Original research article

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PAIN AND GAIN OF BCG MAINTENANCE THERAPY IN NMIBC (NON-MUSCLE-INVASIVE BLADDER CANCER)

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ABSTRACT:

Background: To study the benefits of maintenance dose Bacillus Calmette-Guérin (BCG) and their adverse in the treatment of non-muscle invasive bladder cancer (NMIBC).**Method:** From August 2012 to September 2015, 59 patients with NMIBC (T1, Ta, Cis transitional cell carcinoma) were treated with complete transurethral resection followed by BCG induction and maintenance. We employed 120 mg (full dose) during induction phase was conducted once a month for six consecutive months and maintenance phase with 120 mg instillation at 3, 6 and 12 months with follow up of 1year or more. **Result:** Recurrence free rate was seen in 80.7% (46 patients). No disease progression noted. Local adverse effects were seen in 49 patients (83.05%). These were cystitis grade 1 in 66.10%, cystitis grade 2 in 20.33%, pyuria in 33.89%, gross hematuria in 23.56% and fever with malaise in 15.20%. Dose reduction was needed in 22.81% of patients. No systemic adverse effect seen requiring discontinuation of drug administration. **Conclusion:** Maintenance BCG therapy decrease recurrence and progression of the disease but to the cost of adverse effects. The optimum dose of BCG needs further study.

Keywords: BCG instillation, maintenance therapy, adverse effects, recurrence free rate, non-muscle invasive bladder cancer (NMIBC).

INTRODUCTION:

Morales and Martinez-Pineiro were the first to use BCG to treat patients with superficial bladder cancer, in 1976.**(1,2)** For high-grade NMIBC, a thorough transurethral resection of the bladder tumor (TURBT) followed by an induction course of intravesical Bacillus Calmette-Guerin (BCG) is considered the standard of care per the American Urological Association (AUA) and European Association of Urology (EAU) guidelines.**(3, 4)**

Indefinite number of randomized trials and subsequent meta-analyses have concluded that maintenance BCG therapy is superior to both chemotherapy and induction BCG alone for the prevention of recurrence and progression of NMIBC.**(5,6)** As a result, guidelines recommend BCG as the intravesical therapy of choice for high-risk disease.**(7,8)** Despite the high level of evidence in support of BCG, debate remains as to whether the routine use of maintenance BCG is justified. In addition, although concerns

surrounding BCG-associated adverse events have been expressed in the past, our experience with the use of BCG in patients with bladder cancer has shown that these events can be successfully managed and potentially avoided in the majority of cases.

PATIENTS AND METHODS

The subjects were 59 patients who were histopathologically diagnosed as having Ta, T1 (G2, G3, Cis) after transurethral resection of the bladder mucosa between August 2012 and September 2015, treated by full dose (120 mg) BCG instillation once every month for six months followed by maintenance dose (120 mg) at 3, 6 and 12 month and followed-up for 1 year or more.

Exclusion criteria were: Patients with histology other than urothelial carcinoma, incomplete resection at initial TURBT, a diagnosis of muscle-invasive cancer on the second TURBT. Lost to follow up cases; previous BCG instillation; active tuberculosis lesions; on anti-tuberculosis drugs; active double cancer or severe impairment in cardiopulmonary, renal, hepatic or bone marrow function.

BCG (120 mg: strain) was suspended in 40 ml of physiological saline and transurethrally instilled into the bladder, and the suspension was retained for 2 h after instillation. BCG instillation was performed once a month for six consecutive months in principle. Maintenance BCG therapy was performed at 3, 6 and 12th month. When adverse effects were found, the administration intervals were prolonged to 1–2 weeks.

BCG instillation was initiated 2 weeks after transurethral resection of the bladder tumor (TURBT) for superficial bladder cancer. One month after the final instillation, cystoscopy was performed.

Patients were examined every 3 months after the therapy by cystoscopy and urinary cytology. Biopsy or TURBT were performed when needed. The present investigation was approved by the institutional review board of our hospitals. Informed consent was obtained from all patients.

The incidence of adverse effects related to BCG was analyzed in all patients. The data were entered into an Excel™ (Microsoft) database and analyzed with SPSS. The recurrence-free rate and hazard function were calculated and analyzed by the Kaplan–Meier method.

RESULTS

In our study of 59 patients, characteristics of the patients are summarized in Table 1. There were 56 males and 3 females, with ages ranged from 38 to 75 years. Among Ta, T1 tumors, intermediate grade (G2) in 12 and high grade (G3) TCC in 47 patients. 13 patients were harboring associated CIS. 23 patients had multiple tumors and rest (34) had solitary bladder tumor.

18 patients with high-grade tumors had prior intravesical mitomycin-c instillation within 6 hours of TURBT. Follow up of patients after 1 year of maintenance BCG therapy ranged from 12 months to 40 months with average follow up of 26 months.

Table 1: Shows the characteristics of the patients.

Number of pt	**59**
Sex (M/F)	56/3
Age Range	38-75 years
Grade (G2/G3)	12/45
Tumor number (Solitary/ Multiple)	34/23
Prior intravesical chemotherapy(MMC)	18
Associated CIS	13
Average follow up	26 (12-40) months
Recurrence Free status	80.70% (46)

49 out of 59 patients suffered from adverse effects of BCG immunotherapy (Table 2). Cystitis (grade 1) was the most common adverse effect. Features such as urinary frequency, pelvic discomfort, burning micturition were, noted in 39 patients (66.10%). These patients were managed with NSAIDs and solifenacin. Severe cystitis (grade 2) was noted in 12 patients (20.33%) who underwent subsequent dose reduction i.e. 80 mg of BCG. Pyuria [>50/high power field (HPF)] in (35.08%) which was sterile in most of the cases. Gross hematuria is seen in 14 patients (23.56%), presented after 72 hours of instillation, 5 of them also had severe cystitis. General malaise and fever (>37.5^0 C) were in 9 patients (15.25%), symptoms generally resolve within 48 hours. Dose reduction was done in 13 patients (22.03%). There were no systemic adverse effects requiring discontinuation of the drug administration or complications requiring medication with antituberculosis drugs or surgery. The planned BCG treatment course was completed in all cases.

Mean follow up period was 26 months (range 12-40 months). Recurrence was noted during check cystoscopy in 11 patients and the second TURBT was done. Thus, recurrence free rate was 80.70% (46 patients). Among recurrence cases, 9 patients presented with recurrence only once and following TURBT histopathology suggestive of NMIBC so BCG instillation continued. 2 cases, presented with recurrence twice and were not muscle invasive so same protocol followed. 2 cases drop out of study following cystitis during induction phase and lost to follow up. Kaplan Meier graph for hazard function plotted (Figure 1), suggestive of time of the first recurrence. Recurrence free survival curve depicted in figure 2. In this study, no disease progression noted in any of the patients and all are alive with no evidence of bladder cancer.

Table 2: Shows adverse effect during BCG induction and maintenance therapy.

	Adverse Effects	No. of patients (%)
1	Cystitis grade 1*	39(66.10%)
2	Cystitis grade 2**	12(20.33%)
3	Pyuria***	20(33.89%)
4	Gross Hematuria	14(23.56%)
5	General malaise & fever	9(15.25%)
6	Dose reduction	13(22.81%)
7	Total adverse effect	49(83.05%)
8	Drop outs	2(3.38%)

* Grade 1: moderate symptoms and if cystitis persists <48 h
** Grade 2: severe symptoms and/or >48 h
*** More than 50 pus cells/HPF

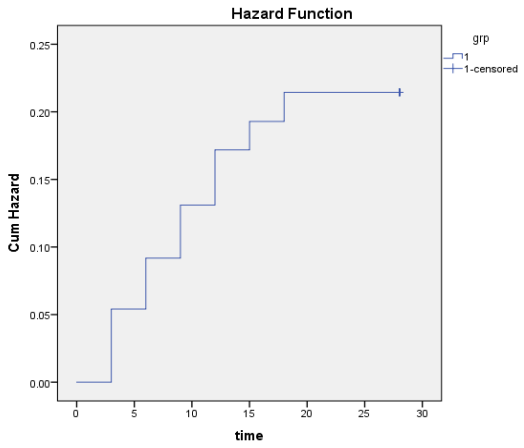

Figure1: Hazard function curve of BCG maintenance

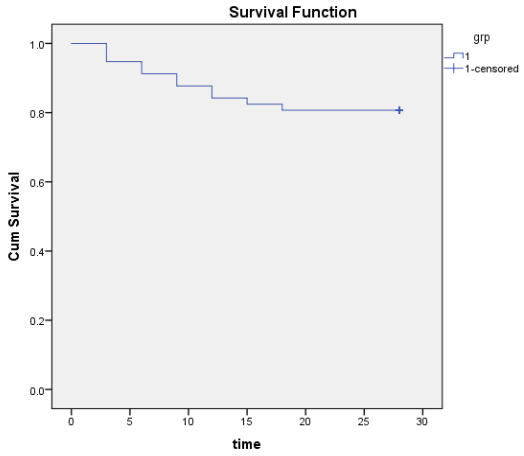

Figure2: Recurrence free survival function curve therapy for 26 months

DISCUSSION

The aim of intravesical therapy is to prevent recurrence, progression, and metastatic disease, as these require dramatic changes in management and put the patient at high risk of poor long-term survival.**(9)** BCG usually begins 2–4 weeks after TURBT treatment and involves lyophilized BCG powder, reconstituted in saline, being administered into the urinary bladder through a urethral catheter. The bacteria attach to the urothelium of the bladder through a fibronectin-dependent process and enters both healthy and malignant cells. This process initiates a significant immune response in the bladder and induces the release of such cytokines as IL-1, IL-2, IL-5, IL-6, IL-8, IL-10, IL-12, IL-18, TNF-α, IFN-γ, and GM-CSF resulting in urothelial infiltration by inflammatory immune cells. BCG significantly reduces these risks by inducing both local and systemic immune responses that are associated with an elimination or reduction of non–muscle-invasive bladder tumors.**(10)** As the immune stimulation induced by BCG wanes with time. Reichert and Lamm showed that
mice that survived TCC (MBT2) transplantation with the BCG immunotherapy experienced no additional benefit from repeat BCG treatment given at 8 mo after initial BCG treatment, suggesting that effective BCG immune stimulation persists in the mouse for 8 months and that maintenance is not needed. Although, repeat BCG given 10–15 months after initial BCG treatment was found to significantly reduce the growth of bladder cancer, suggesting that in the mouse, BCG immune protection wanes by 10–15 months. These findings support the need for maintenance BCG.**(11)**

To evaluate the effectiveness and superiority of BCG maintenance therapy, Hudson et al in 1987 conducted prospective randomized trial which showed no significant difference between BCG

induction and maintenance groups i.e. no recurrence rate 71% and 67% respectively.**(12)** Similar no significant results were obtained by Akaza et al in 1995 i.e. on recurrence rate 74.2% in induction group versus 77.6% in maintenance group.**(13)** These earlier studies showed no promising results for BCG maintenance therapy.

Lamm et al in 2000 published his breakthrough study supporting BCG maintenance therapy. 384 patients were randomized equally in induction group and maintenance group (192 pt in each group). Full dose BCG intravesical instillation schedule was 6 weeks versus 6 weeks + 1 instillation/3 months for 6 months then 1 instillation/6 months for 30 months. Follow up period was 98 months and the non recurrence rate was 41% (78) in induction only group versus 60% (115) in maintenance group (significant).**(14)** Saint et al in 2001 also supported maintenance therapy by publishing the study in 72 patients on full dose BCG with similar dose schedule (6 weeks + 1instl/3 M [6M] + 1instil/6M [30M]) showing non recurrence rate of 84.9% (61) with follow up of 24 months.**(15)**

At present, there is no uniform consensus on the most appropriate BCG maintenance schedule. The EAU acknowledges that, based on the extent of intravesical immune response, three consecutive weekly instillations give a maximum response, and recommends that at least 1 yr of maintenance therapy be provided.**(16)** Although the optimal dose of BCG is unknown, most clinical studies and meta-analyses have utilized standard dosing, and this remains the global standard of care. Patients with multifocal tumors fared better with the standard dose ($p = 0.048$) and there was a trend towards lower recurrence rates in patients with high-risk tumors receiving the full BCG dose ($p = 0.082$). **(17)** Therefore we conducted our study with full dose BCG scheduled for 1-year maintenance therapy and results were comparable to similar studies even with shorter maintenance therapy phase i.e. 80.70%

Since BCG is a live bacterium, it has the potential to produce local and systemic adverse events. The most common side-effect of BCG was Cystitis, occurring in approximately 80% of BCG-treated patients, and is the most frequently cited reason for the postponement of BCG instillations. Haematuria frequently occurs with cystitis and appears to be related to the extent of the previous TURBT. Severe local side-effects associated with BCG therapy were granulomatous prostatitis and epididymo-orchitis, which appear to be caused by BCG-contaminated urine. Although rare, a contracted bladder and ureteral obstructions may also occur. A contracted bladder appears to be associated with multiple TURBTs and maintenance instillations, while ureteral obstructions are likely due to resection and subsequent fibrosis around the ureteral orifice. BCG-associated systemic side-effects are less frequent than local side-effects but are more likely to be severe. Systemic side-effects usually associated with BCG therapy are general malaise, fever, myalgia, and nausea. Low-grade fever has been shown to develop in about 30% of BCG-treated patients, while fever >39.8 C has been reported in 5–20%. These side-effects generally resolve within 48 h, with or without the use of antipyretics. **(18)**

Common reasons for nonadherence to maintenance BCG therapy apart from adverse effects are patient-related factors that have been shown to affect adherence include patients' knowledge and belief about their illness and treatment; motivation to manage their illness; confidence in their ability to follow the treatment regimen; fear of possible side-effects; lack of communication with health care providers; lack of family or social support networks; and unrealistic expectations regarding the outcomes of treatment and the consequences of poor adherence.**(19)**

The present study indicates the beneficial role of BCG maintenance therapy with tolerable adverse effect events. Although these findings might provide the potential for a decrease in the instillation times of BCG, further studies are warranted to address this interesting issue after a careful investigation in more cases with longer follow up.

CONCLUSION

Since its introduction, BCG has become one of the most successful immunotherapy for NMIBC. The optimal BCG schedule still not yet been defined, but prospective and randomized studies including our study suggest that maintenance therapy is the treatment of choice for NMIBC. It should now be rationalized and tailored to the individual patient therapeutic approach based on patient's compliance.

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