methods: *Data for 719 patients diagnosed with NMIBC at the University of Pennsylvania Health System between 1977 and 2009 was reviewed retrospectively. Of these patients, 120 had high grade disease and were treated with either BCG alone or with a single instillation of 40 mg of MMC perioperatively in addition to BCG and were thus included in our study. The primary endpoints of this study included recurrence-free survival, overall and disease-free survival as assessed via Kaplan-Meier analysis.*

Results: *Of the 120 patients identified who received treatment for high grade NMIBC, 97 were treated with BCG alone and 23 received a single instillation of perioperative MMC in addition to BCG. There were no statistically significant differences noted in demographic or pathologic variables. Patients were followed for a median of 4.5 years and a maximum of 21.8 years, with no differences demonstrated in recurrence-free survival ($p = 0.75$), overall survival ($p = 0.93$) or disease-free survival ($p = 0.76$). Both lack of lymphovascular invasion and BCG maintenance therapy reached significance as independent predictors of recurrence-free survival ($p = 0.19$ and $p = 0.28$).*

Conclusions: *While our study indicates that perioperative MMC likely offers little benefit in regards to recurrence or survival in high grade NMIBC, at this point in time, a larger scale, randomized, controlled trial is needed to adequately address this question.*

Key Words: bacillus Calmette-Guérin, BCG, high grade, mitomycin C, non-muscle invasive bladder cancer, urothelial carcinoma

Introduction

Most newly diagnosed bladder cancers (70%-75%) are non-muscle invasive bladder cancers (NMIBC), which by definition are confined to the bladder mucosa or lamina propria; the remaining 25% are invasive into or through the muscularis propria.[1] Of these NMIBC tumors, 70%-75% are confined to the bladder mucosa (stage Ta) and 25% invade beyond mucosa and into the lamina propria (stage T1).[1-3] Carcinoma in situ (Tis) is also considered part of this group and typically occurs in association with high grade nodular tumors, with only 3%-5% occurring as isolated disease.[4] While all three of these stages are grouped under the blanket category NMIBC, or the less favorable term "superficial" bladder cancer, these tumors represent heterogeneous disease, each carrying a different prognosis.

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Ta tumors are typically papillary in appearance and often solitary lesions. Approximately 95% are considered low grade, and while the majority will recur within 5 years of transurethral resection (TURBT), they rarely progress to invasion (< 5%) or lead to death.[1,5-8] Unlike low grade Ta tumors, high grade Ta cancer represents an aggressive disease, with almost all patients recurring within 2-3 years, 20% progressing within 5 years, and 10%-25% ultimately dying from their disease. These tumors have been described as behaving similar to T1 lesions.[9-11]

While still considered a "superficial" lesion, T1 bladder cancer is a highly aggressive tumor, likely related to the fact that it invades the lamina propria, which harbors abundant vascular and lymphatic channels predisposing to tumor dissemination. These tumors can be papillary or nodular in appearance, and typically harbor a worse prognosis than Ta tumors, due to their greater risk for progression to muscle invasive disease. Virtually all T1 tumors are considered high grade, with recurrence rates as high as 90% within 5 years. Additionally, the progression rate to muscle invasive disease is as high as 50% within 5 years in some series; in association with Tis, this number rises to 80%.[7,8,12,13]

As these three tumors carry very different prognoses, their treatments also greatly differ. For patients with small volume, low grade Ta disease, the goal of therapy is to reduce recurrence, which is accomplished with TURBT plus perioperative intravesical chemotherapy. The theorized benefit of perioperative mitomycin C (MMC) is the prevention of tumor cell implantation and the eradication of any small tumor that remains after TURBT.[14]

For patients with higher risk disease, the goal of therapy goes beyond reducing recurrences. These patients require therapy targeting progression with the ultimate goal of increasing cancer-specific survival. An induction course of BCG followed by maintenance therapy is recommended as part of the initial treatment of these tumors (cystectomy is recommended in a subgroup with increased risk of progression).

The choice of BCG with maintenance as further therapy is based upon a AUA meta-analysis comparing TURBT plus BCG with maintenance therapy to TURBT plus MMC with maintenance therapy in high risk patients. This trial demonstrated an estimated 5-year recurrence rate of 34% versus 62%, and a trend towards progression prevention in the BCG arm.[15] While common practice, to date there are no statistically significant data addressing the role of immediate chemotherapy instillation before BCG in tumors at high risk of recurrence in NMIBC.[16]

Our retrospective analysis seeks to determine whether or not the addition of perioperative MMC to treatment with BCG after TURBT is superior to TURBT plus BCG alone in high grade NMIBC. In addition to determining its effect on recurrence, our goal is to demonstrate whether or not the addition of perioperative MMC translates to improved patient survival.

Materials and methods

With our institution's Internal Review Board approval, we performed a retrospective evaluation of a prospectively maintained database at the University of Pennsylvania. The database contains 719 patients diagnosed with NMIBC who were treated at the University of Pennsylvania Health System between 1977 and 2009. Of these patients, 120 had high grade disease and were treated with either BCG alone or with 40 mg of MMC perioperatively in addition to BCG. For patients that received MMC, the instillation was given one time intravesically in the recovery room within 6 hours of their resection with 40 mg of MMC diluted in 50 mL of normal saline (maintained for 2 hours prior to void or drainage). Treatment with BCG included once weekly instillation of TICE BCG for 6 weeks, with maintenance BCG given as indicated according to the SWOG protocol.[17]

Patient data collected and analyzed included age, sex, smoking status, initial tumor stage, presence of multiple tumors, presence of lymphovascular invasion (LVI) and whether or not multiple BCG courses were received (beyond solely induction).

The following endpoints were assessed:

1) *Recurrence-free survival:* Time from initial diagnosis to first recurrence. Patients without recurrence were censored at the date of the last available follow up cystoscopy.
2) *Overall survival:* Percentage of patients still alive at a measured point in time. Patients still alive were censored at the date of the last available follow up cystoscopy.
3) *Disease-free survival:* Percentage of patients without death or recurrence at a measured point in time. Patients still alive and without disease recurrence were censored at the date of the last available follow up cystoscopy.

Statistical analysis

Mean patient ages were compared using an unpaired t-test. All other clinical characteristics were compared using a chi-squared analysis or Fisher's exact test where applicable. Study endpoints were assessed via

Kaplan-Meier analysis with censoring performed as described above. Both univariate and multivariate Cox regression analysis were performed on various study variables. $P < 0.05$ was considered statistically significant. All statistical analyses were performed with GraphPad Prism 3 (San Diego, CA, USA) and SPSS Statistics 22 (Chicago, IL, USA).

Results

A total of 120 patients were identified who received treatment for high grade NMIBC between 1977 and 2009. Ninety-seven of these patients were treated with BCG alone (BCG only group) and 23 received a single instillation of perioperative MMC in addition to BCG (MMC + BCG group). The mean ages of these two groups were 65.9 (IQR 14.3) versus 61.3 (IQR 18.6) years, respectively (p = 0.07). Within the BCG only group, 75% were male versus 74% in the MMC + BCG group (p = 0.89).

Pathological tumor stages at diagnosis are shown in Table 1 with no significant difference seen between the two groups (p = 0.06). Thirty-five percent (8/23) of patients in the MMC + BCG group had multiple tumors versus 18% (17/97) of patients in the BCG only group, although this difference was not significant (p = 0.06). Additionally, 9% (2/23) of patients in the MMC + BCG group had lymphovascular invasion versus 3% (3/97) in the BCG only group, with this difference also not attaining significance (p = 0.18). Finally, 35% (34/97) of patients in the BCG only group received more than one course of BCG (induction plus maintenance) versus 30% (7/23) of patients in the MMC + BCG group (p = 0.28).

As can be appreciated in Figures 1-3, patients were followed for a median of 4.5 years and a maximum

TABLE 1. **Clinical characteristics of the patients**

	BCG only (n = 97)	**MMC + BCG (n = 23)**	**p value**
Mean age, years (IQR)	65.9 (14.3)	61.3 (18.6)	0.07
Sex, n (%)			0.89
Male	73 (75)	17 (74)	
Female	24 (25)	6 (26)	
Smoker, n (%)			0.39
Yes	67 (69)	19 (83)	
No	28 (29)	4 (17)	
Unknown	2 (2)	0 (0)	
Initial tumor stage, n (%)			0.06
Ta	39 (40)	11 (48)	
T1*	34 (35)	12 (52)	
Tis only	22 (23)	0 (0)	
Unknown	2 (2)	0 (0)	
Multiple tumors, n (%)			0.06
Yes	17 (18)	8 (35)	
No	68 (70)	15 (65)	
Unknown	12 (12)	0 (0)	
LVI, n (%)			0.18
Yes	3 (3)	2 (9)	
No	78 (80)	20 (87)	
Unknown	16 (16)	1 (4)	
Multiple BCG courses, n (%)			0.28
Yes	34 (35)	7 (30)	
No	55 (57)	16 (70)	
Unknown	8 (8)	0 (0)	

*T1 includes T1 with Tis disease
LVI = lymphovascular invasion

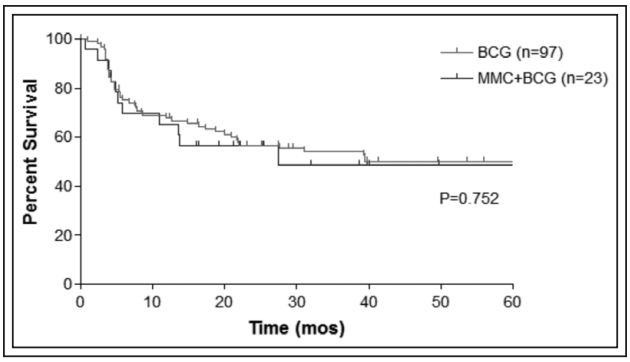

Figure 1. Recurrence-free survival.

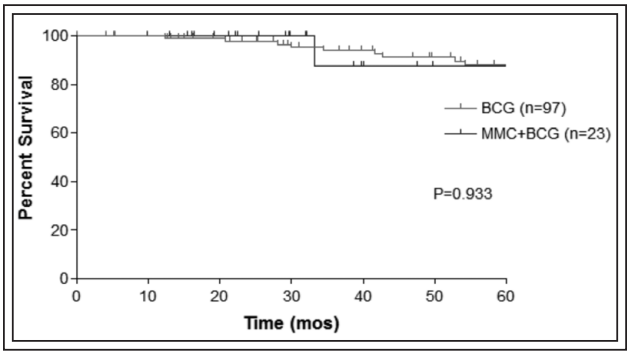

Figure 2. Overall survival.

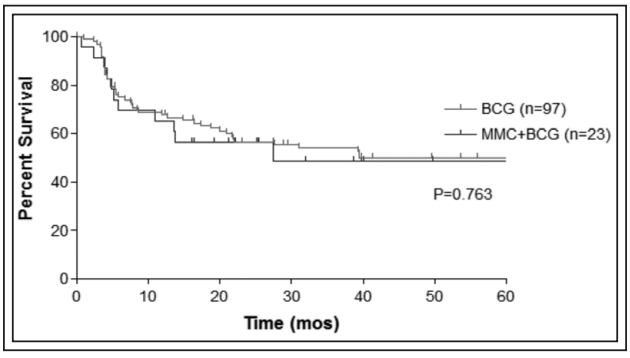

Figure 3. Disease-free survival.

of 21.8 years, with no differences seen in any of the clinical endpoints between the two study groups. At 5 years 50.1% of patients in the BCG only group were free of recurrence vs. 48.4% of patients in the combined treatment group (p = 0.75); median time to first recurrence was 7.6 months versus 5.1 months respectively. Five year overall survival was 88.0% versus 87.5% (p = 0.93) and disease-free survival was 50.1% versus 48.4% (p = 0.76), respectively.

To further determine the influence of the above-mentioned factors on our primary endpoints, we performed both a univariate and multivariate Cox regression analysis predicting recurrence-free survival, Table 2. Both a lack of LVI and maintenance BCG were statistically significant as univariate (HR 0.22 and 0.31; p = 0.00) and independent predictors (HR 0.19 and 0.28; p = 0.00). Even when controlling for these variables, our combined regimen failed to achieve significance as an independent predictor of recurrence-free survival (HR 1.09; p = 0.81).

Discussion

To date there is no standard regimen for the treatment of high grade NMIBC. Some institutions utilize a single perioperative instillation of MMC in addition to BCG based upon the theoretical belief that these two regimens work in synergy. Other centers believe perioperative MMC offers minimal benefit, thus negating its use due to its well-documented side effects.[18]

Our study was undertaken with the goal of determining whether or not the addition of perioperative MMC to treatment with BCG offers any advantage above and beyond BCG alone, in order to help create a more uniform and optimal treatment regimen for this intractable disease. In our study, there was no statistically significant difference in demographic or pathologic variables between the two treatment groups. Our patients were followed for a median of 4.5 years and a maximum of 21.8 years, with no benefit demonstrated in recurrence-free survival (p = 0.75), overall survival (p = 0.93) or disease-free survival (p = 0.76).

While not attaining statistical significance, likely due to the small number of patients in our MMC + BCG group (n = 23), one cannot simply ignore the increased number of patients presenting with multiple tumors (35% versus 18%; p = 0.06) and lymphovascular invasion (9% versus 3%; p = 0.18) in this group. It is possible that these factors influenced the decision to offer patients perioperative MMC, a more aggressive treatment regimen, and a potential reason why this treatment regimen demonstrated no benefit over BCG alone. When controlling for influential factors such as these though, our regimen still did not attain significance as an independent predictor of recurrence-free survival.

Furthermore, as our study is a retrospective analysis, it is not without its limitations. Our analysis was drawn from patients treated at our institution over a long time period (1977 through 2009; although our combined treatment arm only included patients

TABLE 2. **Univariate and multivariate cox regression analyses comparing recurrence-free survival in patients treated with BCG alone versus those treated with BCG and MMC**

	Univariate analysis			Multivariate analysis		
Variable	**HR**	**p value**	**95% CI**	**HR**	**p value**	**95% CI**
Age	1.00	0.93	0.98-1.02			
Male sex	1.02	0.94	0.58-1.81			
Initial tumor stage						
Ta	Referent			Referent		
T1*	1.16	0.59	0.67-2.01	1.46	0.24	0.77-2.77
Tis only	0.87	0.71	0.43-1.76	1.07	0.91	0.36-3.18
Lack of multiple tumors	0.78	0.41	0.43-1.40			
Lack of LVI	0.22	0.00	0.09-0.57	0.19	0.00	0.07-0.54
Lack of maintenance BCG	0.31	0.00	0.18-0.51	0.28	0.00	0.16-0.50
Treatment with MMC	0.90	0.75	0.47-1.74	1.09	0.81	0.53-2.25

*T1 includes T1 with Tis disease
LVI = lymphovascular invasion

treated from 2003 through 2009 and the BCG only arm 1992 through 2009), thus it is highly probable that treatment regimens varied across patients leading to heterogeneity within our two treatment arms. The chosen treatment for each patient was likely influenced by the practitioner responsible for the individual patient, in addition to changes in bladder cancer regimens over time. Similarly, it would have been desirable to have a larger patient population and for both groups to be evenly matched in terms of patient size; this would allow for a more powerful study and the ability to perform a meaningful subgroup analysis.

Badalato et al undertook a similar retrospective study to ours comparing induction BCG alone to 40 mg of MMC perioperatively with induction BCG for NMIBC. This study included 212 patients in the BCG only arm and 48 patients in the MMC + BCG arm. Over a median follow up of 2.9 years, no difference was demonstrated in overall survival. Recurrence-free survival was superior among patients receiving the combined therapy (5-year survival 37.5% versus 56.3%; p = 0.02), although as an independent predictor, this regimen did not reach statistical significance (HR 0.61, CI 0.36-1.01; p = 0.06). Other factors to consider are that the BCG only arm had fewer stage Ta patients (38% versus 50%) and more patients with Tis only disease (18% versus 4%) with this difference statistically significant (p = 0.04) and likely increasing the benefit seen with the combined regimen. Finally, this study contained patients with both low and high grade NMIBC as well as those receiving maintenance BCG in addition to an induction course leading to heterogeneity within both treatment arms.[19]

Cai et al performed a prospective, randomized, double-blind controlled study in 161 patients with high risk NMIBC treated at a single institution between 2005 and 2007, comparing two groups, patients receiving: 1) perioperative epirubicin (80 mg/50 mL normal saline) plus BCG (n = 80) or 2) BCG alone (n = 81). Of note, this study only included patients with recurrent urothelial cancer, in order to obtain a homogeneous group for analysis, and excluded T1G3 disease. BCG was given at least 21 days from TURBT as a once weekly 6 time instillation with boosters at 3, 6, 12, 18, 24, 30 and 36 months. Over a median follow up of 1.2 years, no difference was demonstrated in disease-free survival (57.5% versus 50.6%; p = 0.82), recurrence rate (42.5% versus 49.4%; p = 0.82) or time to first recurrence (6 months versus 7 months; p = 0.095).[20]

Based upon the results of our study, one could conclude that a single perioperative instillation of MMC offers no benefit above and beyond treatment with BCG in regards to recurrence and survival for the treatment of high grade NMIBC. When considering the results of the Badalato et al study, with the limitations mentioned above, there stands the possibility that this combined regimen leads to fewer recurrences, but that this benefit might not translate in to superior survival. Finally, the Cai et al study offers further support, in a randomized, double-blind controlled study, that perioperative intravesical chemotherapy may have no role in this population. Although, this study is not

directly comparable to ours as the chosen chemotherapy was epirubicin, the population was limited to recurrent disease and all patients received maintenance BCG.

With the limitations inherent to our retrospective study, the only conclusion that can be made for sure is that a larger, randomized, controlled trial is necessary to answer once and for all whether or not the addition of perioperative MMC, or intravesical chemotherapy in general, offers any benefit to BCG alone in the treatment of high grade NMIBC.

Conclusions

While common practice, to date there is very little data addressing whether or not perioperative MMC offers an additional benefit above and beyond treatment with BCG for high grade NMIBC. Our study, which was limited to this cohort, demonstrated that there was no benefit in regards to recurrence or survival. Based upon our results as well as those of the other studies presented in this paper, it is reasonable to conclude that at this point in time a larger scale, randomized, controlled trial is needed to determine whether or not this combined regimen benefits patients in terms of recurrence, progression and survival. □

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