Indian Journal of Surgical Oncology (December 2021) 12(4):796–801
https://doi.org/10.1007/s13193-021-01439-w

ORIGINAL ARTICLE

Intravesical Bacillus Calmette-Guerin (BCG) Therapy for Non-muscle Invasive Bladder Cancers: Long-term Results of a Modified Schedule

Kanuj Malik[1] · Anand Raja[1] · Lalgudi Subramaniam Ravishankar[2] · Kathiresan Narayanaswamy[3] · Venkatraman Radhakrishnan[4] · Tenali Gnana Sagar[4]

Received: 23 October 2020 / Accepted: 1 September 2021 /Published online: 9 September 2021

Abstract
Intravesical BCG therapy is an integral part of management of non-muscle invasive bladder cancers. Our aim is to analyze the non-muscle invasive bladder cancer patients treated at our center with a modified schedule intravesical BCG therapy. Data from patients treated at our center from 2009 to 2017 was collected from patient records and analyzed. A 6-weekly 120-mg induction course followed by 6 monthly 120 mg has been used at our institute for NMIBC. Clinicopathological and treatment variables were collected. A total of 119 patients were treated at our center with a median follow-up period of 4.18 years with the above schedule. Nearly 96% patients were able to complete induction therapy and 79% completed the maintenance therapy. The 5-year recurrence-free survival was 83%. The recurrence and progression rates were 16.8% and 4.2% respectively. About 60% of the patients suffered from side effects of BCG with 11% having class 3 or 4 toxicity. Our regimen of monthly maintenance intravesical BCG for 6 months shows good control rates with high compliance, similar to those of other contemporary series, although with higher incidence of high-grade toxicity.

Keywords BCG vaccine · Clinical protocols · Follow-up studies · Patient compliance · Urinary bladder neoplasm

Introduction

Bladder cancer is the ninth most common cancer worldwide with 75% presenting as non-muscle invasive bladder cancer (NMIBC). [1] Since the first report of bacillus Calmette-Guerin (BCG) as an immunomodulator in 1959, various well-conducted randomized controlled trials (RCTs) have proven BCG immunotherapy to be the most effective treatment for preventing recurrence and progression of NMIBC. [2] However, an ideal intravesical BCG schedule should balance the efficacy against the compliance and toxicity. This has led to further research with modified doses, strains, and schedules. We conducted an audit of patients treated at our Institution to evaluate the treatment compliance, adverse effects, and recurrence patterns using a modified BCG schedule.

Material and Methods

We conducted a retrospective analysis of all patients treated with intravesical BCG therapy at our center from 2009 to 2017. Clinicopathological and treatment variables were collected from patient case records. The date and status at last follow-up were confirmed through telephonic follow-up if patients could not attend the scheduled visit to hospital. Clinicopathological variables included age, sex, stage, grade, and number of tumors. More than 1 tumor was considered as multiple tumors. Treatment variables included the compliance with treatment, adverse effects, recurrence, and progression rates.

Institute where the study was carried out: Cancer Institute (WIA), Adyar, Chennai, Tamil Nadu, India

✉ Anand Raja
dr_anand@yahoo.com

[1] Department of Surgical Oncology, Cancer Institute (WIA), No. 38 Sardar Patel Marg, Adyar, Chennai, Tamil Nadu 600020, India

[2] Department of Surgical Oncology, Cancer Institute (WIA), Chennai, India

[3] Department of Surgical Oncology, Apollo Hospital, Chennai, India

[4] Department of Medical Oncology, Cancer Institute (WIA), Chennai, India

All adverse effects were classified according to Saint's adverse event scale. [3]

The treatment of non-muscle invasive bladder cancer at our center includes a gross complete transurethral resection of bladder tumor (TURBT) followed by a staging ReTURBT in all patients performed within 4–6 weeks. We perform a staging ReTURBT as a routine procedure in all patients except solitary low-grade completely resected tumors. If the initial TURBT is incomplete, a completion ReTURBT is performed, which is also followed by staging ReTURBT. All patients with stage T1 or Ta with one of the following: multiple tumors, grade > 1, or associated with carcinoma in situ were proceeded for intravesical BCG therapy after 4 weeks of staging ReTURBT. A urine culture test was performed prior to initiating BCG therapy and culture-based antibiotics therapy was administered in the presence of significant growth. After an atraumatic catheterization, these patients were then given weekly BCG for 6 weeks. One hundred twenty milligrams of Onco BCG (SII-ONCO-BCG, Russian strain, $1–19.2 \times 10^8$ colony-forming units) was mixed with 50 ml of saline and retained in the bladder for 2 h. A urine microscopy was performed prior to each further BCG instillation. In the presence of pus cells or if the patient was having dysuria, a urine culture is done. Following completion of induction course, a check cystoscopy and urine cytology were performed after 4 weeks. If there was no evidence of recurrence, patients were given a prophylactic monthly maintenance BCG for 6 months in the same dose. If there was any evidence of disease, patients undergo a repeat TURBT. Based on the histopathology report, if there was no grade or stage progression, patients were started on monthly maintenance course for 6 months. If there was grade or stage upmigration, alternative treatments were offered. After completion of maintenance treatment, all patients undergo regular 3-monthly cystoscopy and urine cytology for 3 years, then 6 monthly for 2 years and yearly thereafter irrespective of prior grade or stage. Detailed history related to symptoms regarding adverse event was taken at each hospital visit.

In this study, only patients who were started on 120-mg BCG dose were included in the analysis. Patients who were started on lower dose of intravesical BCG due to physician discretion were excluded. Patients treated outside with prior intravesical chemotherapy or BCG and then presenting to us with recurrence were excluded as the details regarding strain and doses were not available. Treatment breaks were defined as not able to initiate the next instillation as per schedule. They were subcategorized into those due to BCG toxicity and others. The duration of treatment break was defined from the date of scheduled instillation to the date of actual instillation. Any patient who did not receive the scheduled instillation was included in treatment default. The recurrence-free survival was calculated from the date of first TURBT.

All statistics were done using SPSS software version 17 (IBM, Chicago, USA) and applying the Student *T* test for non-parametric variables and the chi-square test for categorical variables, with the level of significance set at $p < 0.05$. The survival was calculated using Kaplan–Meier curves.

Results

A total of 130 patients received intravesical BCG for non-muscle invasive bladder cancer at our institute from 2009 to 2017 of which 119 were included in the analysis. Seven patients had recurrent tumors, 3 were given BCG 80-mg dosage, and 1 patient had a history of renal pelvis tumor, hence were excluded from the analysis. The clinical profile of our patients is given in Table 1. The median follow-up duration was 4.18 years (5 months to 10.7 years).

Treatment Compliance

Table 2 shows the compliance of patients with weekly and monthly BCG. Nearly 96.6% of the patients completed all 6 cycles of induction weekly BCG with 33% having treatment

Table 1 Clinicopathological profile of the patients

Characteristic	
Total no. of patients	119
Mean age (range) (years)	57.81 (21–81)
Sex	
Male	91 (76.5%)
Female	28 (23.5%)
Stage	
Ta	1 (0.9%)
T1	118 (99.1%)
No. of lesions:	
Solitary	78 (65.5%)
Multiple	41 (34.5%)
Grade:	
1	16 (13.4%)
2	66 (55.5%)
3	37 (31.1%)
Place of first TURBT	
Outside	59 (49.6%)
Our Institute	60 (50.4%)
No. of patients undergoing ReTURBT	
Yes	117 (98.3%)
No	2 (1.7%)
No. of ReTURBT done	
1	92 (78.6%)
2	22 (18.8%)
3	3 (2.5%)

Table 2 Compliance of patients with weekly and monthly BCG

No. of patients starting weekly BCG	119 (100%)
No. of patients completing weekly BCG	115 (96.6%)
No. of patients having breaks/defaulting due to BCG	38 (31.9%)
Mean duration of default (days) in weekly BCG	17 (3–51)
No. of patients starting monthly BCG	108 (90.7%)
No. of monthly BCG cycles	
0	11 (9.2%)
1	5 (4.2%)
2	4 (3.4%)
3	3 (2.5%)
5	2 (1.7%)
6	94 (79%)
No. of patients having breaks/defaults in monthly BCG schedule due to BCG	21/108 (19.4%)
Mean duration of default (days)in monthly BCG	40 (14–90)

breaks (not able to initiate next instillation per schedule)/default due to the therapy. Four patients discontinued weekly BCG treatment after initiation. Of these, 2 had severe dysuria due to BCG and refused further treatment and 2 defaulted due to personal reasons. Thirty-six patients had treatment breaks mostly due to dysuria which was managed by antibiotics. Two other patients had treatment break unrelated to BCG toxicity. In contrast to induction BCG, only 79% were able to complete all 6 cycles of monthly maintenance BCG with 17% having treatment breaks. Of the 115 patients who completed 6 cycles of weekly BCG and were eligible for monthly BCG, 7 more defaulted due to personal reasons. Fourteen more patients were not able to complete the full course, of which 8 discontinued due to BCG toxicity and 6 due to BCG unrelated reasons.

Toxicity

Fifty-nine percent of the patients (71) suffered from toxicity due to BCG (Table 3), with majority of patients presented with class I dysuria and mild hematuria which was managed conservatively. Twelve patients suffered from class 3 toxicity including granulomatous prostatitis, granulomatous lesion over the scrotum, and the remaining having cystitis more than 7 days. Two patients developed sepsis post-BCG instillation following which therapy had to be stopped.

Table 3 Adverse events to BCG therapy

Toxicity grade	Number of patients (percentage)
No side effect	48 (40.3%)
Class 1	39 (32.7%)
Class 2	18 (15.1%)
Class 3	12 (10.08%)
Class 4	2 (1.6%)

Recurrence and Survival Analysis

Of the 20 patients who developed recurrence, 2 had BCG refractory disease (disease while on treatment), 8 patients developed recurrence within 6 months of completion of monthly BCG while 10 patients developed recurrence on follow-up. The recurrence rate in patients who did not complete treatment was 24% as compared to 14.9% in patients who completed treatment ($p=0.66$). Five patients showed either grade or stage upmigration at the time of recurrence (Table 4). Two of the 3 patients with stage progression at the time of recurrence expired prior to any further treatment whereas one patient underwent radical cystectomy. Both patients with grade progression underwent TURBT followed intravesical BCG instillation with similar schedule. Figure 1 shows the Kaplan–Meier survival curve for RFS. The 5-year recurrence-free survival (RFS) was 83% and 10-year RFS was 76.8%. A delay in initiation of treatment of more than 6 weeks was associated with poor RFS (105.8 m vs 54.1 m; $p=0.07$). Although multiple tumors and high grade were not individually significant, patients having both the characteristics had significantly poor RFS (104.9 vs 71.9 m, $p<0.05$).

Discussion

Since the introduction of intravesical BCG by Morales in 1976, it has become an integral part of management of NMIBC. [4] We have analyzed the results of our NMIBC patients who were treated with intravesical BCG immunotherapy. The clinical profile of our patients is similar to those of world literature, with old age and male gender being affected preferentially. [1] Since ours is a tertiary center, nearly 50% of the patients had their first TURBT done outside and were referred to us after a diagnosis of urothelial malignancy. We ensure that tumor is completely removed prior to starting intravesical therapy, hence our ReTURBT rate approach 98% prior to induction BCG.

Table 4 Recurrence and progression rates

Recurrence rate	20/119 (16.8%)
Recurrence with no upmigration of grade or stage	15/119 (12.6%)
Progression rate	05/119 (4.2%)
Grade progression	2/119
Stage progression	3/119

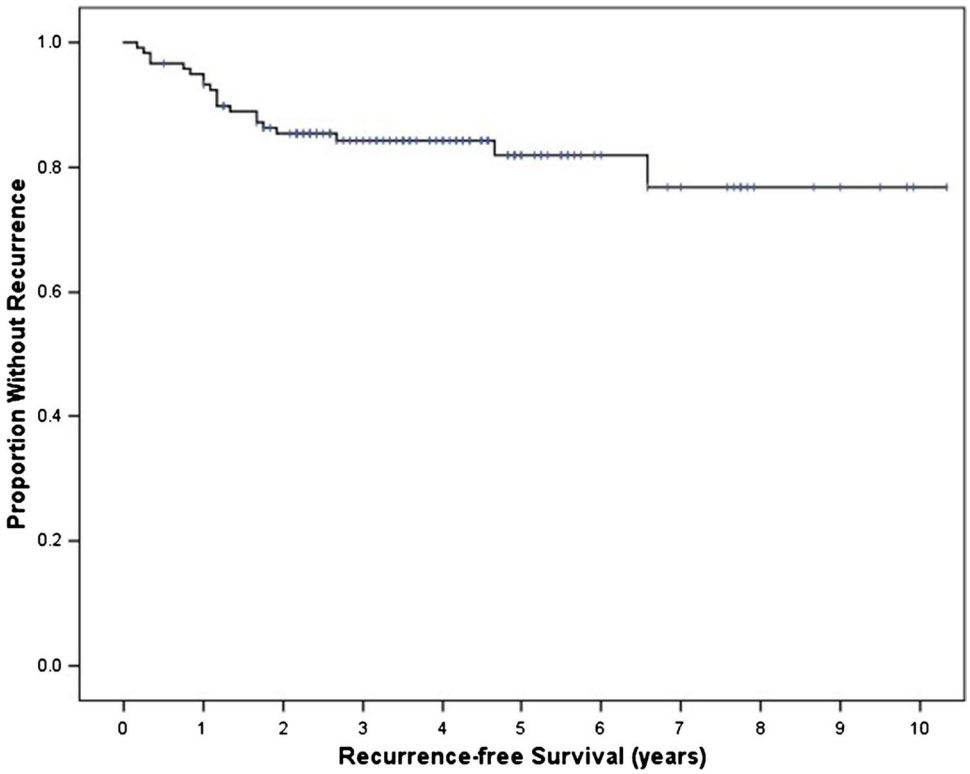

Fig. 1 Kaplan–Meier curve for recurrence-free survival of entire cohort

Presently, various systematic reviews and meta-analysis have proven the efficacy of maintenance BCG, and the optimum schedule is far from ready. [5, 6] The BCG regimen which has provided the best results till date was proven in randomized trial conducted by Lamm et al. under the auspices of Southwest Oncology Group. [7] However, various drawbacks were associated with this lengthy treatment including high percentage of patients not completing the full schedule and high toxicity rate. Multiple RCTs have been conducted to look for alternate regimens, of which two studies have used monthly regimen similar to ours. The first is a randomized trial conducted by Badalment et al., used a weekly regimen of 120 mg BCG for 6 weeks followed by a monthly regimen of 120 mg BCG for 2 years. [8] This study showed no benefit of adding maintenance BCG to recurrence- or progression-free survival. However, it had small sample size and was underpowered. Also 64% of the patients did not complete the full schedule with another 33% requiring dose reductions. A ReTURBT has become part of the standard guidelines as it has shown direct correlation with tumor upstaging, recurrence-free survival, and BCG response. [9] This trial did not have a ReTURBT as part of their protocol. Furthermore, the 3-year RFS in the patients receiving maintenance BCG was only 47%, which is very low as compared to the contemporary series. At our center, we perform ReTURBT for all patients planned for BCG, and have a 3-year RFS of 84.3%. Another RCT by Akaza et al. used a 80-mg weekly BCG induction dose for 8 weeks followed by 40-mg monthly BCG maintenance dose for 1 year. [10] They reported a significantly improved RFS for patients who had partial response to induction BCG. The 3-year recurrence-free survival approached 77.6% in the maintenance group.

The concept of at least 1 year of BCG maintenance stems from the meta-analysis by Bohle et al., however, of the 4 RCT used for comparison, 2 had only induction BCG, and one had BCG given in reduced doses. [11] The only RCT which used 120-mg maintenance BCG for 4 months and included in the meta-analysis showed a reduction in recurrence rate. [12] Although the 3-weekly maintenance regimen is the only schedule to have immunological basis and shows a reduction in progression rates, the prolonged schedule of 3 years used in the SWOG trial was associated with 84% withdrawal rate. [7] In their study, Lamm et al. acknowledged that 3-year duration was selected at convenience. The treatment completion rate in our cohort is 79%, which is comparatively higher than reported in various RCT, ranging from 16 to 63%. [13] Studies from Japan using maintenance BCG for only 18 months also had withdrawal rates of 63–76%. [14, 15] The most common reason for withdrawal from treatment includes drug-related adverse events. Our smaller schedule ensured compliance of treatment. Our progression rate is 4.2% which is comparable to that of other contemporary series, ranging from 0 to 12%. [13] In a retrospective analysis by Serretta et al., treatment compliance was evaluated for a 3-weekly maintenance regimen of 1 year. [16] They reported a 7.5% drop-out rate for induction course, which is almost similar to ours (3.4%); however, 17.5% did not start maintenance and another 22.6% dropped out from it, which in our study

is 9.2% and 11.7% respectively. They attributed it to persistent untreated mild local side effects associated with their 3-weekly schedule, so that only 52.3% were able to complete 1-year treatment. When evaluated separately in our study, nearly 33% had treatment breaks (delay in start of next instillation) in the weekly BCG and 26% had treatment breaks in the monthly BCG schedule due to BCG toxicity, but it did not convert into stopping the treatment. Although no study clearly illustrates the impact of delay in initiating BCG and subsequent treatment delays on prognosis, we feel that it may have an impact on the recurrence rates.

The incidence of side effects in our population is different when compared with similar population using similar dose of BCG. [17, 18] In our cohort, 40% of the patients had no side effects as compared to 25–30% in other studies; however, we had higher class 3 and 4 toxicities. In an RCT conducted by Vijjan et al. using 120 mg of BCG without maintenance BCG, only 5% patients had class 3 toxicity and no patient had class 4. [17] On reviewing the world wide literature, the standard dose of 81 mg using Connaught strain has superior outcomes in reducing recurrences albeit with a higher risk of systemic side effects as compared to lower doses. [19] Although the oncological outcomes of 120-mg dose are comparable to low doses as shown in the literature, the side effect profile is significantly worse, as seen in our series also. When different strains were evaluated, one of the meta-analyses showed no difference in the efficacy of various strains available. [20] The Russian strain used in the current study, along with Connaught strain, has shown the highest in vitro antitumor effects among different strains. [21] The more potent immunostimulation by early strains like Russian strain as shown by Hayashi et al. may result in higher rates of toxicity associated with it. [22] As this is a retrospective analysis with small sample size, this schedule needs further research in the form of randomized control trial, probably using a smaller dose, for further confirmation.

Conclusion

Overall, our regimen of monthly maintenance intravesical BCG for 6 months shows good control rates with high compliance, similar to those of other contemporary series, although with higher incidence of high-grade toxicity.

Acknowledgements We thank Dr. Chandra Kumar Krishnan for doing statistical analysis.

Author Contribution All authors contributed equally to the research and manuscript.

Declarations

The research was conducted in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest The authors declare no competing interests.

References

1. International Agency for Research on Cancer (IARC) (2014) World Health Organization (WHO) GLOBOCAN 2012: cancer incidence and mortality worldwide in 2012 [Internet]. Lyon, France: International Agency for Research on Cancer
2. Old LJ, Clarke DA, Benacerraf B (1959) Effect of bacillus Calmette-Guerin infection on transplanted tumours in the mouse. Nature 184(Suppl 5):291–292
3. Saint F, Irani J, Patard J et al (2001) Tolerability of bacillus Calmette-Guerin maintenance therapy for superficial bladder cancer. Urology. 57:883–8
4. Morales A, Eidinger D, Bruce AW (1976) Intracavitary bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol 116(2):180–183
5. Malmstrom P, Sylvester R, Crawford D et al. An individual patient data meta-analysis of the long-term outcome of randomized studies comparing intravesical mitomycin C versus bacillus Calmette-Gue´rin for non–muscle-invasive bladder cancer.
6. Sylvester RJ, van der Meijden APM, Lamm DL (2002) Intravesical bacillus Calmette-Gue´rin reduces the risk of progression in patients with superficial bladder cancer: a metaanalysis of the published results of randomized clinical trials. J Urol 168:1964–1970
7. Lamm DL, Blumenstein BA, Crissman JD et al (2000) Maintenance bacillus Calmette – Guerin immunotherapy for recurrent Ta, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized southwest oncology group study. J Urol 163:1124–1129
8. Badalament RA, Herr HW, Wong GY et al (1987) A prospective randomized trial of maintenance versus nonmaintenance intravesical bacillus Calmette-Guerin therapy of superficial bladder cancer. J Clin Oncol 5:441–449
9. Herr HW (1999) The value of a second transurethral resection in evaluating patients with bladder tumours. J Urol 162:74–76
10. Akaza H, Hinotsu S, Aso Y, Kakizoe T, Koiso K (1995) Bacillus Calmette-Guérin treatment of existing papillary bladder cancer and carcinoma *in situ* of the bladder. Four-year results Cancer 75:552–559
11. Bohle A, Bock PR (2004) Intravesical bacille-Calmette Guerin versus mitomycin Cin superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. Urology 63:682–687
12. Nogueira MJL, Solsona E, Unda M (2000) A multicenter randomized prospective study comparing three intravesical therapies, two with bacillus Calmette-Gue´rin immunotherapy and one with mitomycin C chemotherapy in medium and low risk superficial bladder tumors. Eur Urol 37:447
13. Chen S, Zhang N, Shao J, Wang X (2018) Maintenance versus non-maintenance intravesical bacillus Calmette-Guerin instillation for non-muscle invasive bladder cancer: a systematic review and meta-analysis of randomized clinical trials. Int J Surg. https://doi.org/10.1016/j.ijsu.2018.02.045
14. Hinotsu S, Akaza H, Naito S et al (2011) Maintenance therapy with bacillus Calmette-GuerinConnaught strain clearly prolongs recurrence-free survival following transurethral resection of bladder tumour for non-muscle-invasive bladder cancer. BJU Int. 108:187–95
15. Nakai Y, Anai S, Tanaka N et al (2016) Insignificant role of bacillus Calmette-Guérin maintenance therapy after complete

transurethral resection of bladder tumor for intermediate and high-risk non-muscle-invasive bladder cancer: results from a randomized trial. Int J Urol 23:854–860
16. Serretta V, Gesolfo CS, Alonge V, Cicero G, Moschini M, Colombo R (2016) Does the compliance to intravesical BCG differ between common clinical practice and international multicentric trials? Urol Int 96:20–24
17. Vijjan V, Mandhani A, Kapoor R et al (2006) A randomized trial comparing low dose (40 or 80 mg) with standard dose (120 mg) of bacillus Calmette-Guerin for superficial bladder cancer. Indian J Urol 22:317–321
18. Agrawal MS, Agrawal M, Bansal S, Agrawal M, Lavania P, Goyal J (2007) The safety and efficacy of different doses of bacillus Calmette-Guerin in superficial bladder transitional cell carcinoma. Urol 70:1075–1078
19. Astram A, Khadijah A, Yuri P et al (2014) Effective dose and adverse effects of maintenance bacillus Calmette-Guerin in intermediate and high risk non-muscle invasive bladder cancer: a meta-analysis of randomized clinical trial. Acta Med Indones 46:298–307
20. Ojea A, Nogueira JL, Solsona E et al. A multicentre, randomised prospective trial comparing three intravesical adjuvant therapies for intermediate-risk superficial bladder cancer: low-dose bacillus Calmette-Guerin (27 mg) versus very low-dose bacillus Calmette-Guerin (13.5 mg) versus mitomycin C. Eur Urol. 2007; 52:1398–406.
21. Boehm BE, Cornell JE, Wang H, Mukherjee N, Oppenheimer JS, Svatek RS (2017) Efficacy of bacillus Calmette-Guerin strains for treatment of non muscle invasive bladder cancer: a systematic review and network meta-analysis. J Urol 198:503–510
22. Secanella-Fandos S, Luquin M, Julian E (2013) Connaught and Russian strains showed the highest direct antitumor effects of different bacillus Calmette-Guerin substrains. J Urol 189:711–718
23. Hayashi D, Takii T, Fujiwara N et al (2009) Comparable studies of immunostimulating activities in vitro among mycobacterium bovis bacillus Calmette-Guerin (BCG) substrains. FEMS Immunol Med Microbiol 56:116–128