ORIGINAL ARTICLE

Vol. 38 (4): 474-479, July - August, 2012

The value of perioperative mitomycin C instillation in improving subsequent bacillus calmette-guerin instillation efficacy in intermediate and high-risk patients with non-muscle invasıve bladder cancer: a prospective randomized study

Ömer Gülpınar, Ahmet H. Halilioğlu, Mehmet İlker Gökçe, Çagatay Göğüş, Sümer Baltacı

University of Ankara, School of Medicine, Department of Urology (OG, MIG, ÇG, SB), and University of Ufuk, School of Medicine, Department of Urology (AHH), Ankara, TURKEY

ABSTRACT

Purpose: We evaluated the efficacy of perioperative mitomycin C (MMC) instillation to improve subsequent bacillus Calmette-Guérin (BCG) instillation efficacy in intermediate and high risk patients with non-muscle invasive bladder cancer (NMIBC).

Materials and Methods: From November 2004 to May 2006, 51 patients with intermediate or high risk NMIBC were enrolled in this prospective randomized trial. In group A, patients were treated with perioperative MMC (40 mg MMC in 40 mL saline was administered within 6 hours of surgery) followed by delayed (at least 15 days from surgery) BCG instillations (once a week for 6 weeks, 5 x 108 colony-forming units in 50 mL saline). Patients in group B were treated with delayed BCG instillations alone. The primary end points were recurrence-free interval and recurrence rate.

Results: There were 25 and 26 patients in groups A and B, respectively. Median follow-up was 41.3 months (range 8 to 64) in group A and 40.9 months (range 6 to 68) in group B. Recurrence rate was 36% (9 of 25) and 19.3% (5 of 26) in group A and B, respectively (p = 0.052). Median time to the fırst recurrence was 8 months in group A and 7 months in group B (p = 0.12).

Conclusions: The present study showed no statistically significant difference in terms of recurrence rate and median time to first recurrence between intermediate or high-risk patients with NMIBC who were treated with early single dose instillation of MMC plus delayed BCG and those who were treated with only BCG.

ARTICLE INFO

Key words:
Urinary Bladder Neoplasms; Chemotherapy; Adjuvant; Immunotherapy; BCG Vaccine

Int Braz J Urol. 2012; 38: 474-79

Submitted for publication:
January 16, 2012

Accepted after revision:
July 27, 2012

INTRODUCTION

Bladder cancer (BCa) is a non-muscle invasive papillary tumor in 75-85 % of cases (1). The recurrence and progression rate after transurethral resection of bladder tumors (TURBT) are 50-70% and 10-15%, respectively (2). Risk factors for tumor recurrence and/or progression are tumor localization, tumor size, prior recurrences, presence of tumor at first follow-up cystoscopy, stage, grade and associated carcinoma in situ (CIS) (2). In an attempt to decrease the risk of recurrence and to prevent or delay progression to muscle invasive disease, presently published clinical guidelines recommend that patients should receive adjuvant intravesical instillations

of chemotherapy or immunotherapy after TURBT. Additionally, the European Association of Urology (EAU) guidelines strictly recommend that one immediate post-operative instillation of chemotherapy should be given to all patients after TURBT of presumably non-muscle invasive bladder cancer (3).

Bacillus Calmette-Guérin (BCG) instillation is generally regarded as the most effective treatment for patients with high-risk tumors. EAU guidelines again recommend immediate instillation of chemotherapy before intravesical BCG instillation in patients at an intermediate or high risk of tumor progression (3). However, a recent study has shown that for the high risk patients with non-muscle invasive bladder cancer (NMIBC) a single instillation of perioperative intravesical chemotherapy before subsequent BCG instillation would not influence the progression or recurrence rate compared with patients treated with BCG therapy only (4). In this prospective, randomized study, we have tried to evaluate the efficacy of perioperative mitomycin (MMC) instillation to improve subsequent BCG instillation efficacy in intermediate and high risk patients with NMIBC.

MATERIALS AND METHODS

From November 2004 to May 2006 all consecutive patients who had undergone TURBT at our center for pathologically confirmed stage Ta, T1 urinary bladder cancer were selected for this study. Patients with intermediate or high risk for recurrence and progression according to the EAU guidelines were included (5). Patients with stage pTaG1or pTaG2 tumors were included into the study population, only if they had a tumor size > 3 cm or recurrent or multifocal tumors. Patients with CIS, pTaG3 tumors and all pT1 tumors were included in the study. All patients with TaG3 or T1G3 tumors underwent a second-look resection. These patients were included into the study only if the second-look resection revealed no muscle invasive disease. Additional prerequisites for inclusion were normal liver and kidney function tests, no instillations of chemotherapy or immunotherapy during the previous 6 months before entering the study and ability to follow the instillation and follow-up schedules. Histopathologic evaluation was done according to the 1997 TNM classification and 1998 WHO/International Society of Urologic Pathology scale.

Exclusion criteria were muscle-invasive bladder tumor, evidence of lymph node metastasis or distant metastasis, upper urinary tract tumors, tumors that could not be completely removed transurethral, presence of a second primary malignancy, pregnancy and immune deficiency.

Informed consent was obtained in all cases. The study was approved by the respective institutional review boards.

Treatment and Randomization Schedule

After complete transurethral resection of all visible lesions, patients were randomized into 1 of 2 treatment groups. In group A, patients were treated with TURBT plus MMC (40 mg MMC in 40 mL saline was administered within 6 hours of surgery) followed by delayed BCG instillations (once a week for 6 weeks, 5 x 108 colony-forming units in 50 mL saline) at least 15 days from TURBT. Patients in group B were treated with TURBT plus delayed BCG instillations (once a week for 6 weeks, 5 x 108 colony-forming units in 50 mL saline). Patients were instructed to retain the installation volume for at least 60 min. but not longer than 2 hours.

Patient Follow-up and Study End Points

Follow-up consisted of cystoscopy, urinary cytology and ultrasonography every third month for the first 2 year and, if there was no recurrence, every 6 month until 5 year from the beginning of the treatment. The primary end points were recurrence-free interval, defined as the time from randomization to the date of histologically confirmed recurrence and recurrence rate. Progression was defined as muscle invasive tumor or metastatic disease.

Statistical Analysis

Analyses were performed using a SPSS software package (version 11.0 for Windows, SPSS Inc., Chicago, Illinois). Data were expressed as numbers and percentages for discrete

variables and as means ± SD for continuous variables. The chi-square analysis or Fishers exact test were used to assess the significance of differences between dichotomic variables. Continuous variables were compared by Student's t test or Mann-Whitney U test. The log rank test was used for multivariate analysis. Multivariable Cox proportional hazards regression was used to investigate whether instillation of mitomycin C was associated with recurrence of urothelial carcinoma and the outcome was adjusted for age, sex, tumor stage, size, grade, previous recurrence rate, presence of CIS and multifocality. Kaplan-Meier curves were developed to compare recurrence free survival estimates of the two groups. The limit of statistical significance was defined as $p < 0.05$.

RESULTS

During the study period 109 patients had undergone TURBT and 51 of them were enrolled in this study. There were 25 and 26 patients in group A and group B, respectively. Summary of clinical data of the two groups are shown in Table-1. The percentage of patients with high grade tumors was 32% in group A and 23% in group B ($p = 0.41$). Mean number of tumors ($p = 0.08$) and percentage of multifocal tumors was higher in group B ($p = 0.45$) but these differences were not statistically significant as well. Median follow-up was 41.3 months (range 8 to 64) in group A and 40.9 months (range 6 to 68) in group B.

Recurrence rates was 36% (9 of 25) and 19.3% (5 of 26) in group A and B, respectively ($p = 0.052$). Median time to the first recurrence was 8 months in group A and 7 months in group B without any difference between two groups ($p = 0.12$). Kaplan-Meier analysis for recurrence-free survival showed no significant differences between group A and group B (log rank = 0.959) (Figure-1). Multivariate analysis indicated that tumor size, tumor stage, previous recurrence rate, presence of CIS and tumor grade were independent prognostic factors for the development of recurrence (Table-2). Age, sex, multifocality and single dose MMC instillation were not shown to be associated with decreased rate of recurrence.

One patient in each group had progression to invasive disease and radical cystectomy was performed in these 2 cases. Both patients

Table 1 - Clinical data concerning the demographic characteristics and tumor releated factors.

Parameter	Group A	Group B	P value
Age	58.2	58.0	P = 0.21
Male ratio	84.0%	76.9%	P = 0.14
Previous treatment rate	68%	72%	P = 0.50
Mean tumor size ± SD (cm)	3.04 ± 1.2	3.06 ± 1.4	P = 0.41
Mean tumor number ± SD (cm)	2.64 ± 1.1	3.16 ± 1.4	P = 0.08
High grade tumor %	32.0	23.1	P=0.41
T1 tumor %	44.0	46.2	P=0.54
Carcinoma in situ %	16.0	19.2	P=0.34
Multifocal tumor %	64.0	69.2	P=0.45

Figure 1 - Kaplan-Meier analysis for recurrence-free survival.

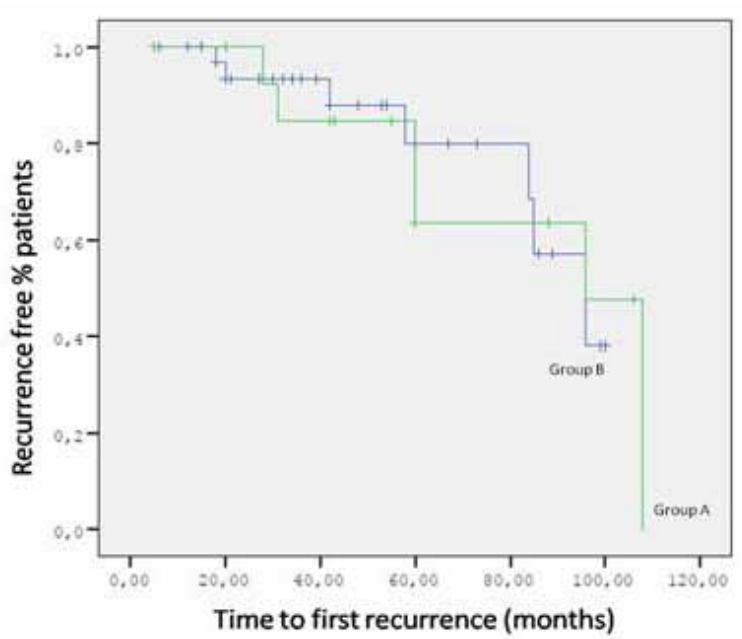

Table 2 - Multivariate analysis for recurrence.

Parameter	Hazard ratio (95% CI)	P value
Age >65	0.72 (0.24-1.47)	0.41
Sex (male)	1.41 (0.89-1.85)	0.57
Tumor stage (pT1)	1.72 (1.24-2.41)	0.02
Tumor size (> 3 cm)	2.4 (1.15-3.41)	0.01
Tumor grade	2.9 (1.57-6.21)	0.004
Previous recurrence rate	1.56 (1.11-2.58)	0.01
Mitomycin C instillation	0.69 (0.45-1.47)	0.61
Presence of carcinoma in situ	2.51 (1.56-3.43)	0.01
Presence of multifocal tumor	0.89 (0.58-1.76)	0.59

had T1G3, multifocal urothelial carcinoma and progression was observed at 11th and 16th months after randomization.

The two groups had similar rates of side effects (p = 0.457). No pain or difficulty in urination was observed related to MMC instillation. Only 2 patients in group A and 3 patients in group B complained of dysuria.

DISCUSSION

The etiology and primary risk factors of BCa are well understood, but its high rate of recurrence and considerable progression rate complicate treatment, with implications for costs and health-related quality of life. Although intravesical adjuvant or prophylactic treatment is well established and part of the routine in the clinical treatment of patients with NMIBC, the optimal treatment strategy is still under debate (5,6).

In a meta-analysis of seven randomized trials, Sylvester et al. suggested that one immediate instillation of chemotherapy after TURBT decreased the percentage of patients with recurrence by 12% and the odds of recurrence by 39% (7). Although this meta-analysis and the European Association of Urology Guidelines on Bladder Cancer recommend a single immediate postoperative installation of chemotherapy in all cases of NMIBC and adjuvant intravesical immunotherapy with BCG in patients with high risk NMIBC (1), interestingly, there is no sufficient data about whether the early single dose chemotherapy improves the delayed BCG installation efficacy. In only one prospective, randomized study this point has been studied and it concluded that there was no statistically significant differences in terms of disease-free time and recurrence rate between high risk patients with NMIBC who had undergone preoperative epirubicin instillation plus delayed BCG and those who had undergone delayed BCG alone (4). Therefore, the authors suggested that the use of early single dose instillation of intravesical therapy does not seem advisable in all cases of NMIBC (4). In that well designed study, patients with high grade pT1 bladder cancer were excluded and maintenance BCG was given to all patients. In our study, we did not exclude patients with T1 high grade disease and all patients with high grade tumors underwent a second-look resection. These patients were included into the study only if the second-look resection revealed no muscle invasive disease. Additionally, Cai et al. gave maintenance BCG to all their patients. In our study, we did not give maintenance BCG to our patients. Although maintenance BCG is the preferred treatment after TURBT of high risk NMIBC, in an editorial, Herr HW examined the strength of the evidence for routine use of maintenance BCG to prevent tumor progression and he concluded that critical analysis of the evidence does not support the liberal use of maintenance BCG as currently practiced (8). However, we should state that 2012 EAU guidelines recommend that patients with high risk of progression, for whom cystectomy is not carried out, BCG including at least 1 year maintenance is indicated and today this mode of therapy represents the clinical practice in such cases (9).

In our study, we have found no statistically significant difference in terms of disease-free survival, recurrence rate and median time to first recurrence between patients who were treated with early single dose instillation of MMC plus delayed BCG and those who were treated with only BCG. Multivariate analysis indicated that tumor size, tumor stage, previous recurrence rate and tumor grade were independent prognostic factors for the development of recurrence, but age, sex, and single dose MMC instillation were not shown to be associated with decreased rate of recurrence. One patient in each group had tumor progression during follow-up. Our findings are consistent with the similar study performed by Cai et al. (4). In that study, chemotherapeutic agent was epirubicin for early single dose instillation and there was no statistically difference between two groups. We, like Cai et al., think that the efficacy of BCG therapy on high risk bladder cancer is probably not modified by perioperative single dose instillation of chemotherapeutic agent due to the more frequently reported resistance of high risk bladder cancer to chemotherapeutic agent compared to BCG (5).

Early single dose MMC installation is not a treatment without side effects (10), at the same time it has also a cost. The present study and the study by Cai et al. suggest that early single dose perioperative instillation of chemotherapeutic agent followed by BCG in comparison to those who had undergone delayed BCG alone in the management of high risk NMIBC have no significant advantages in terms of disease-free time and recurrence rate. We think that well-conducted randomized phase 3 trials are needed in order to definitely determine the value of an immediate instillation to intermediate and high risk patients.

CONCLUSIONS

The present study showed no statistically significant difference in terms of disease-free survival, recurrence rate and median time to first recurrence between intermediate or high-risk patients with NMIBC who were treated with early single dose instillation of MMC plus delayed BCG and those who were treated with only BCG.

ABBREVIATIONS

BCa: Bladder cancer
TURBT: Transurethral resection of bladder tumors
CIS: Carcinoma in situ
EAU: European Association of Urology
NMIBC: Non-muscle invasive bladder cancer:
MMC: Mitomycin

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Babjuk M, Oosterlinck W, Sylvester R, Kaasinen E, Böhle A, Palou-Redorta J, et al.: EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder. Eur Urol. 2008; 54: 303-14.
2. Sylvester RJ, van der Meijden AP, Oosterlinck W, Witjes JA, Bouffioux C, Denis L, et al.: Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol. 2006; 49: 466-5; discussion 475-7.
3. Babjuk M, Oosterlinck W, Sylvester R: Guidelines on TaT1 (Non-muscle invasive) Bladder Cancer. European Association of Urology Guidelines, 2010 edition. Arnhem- the Netherlands,Drukkerij Gelderland. 2010; pp. 1-20.
4. Cai T, Nesi G, Tinacci G, Zini E, Mondaini N, Boddi V, 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: 110-5.
5. Oosterlinck W, Lobel B, Jakse G, Malmström PU, Stöckle M, Sternberg C, et al.: Guidelines on bladder cancer. Eur Urol. 2002; 41: 105-12.
6. Smith JA Jr, Labasky RF, Cockett AT, Fracchia JA, Montie JE, Rowland RG: Bladder cancer clinical guidelines panel summary report on the management of nonmuscle invasive bladder cancer (stages Ta, T1 and TIS). The American Urological Association. J Urol. 1999; 162: 1697-701.
7. Sylvester RJ, Oosterlinck W, van der Meijden AP: A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. J Urol. 2004; 171(6 Pt 1): 2186-90.
8. Herr HW: Is maintenance Bacillus Calmette-Guérin really necessary? Eur Urol. 2008; 54: 971-3.
9. Babjuk M, Oosterlinck W, Sylvester R: Guidelines on Non-muscle invasive (TaT1 and CIS) Bladder Cancer. European Association of Urology Guidelines, 2012 edition. Arnhem-the Netherlands,Drukkerij Gelderland. 2012; pp. 4-35.
10. Nieuwenhuijzen JA, Bex A, Horenblas S: Unusual complication after immediate postoperative intravesical mitomycin C instillation. Eur Urol. 2003; 43: 711-2.

Correspondence address:
Dr. Mehmet İlker Gökce
Ankara Üniversitesi Tıp Fakültesi
Ürolloji A.D. Sıhhıye
06520 Ankara Turkey
Fax: + 90 312 204-4055
E- mail: migokce@yahoo.com