Maximizing intravesical therapy options: is there an advantage to the administration of perioperative mitomycin C prior to an induction course of BCG?

Gina M. Badalato, MD, Gregory Hruby, Mani Razmjoo, James M. McKiernan, MD
Department of Urology, Columbia University Medical Center, New York, New York, USA

BADALATO GM, HRUBY G, RAZMJOO M, MCKIERNAN JM. Maximizing intravesical therapy options: is there an advantage to the administration of perioperative mitomycin C prior to an induction course of BCG? The Canadian Journal of Urology. 2011;18(5):5890-5895.

Introduction: *This study sought to evaluate cancer-specific outcomes among patients who received perioperative mitomycin C (MMC) prior to induction BCG versus those who received induction BCG alone.*

Materials and methods: *Between January 2000 and August 2010, 260 patients were identified who underwent a course of induction BCG with or without concomitant perioperative MMC. Specifically, patients who received 40 mg MMC following transurethral resection of all visible tumor followed by an induction course of BCG were compared to a similar cohort of patients who received induction BCG alone. The primary endpoints were overall and recurrence-free survival (RFS).*

Results: *A total of 212 patients were identified who received induction BCG alone, and 48 who received perioperative MMC with induction BCG. The aggregate patient cohort was comprised of those with non-muscle invasive disease (NMI), and there was no difference between groupings with respect to common demographic and pathologic variables. Over a median follow up of 34.5 months, there was no difference in overall survival between cohorts. RFS was superior among patients who received combined therapy (5 year survival: 37.5% versus 56.3%, p = 0.023). Nevertheless, the regimen of intravesical therapy did not reach significance as an independent predictor (HR 0.61, p = 0.055, CI 0.36-1.01).*

Conclusion: *Although the combination therapy group demonstrated a significant RFS advantage, the intravesical therapy regimen did not independently modulate this benefit. Further investigation is warranted to determine if immediate MMC prior to a course of induction BCG confers a benefit to RFS. Nevertheless, this pilot investigation sets an important precedent on the management of NMI bladder cancer, nonwithstanding the absence of contemporary large scale, randomized trials.*

Key Words: BCG, mitomycin C, combination intravesical therapy, recurrence-free survival

Introduction

The practice of using multiple antineoplastic drugs in combined regimens has not been applied consistently in the use of intravesical agents for the treatment of transitional cell cancer (TCC) of the bladder. The immunotherapeutic BCG and the chemotherapeutic mitomycin C (MMC) are hypothesized to have a potentially synergistic effect in combination. In fact, in vitro models using combination therapy with bladder cancer cells demonstrated enhanced antineoplastic activity compared to treatment with chemotherapy or BCG alone.[1] Furthermore, clinical data, mostly from northern Europe, has addressed concurrent therapy with mitomycin and BCG, attributing two roles to mitomycin: that of an anitprolifierative action and of a tissue-scarring or surface-modifying attribute that enables BCG to attach more efficiently to urothelium.[2-8] Three small studies have since focused on the import of these findings as it pertains to non-muscle invasive (NMI) bladder cancer, demonstrating low recurrence rates utilizing varying protocols for the administration of epirubicin and BCG chemoimmunoprophylaxis.[9-11]

Accepted for publication April 2011

Address correspondence to Dr. Gina M. Badalato, Department of Urology, Columbia University Medical Center, 161 Fort Washington Avenue, Herbert Irving Pavilion, New York, NY 10032 USA

Based on these precedents, this investigation sought to determine whether a clinical benefit might be rendered among patients with TCC of the bladder who received a single dose of MMC prior to the initiation of a BCG regimen. Specifically, this study sought to evaluate cancer-specific outcomes among patients who received perioperative MMC prior to induction BCG versus those who received induction BCG alone.

Materials and methods

Patients were retrospectively identified from the Institutional Review Board-approved Urologic Oncology Database. Tumors were staged according to the 6th edition of the TNM system of the American Joint Cancer Committee/Union Internationale Contre le Cancer Staging Manual.[12] Between January 2000 and August 2010, 267 patients were identified who underwent a course of induction BCG with or without concomitant perioperative MMC. In particular, patients who received 40 mg MMC following transurethral resection of all visible tumor followed by an induction course of BCG were compared to a similar cohort of patients who received induction BCG alone. The induction course of BCG was administered according to SWOG protocol, and this therapy did not necessarily include subsequent maintenance treatments. Patients with tumors in the upper urinary tract were excluded.

Patients were then stratified by the intravesical treatment regimen received, namely combination or monotherapy, and both univariate and multivariate analytic models were created. Kaplan-Meier curves were extrapolated to evaluate primary endpoints of overall and recurrence-free survival for each cohort, and the groups were in turn compared using the log-rank test. Statistical analysis was done using SAS version 9.1, with $p < 0.05$ considered significant.

Results

A total of 212 patients were identified who received induction BCG alone, and 48 who received perioperative

TABLE 1. **A comparison of demographic and pathologic variables amongst combination and monotherapy groups**

	Induction BCG alone	**Perioperative MMC + induction BCG**	**p value**
Total cohort	212	48	
Clinical data			
Age, yr, mean (SD)	69.6 + 11.5	69.64 +11.3	0.931
Gender (%)			0.684
Male	152/212 (71.7)	33/48 (68.7)	
Female	60/212 (28.3)	15/48 (31.2)	
Race (%)			0.464
Caucasian	165 (77.8)	42 (87.5)	
African American	14 (6.6)	2 (4.2)	
Hispanic	19 (9.0)	3 (6.2)	
Other	14 (6.6)	1 (2.1)	
Pathological data			
Stage at initial biopsy (%)			0.043
Ta	80 (37.7)	24 (50.0)	
Tis[a]	38 (17.9)	2 (4.2)	
T1	94 (44.3)	22 (45.8)	
CIS (%)[b]	61/212 (28.8)	12/48 (25.0)	0.599
LVI (%)	4/212 (1.9)	2/48 (4.2)	0.342
High grade (%)	148/212 (69.8)	38/48 (79.1)	0.195

[a]denotes patients with stage Tis only.
[b]denotes patients with concurrent CIS, exclusive of those with Tis as a stage.
BCG = Bacillus Calmette-Guerin; MMC = mitomycin C; SD = standard deviation
CIS = carcinoma in situ; LVI = lymphovascular invasion

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

	Univariate analysis			Multivariate analysis		
Variable	**HR**	**p value**	**95% CI**	**HR**	**p value**	**95% CI**
Age	1.01	0.144	1.00-1.03			
Race						
African American	1.10	0.788	0.54-2.27			
Hispanic	0.89	0.724	0.46-1.70			
Other	1.05	0.894	0.49-2.27			
Male sex	1.19	0.373	0.81-1.73			
Initial stage						
Ta	1.00	referent		referent		
Tis	1.22	0.425	0.74-2.01	1.52	0.214	0.79-2.93
T1	0.91	0.624	0.62-1.33	0.94	0.749	0.63-1.39
CIS	0.88	0.521	0.59-1.30	0.71	0.205	0.42-1.21
LVI	0.72	0.578	0.23-2.27	0.88	0.836	0.28-2.83
High grade	0.84	0.344	0.58-1.21	0.89	0.586	0.60-1.33
Receipt of MMC	0.58	0.030	0.35-0.95	0.61	0.055	0.36-1.01

HR = hazard ratio; MMC = mitomycin C; CIS = carcinoma in situ; LVI = lymphovascular invasion

MMC in conjunction with induction BCG. The mean follow up was 43.6 ± 38.1 months (median 35) in the BCG group and 33.0 ± 21.3 months (median 32.5) (p = 0.0583) in the MMC/BCG cohort. Approximately 78/212 (36.8%) and 23/48 (47.9%) patients in the BCG alone and BCG/MMC groups, respectively, went on to receive maintenance BCG (p = 0.214). A large proportion of patients in both cohorts had T1 disease in a similar distribution (BCG: 94 (44.3%) versus BCG/MMC: 22 (45.8%)); however, the groupings were disparate (p = 0.043) with respect to the frequency of Ta (BCG: 80 (37.7%) versus BCG/MMC 24 (50.0%)) and Tis disease (BCG: 38 (17.9%) versus BCG/MMC: 2 (4.2%)), Table 1. There was no statistical difference between groups with respect to demographic variables of age (p = 0.931), gender (p = 0.684), or race (= 0.464); similarly, no difference in pathological variables of concomitant CIS (p = 0.599), the presence of lymphovascular invasion (LVI) (p = 0.342), and the detection of high grade disease (p = 0.195) was noted between cohorts, Table 1.

Although log-rank analysis did not substantiate a difference between cohorts with respect to overall survival, recurrence-free survival was superior in patients who received combined intravesical therapy, Figure 1. In fact, the 5 year recurrence free survival among the BCG alone group was 37.5% as compared to 56.3% in the combination therapy grouping (p = 0.023). This association was confirmed in a univariable cox regression model predicting recurrence-free survival (HR 0.58, p = 0.030, CI 0.35-0.95), Table 2. However, in a multivariable model, controlling for initial biopsy stage and the presence of CIS, LVI, and high grade disease, receipt of MMC was no longer predictive of recurrence-free survival by a narrow margin (HR 0.61, p = 0.055, CI 0.36-1.01), Table 2.

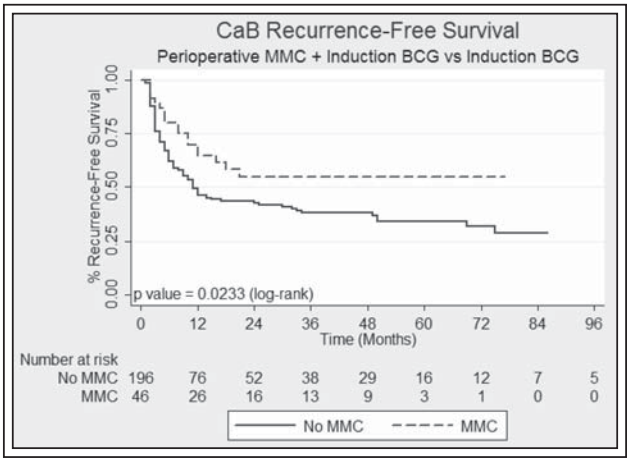

Figure 1. Recurrence-free survival among both cohorts; there is a significant survival advantage favoring those patients who received combination therapy (p = 0.0233).

Discussion

The present study demonstrates that patients receiving immediate MMC prior to an induction course of BCG sustain a favorable recurrence-free survival, albeit further work is required to determine if the course of intravesical therapy independently modulates this outcome. Although the efficacy of combining these two agents has been examined in prior work, to our knowledge, this is the largest contemporary report to evaluate outcomes associated with a single perioperative dose of mitomycin prior to BCG induction, a scheme of administration which is common in clinical practice.

Historically, three prospective randomized trials have been borne out in recent years that compare BCG monotherapy to combination with intravesical chemotherapy; these trials have generally included high risk NMI bladder cancer patients with no specific attention to the role of carcinoma-in-situ (CIS). Cai et al, much in the vein of the current study, evaluated the impact of one immediate epirubicin instillation preceding the administration of BCG.[13] The comparative regimes resulted in a 57.5% recurrence-free rate in the combined group, as opposed to 50.6% in the BCG-alone group, a differential that was not statistically significant ($p = 0.82$). In another study, the regular administration of electromotive MMC in combination with BCG resulted in not only a lower recurrence rate (41.9% versus 57.9%, $p = 0.0012$), but also a significantly lower disease-specific mortality within the combination group (5.6% versus 16.2%, $p = 0.01$).[14] The degree to which the electromotive delivery of MMC contributed to this remarkable differential among cohorts cannot be extrapolated from the data. The final study included a total of 56 Ta-T1 tumors of unknown grade, whereby patients received immediate MMC at the time of TUR in addition to four weekly courses of this agent.[15] Patients relegated to the BCG alone arm were exempt from immediate instillation, and received only BCG weekly for 6 weeks. Subjects in both cohorts went on to receive BCG monthly for 1 year. The combination group sustained a significantly longer time to first recurrence, substantiating multiple prior reports on the efficacy of alternating therapy by the Finnbladder Group.[5]

As a recent complement to the aforementioned collection of prospective trials, EORTC 30993 features the results of a randomized phase II trial involving combined therapy in patients with NMI disease along with CIS, be it primary, secondary, or concurrent. These patients received six weekly instillations of MMC followed by six weekly instillations of BCG or a total of 9 weekly instillations of BCG with an intervening rest period. Complete response and disease-free rates were similar to those receiving BCG alone, however, establishing that sequential intravesical chemotherapy and BCG had no role for the treatment of CIS. Of note the timing and protocol of administration in the EORTC trial was different than the regimen detailed in this investigation, so the cancer-specific results cannot be directly extrapolated to the cohort of patients described herein. Nevertheless, the role of CIS was accounted for in the current study, and, as evidenced by the findings of EORTC 30993, this feature should be an important consideration not only in clinical management, but also in the critique and formulation of related investigations moving forward.[16]

In addition to its relevancy to multiple antecedent studies, the results of the current investigation were substantiated by findings reported in abstract form by Kader in a prospective protocol with a similar program of intravesical treatment; although, the latter study involved a smaller cohort of patients with NMI disease.[17] In this study of 128 patients followed over a mean of 26 months, 63% of the patients receiving MMC were recurrence-free at last follow up, as compared to 45% in the BCG monotherapy group. Furthermore, an analysis of the side effect profile revealed an even distribution amongst groups, with 30% of patients in each group reporting an adverse event, the majority of which constituted lower urinary tract symptoms. This report thus corroborates the findings discussed herein with respect to the sequence and timing of medication administration. Furthermore, given the prospective design of the Kader study, insight into the side effect profile was afforded, which was equivalent among both cohorts, for each program of therapy.

Although the results described in this report and in the aforementioned abstract are promising, many questions involving the molecular mechanisms behind these clinical observations remain poorly defined. A basis for these explanations involves the premise that MMC must be administered immediately following tumor resection in order to reduce the risk of tumor reimplantation following transurethral resection. In accordance with this recommendation, data from a randomized trial has cited that one instillation of MMC alone immediately following resection reduced the risk of tumor recurrence by approximately 34%.[18-21] Moreover, as it pertains to the literature on combination therapy, several of the studies involving combination therapy feature the administration of BCG prior to MMC, thus allowing for the hypothesis that BCG-induced inflammation might "prime" bladder urothelium for the delivery and action of MMC. Whether the effect of MMC is additive or synergistic with BCG in this scenario remains unknown. However, BCG is postulated to initially provoke a

cytokine and T-cell mediated response against tumor;[22] with the administration of MMC, the active metabolites of this agent then add to the antineoplastic effects by cross-linking DNA to all tissue layers of the bladder affected by superficial bladder cancer.[23,24] While these explanations make mechanistic sense, they seemingly do not apply to the sequence of administration described in this study, whereby MMC is given prior to BCG. Also, these postulates seem to hinge on the concept of multiple administrations of BCG and MMC, and may not fully account for the presumed durable impact of immediate, one-time administration of MMC following transurethral resection. Thus, whether the benefit from immediate MMC and induction BCG is derived from the sequential, independent action of these agents or through a complementary mechanism, perhaps involving urothelial surface modification, remains indeterminate.[2-8]

Furthermore, in addition to speculating on the molecular mechanisms underpinning these clinical observations, consideration might also be given to the limitations of this study. First, the retrospective nature of this analysis restricts the ability to standardize cohorts as might have been afforded via prospective randomization. For instance, although the groups were matched with respect to many important demographic and pathologic characteristics, a disproportionate number of patients with Tis were included in the monotherapy cohort (17.9% versus 4.2%); and, this disparity might have contributed to the fact receipt of MMC did not reach significance on multivariable analysis. A randomized controlled-trial would thus afford the ideal medium to ensure that clinically more aggressive appearing tumors were not discriminately being assigned to one therapy in particular. In conjunction with this, a larger cohort would ensure that the study was powered sufficiently to substantiate the differences in outcome between combined versus monotherapy, as alluded to herein. In this way, this investigation might serve as a precursor or pilot study for larger-scale investigations on this clinically relevant issue. Furthermore, quality of life and side effect information was not available for consideration at the time this retrospective review was performed, and, in addition to therapeutic efficacy, these considerations remain important considerations before combination therapy can be implemented. Side effect profiling for combination therapy is particularly important in order to determine how this program modulates the frequency of known adverse effects associated with BCG and mitomycin C individually;[21,25-27] furthermore, it must be established if these adverse events occur in a summative fashion in the setting of combined therapy and whether tolerability will be affected as a consequence.

Despite these limitations, however, this study adds a valuable contribution to the growing body of literature on combination intravesical algorithms in the management of TCC of the bladder. Future investigations stand to determine if perioperative MMC prior to induction BCG may increase recurrence-free survival.

Conclusion

The administration of perioperative MMC prior to an induction course of BCG did not confer an overall survival advantage. Although the combination therapy group demonstrated a significant recurrence-free survival advantage, the intravesical therapy regimen did not independently modulate this benefit. Further investigation is warranted to determine if immediate MMC prior to a course of induction BCG confers a benefit to recurrence-free survival. Given the clinical relevance of these conclusions, the findings discussed herein may serve as pilot data to guide such a larger-scale, randomized-controlled trial. □

References

1. Rajala P, Kaasinen E, Rintala E et al. Cytostatic effect of different strains of Bacillus Calmette-Guerin on human bladder cancer cells in vitro alone and in combination with mitomycin C and interferon-alpha. *Urol Res* 1992;20(3):215-217.
2. Kaasinen E, Rintala E, Hellstrom P et al. Factors explaining recurrence in patients undergoing chemoimmunotherapy regimens for frequently recurring superficial bladder carcinoma. *Eur Urol* 2002;42(2):167-174.
3. Kaasinen E, Rintala E, Pere AK et al. Weekly mitomycin C followed by monthly bacillus Calmette-Guerin or alternating monthly interferon-alpha2B and bacillus Calmette-Guerin for prophylaxis of recurrent papillary superficial bladder carcinoma. *J Urol* 2000;164(1):47-52.
4. Kaasinen E, Wijkstrom H, Malmstrom PU et al. Alternating mitomycin C and BCG instillations versus BCG alone in treatment of carcinoma in situ of the urinary bladder: a nordic study. *Eur Urol* 2003;43(6):637-645.
5. Rintala E, Jauhiainen K, Kaasinen E, Nurmi M, Alfthan O. Alternating mitomycin C and bacillus Calmette-Guerin instillation prophylaxis for recurrent papillary (stages Ta to T1) superficial bladder cancer. Finnbladder Group. *J Urol* 1996;156(1):56-59; discussion 59-60.
6. Rintala E, Jauhiainen K, Rajala P, Ruutu M, Kaasinen E, Alfthan O. Alternating mitomycin C and bacillus Calmette-Guerin instillation therapy for carcinoma in situ of the bladder. The Finnbladder Group. *J Urol* 1995;154(6):2050-2053.
7. Van der Meijden AP, Hall RR, Macaluso MP, Pawinsky A, Sylvester R, Van Glabbeke M. Marker tumour responses to the sequential combination of intravesical therapy with mitomycin-C and BCG-RIVM in multiple superficial bladder tumours. Report from the European Organisation for Research and Treatment on Cancer-Genitourinary Group (EORTC 30897). *Eur Urol* 1996;29(2): 199-203.

8. Witjes JA, Caris CT, Mungan NA, Debruyne FM, Witjes WP. Results of a randomized phase III trial of sequential intravesical therapy with mitomycin C and bacillus Calmette-Guerin versus mitomycin C alone in patients with superficial bladder cancer. *J Urol* 1998;160(5):1668-1671;discussion 1671-1672.
9. Bono AV, Lovisolo JA, Saredi G. Transurethral resection and sequential chemo-immunoprophylaxis in primary T1G3 bladder cancer. *Eur Urol* 2000;37(4):478-483.
10. Erol A, Ozgur S, Basar M, Cetin S. Trial with bacillus Calmette-Guerin and epirubicin combination in the prophylaxis of superficial bladder cancer. *Urol Int* 1994;52(2):69-72.
11. Uekado Y, Hirano A, Shinka T, Ohkawa T. The effects of intravesical chemoimmunotherapy with epirubicin and bacillus Calmette-Guerin for prophylaxis of recurrence of superficial bladder cancer: a preliminary report. *Cancer Chemother Pharmacol* 1994;35(Suppl): S65-S68.
12. Greene FL, Page DL, Fleming ID et al. AJCC Cancer Staging Manual, 6th Edition. New York, Springer, 2002.
13. Cai T, Nesi G, Tinacci G et al. Can early single dose instillation of epirubicin improve bacillus Calmette-Guerin efficacy in patients with nonmuscle invasive high risk bladder cancer? Results from a prospective, randomized, double-blind controlled study. *J Urol* 2008;180(1):110-115.
14. Di Stasi SM, Giannantoni A, Giurioli A et al. Sequential BCG and electromotive mitomycin versus BCG alone for high-risk superficial bladder cancer: a randomised controlled trial. *Lancet Oncol* 2006; 7(1):43-51.
15. El Mohsen M, Shelbaia A, El Ghobashy S et al. Sequential chemoimmunotherapy using Mitomycin followed by bacillus Calmette-Guerin versus single agent immunotherapy (BCG) for recurrent superficial bladder tumors. *UroToday Int J* 2010:3.
16. Oosterlinck W, Kirkali Z, Sylvester R et al. Sequential intravesical chemoimmunotherapy with mitomycin C and Bacillus Calmette-Guerin and with Bacillus Calmette-Guerin alone in patients with carcinoma in situ of the urinary bladder: results of an EORTC genito-urinary group randomized phase 2 trial (30993). *Eur Urol* 2011;59(3):438-446.
17. Kader OAE. Immediate mitomycin C instillation followed by usual BCG course versus usual BCG alone for superficial transitional cell carcinoma of the bladder (4 years experience), AUA Abstract #1473. Fakous, Egypt, 2010.
18. Solsona E, Iborra I, Ricos JV, Monros JL, Casanova J, Dumont R. Effectiveness of a single immediate mitomycin C instillation in patients with low risk superficial bladder cancer: short and long-term followup. *J Urol* 1999;161(4):1120-1123.
19. Tolley DA, Parmar MK, Grigor KM et al. The effect of intravesical mitomycin C on recurrence of newly diagnosed superficial bladder cancer: a further report with 7 years of follow up. *J Urol* 1996;155(4): 1233-1238.
20. Shelley MD, Mason MD, Kynaston H: Intravesical therapy for superficial bladder cancer: a systematic review of randomised trials and meta-analyses. *Cancer Treat Rev* 2010;36(3):195-205.
21. Shapiro O, Jones K, Wang C, Landas S, Haas GP. Risk of post-operative intravesical mitomycin C instillation following transurethral bladder tumor resection. *Can J Urol* 2006;13(6):3317-3320.
22. Alexandroff AB, Jackson AM, O'Donnell MA, James K. BCG immunotherapy of bladder cancer: 20 years on. *Lancet* 1999; 353(9165):1689-1694.
23. Di Stasi SM, Giannantoni A, Massoud R, et al: Electromotive versus passive diffusion of mitomycin C into human bladder wall: concentration-depth profiles studies. *Cancer Res* 1999;59(19): 4912-4918.
24. Chen F, Zhang G, Iwamoto Y, See WA. BCG directly induces cell cycle arrest in human transitional carcinoma cell lines as a consequence of integrin cross-linking. *BMC Urol* 2005;5:8.
25. Caso J, Qin D, Sexton WJ. Eosinophilic cystitis following immediate post-resection intravesical instillation of mitomycin-C. *Can J Urol* 2010;17(3):5223-5225.
26. Sylvester RJ. Bacillus Calmette-Guerin treatment of non-muscle invasive bladder cancer. *Int J Urol* 2011;18(2):113-120.
27. Bolenz C, Cao Y, Arancibia MF, Trojan L, Alken P, Michel MS. Intravesical mitomycin C for superficial transitional cell carcinoma. *Expert Rev Anticancer Ther* 2006;6(8):1273-1282.