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Original Research Article

COMPLICATIONS OF INTRAVESICAL BACILLUS CALMETTE-GUÉRIN THERAPY IN NON-MUSCLE-INVASIVE BLADDER CANCER: A PROSPECTIVE STUDY FROM A TERTIARY CARE CENTER

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ABSTRACT

Background: Non-muscle-invasive bladder cancer (NMIBC) accounts for the majority of newly diagnosed bladder cancer cases. Intravesical Bacillus Calmette-Guérin (BCG) immunotherapy is a well-established adjuvant treatment that reduces recurrence and progression. However, BCG therapy is associated with a wide range of complications, which may affect treatment adherence and outcomes. The objective is to evaluate the incidence and severity of complications associated with intravesical BCG immunotherapy in patients with superficial bladder cancer treated at a tertiary care centre. **Materials and Methods:** A prospective descriptive study was conducted at the Department of Urology, Government Medical College, Kottayam, from 1st March 2022 to 31st March 2023. A total of 176 patients aged below 70 years with histologically confirmed NMIBC (Ta, T1, CIS) who underwent transurethral resection followed by BCG immunotherapy were included. Patients received a standard 6-week induction course and monthly maintenance doses. Complications were recorded during the induction and maintenance phases, and data were analyzed using descriptive statistics. **Result:** Of the 176 patients, 84 (47.7%) experienced BCG-related complications—41 during induction and 43 during maintenance. Local complications were more common, with dysuria (48.8%) and cystitis (27.4%) being the most frequently reported. Systemic complications included persistent fever (n=3), reactive arthritis (n=1), and one case of miliary tuberculosis. BCG therapy was discontinued in 21 patients (12%) due to adverse events, while 10 patients (6%) underwent radical cystectomy due to disease progression or recurrence. **Conclusion:** While intravesical BCG remains integral in NMIBC management, nearly half of the patients experienced complications, highlighting the need for close monitoring and individualized management strategies to mitigate adverse effects and ensure treatment efficacy.

INTRODUCTION

Bladder cancer remains a significant global health concern, ranking as the ninth most commonly diagnosed cancer and the thirteenth leading cause of cancer-related mortality worldwide.[1] A substantial majority of newly diagnosed cases present as non-muscle invasive bladder cancer (NMIBC), which includes carcinoma in situ (CIS), Ta, and T1 stages.[1,2] Despite initial surgical management, recurrence is common, necessitating effective adjuvant therapies.

The gold standard for initial management of NMIBC is transurethral resection (TUR) of all visible papillary lesions.[1,2] However, high recurrence and progression rates post-TUR have led to integrating intravesical immunotherapy with Bacillus Calmette-Guérin (BCG) as a cornerstone of adjuvant treatment. BCG is currently recommended in international guidelines for high-grade and selected low-grade NMIBC, owing to its well-established efficacy in reducing recurrence and progression to muscle-invasive disease.[3-5] Meta-analyses of randomized trials consistently support the maintenance of BCG in improving oncological outcomes following TUR.[1,2-6]

Despite its therapeutic benefit, BCG immunotherapy is associated with a broad spectrum of complications, ranging from mild local symptoms to

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serious systemic effects.[7,8] Approximately 8% of patients may discontinue therapy due to adverse events.[8] These complications may manifest during treatment or may appear months to years after cessation, including self-limiting lower urinary tract symptoms (LUTS), severe sepsis, or disseminated infections.[7,8] For instance, data from the EORTC Genito-Urinary Cancers Group reported that 69.5% of patients experienced either local (62.8%) or systemic (30.6%) complications, with chemical cystitis (35.0%) and general malaise (15.5%) being the most common.[1,2] Additionally, a comprehensive review of 282 BCG infection cases highlighted disseminated (34.4%), genitourinary (23.4%), and osteomuscular (19.9%) involvements as frequent patterns of infection.[1]

BCG-related complications necessitate early recognition, accurate diagnosis, and prompt intervention, especially in cases involving disseminated or atypical presentations.[2] Moreover, treatment interruptions due to adverse effects represent a significant barrier to achieving optimal outcomes with BCG therapy.[1,2] Understanding these complications' incidence, timing, and severity in a real-world clinical setting is essential for clinical decision-making, patient counselling, and treatment optimization.

Hence, the present study aimed to analyze the incidence and severity of complications associated with intravesical BCG therapy in patients with superficial bladder cancer treated at our tertiary care centre.

MATERIALS AND METHODS

This prospective descriptive study was conducted over one year in the Department of Urology, Government Medical College, Kottayam, starting from the date of Institutional Review Board (IRB) approval. The objective was to determine the incidence and severity of complications associated with intravesical Bacillus Calmette-Guérin (BCG) immunotherapy in patients diagnosed with superficial bladder cancer (non-muscle-invasive bladder cancer—NMIBC). Written informed consent was obtained from all participants, and detailed demographic and clinical data were recorded.

Patients included in the study were those under 70 years of age with histologically confirmed NMIBC (including stages Ta, T1, and carcinoma in situ) who were deemed fit for BCG therapy. Patients unwilling to participate or with incomplete clinical records were excluded. Initial evaluation included complete medical history, physical examination, cystoscopy, and imaging (ultrasound and CT, where necessary). All patients underwent transurethral resection of bladder tumours (TURBT), and tumour staging and grading were done as per the 2017 TNM classification and WHO grading system. Patients deemed eligible for BCG were informed about the immunotherapy protocol and its potential adverse effects.

Intravesical BCG immunotherapy was initiated 2–3 weeks after TURBT following confirmation of the histopathological diagnosis. The immunotherapy regimen included six weekly induction doses and 18 monthly maintenance doses. Each dose consisted of 80 mg ONCO BCG suspended in 50 ml of normal saline, administered intravesically using an 8-French infant feeding tube under gravity. Patients were instructed to retain the suspension for two hours, changing position every 15 minutes to ensure optimal mucosal contact. Before each instillation, a clinical assessment and urinalysis were performed; instillation was deferred if any signs of infection or complications were present.

Patients were monitored closely for BCG-related complications, including local symptoms such as dysuria, hematuria, and LUTS, as well as systemic signs like fever or sepsis. Minor symptoms were managed on an outpatient basis with supportive measures or antibiotics based on culture sensitivity. Severe complications such as granulomatous prostatitis or epididymoorchitis were managed in consultation with infectious disease specialists, and suspected cases of systemic BCG infection underwent further workup, including AFB cultures and imaging. Follow-up cystoscopy, urine cytology, and biopsy (if indicated) were performed every three months during therapy and every six months thereafter. Data were entered in Microsoft Excel and analyzed using IBM SPSS software version 20. Descriptive statistics were used for data analysis.

RESULTS

A total of 176 patients diagnosed with superficial bladder cancer who underwent transurethral resection of bladder tumour (TURBT) followed by intravesical Bacillus Calmette-Guérin (BCG) immunotherapy from March 2022 to March 2023 were enrolled in the study. All patients fulfilled the inclusion and exclusion criteria and provided written informed consent. Each patient underwent a comprehensive clinical evaluation, including a detailed history, physical examination, and relevant laboratory and imaging investigations.

The ages of the patients ranged from 35 to 94 years. Most patients were in the sixth (33%) and seventh (32%) decades of life. Approximately 23% of patients were below 60, while 11.4% were over 80. A significant male predominance was observed, with 159 patients (90.4%) being male and 17 patients (9.6%) female. The most common presenting symptom was painless hematuria, reported in 147 patients (83.5%), either in isolation or in combination with lower urinary tract symptoms (LUTS) or dysuria. Less common symptoms included suprapubic pain and vague abdominal discomfort. Two cases were detected incidentally during imaging performed for unrelated

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complaints. The symptoms' duration before presentation ranged from less than one month to up to 24 months.

Regarding tumour characteristics, 133 patients (75.6%) were classified under the intermediate-risk group, predominantly with T1G1 disease, while 43 patients (24.4%) belonged to the high-risk group, including cases of T1G3 and carcinoma in situ (CIS). Among the 84 patients (47.7%) who developed complications during BCG therapy, 41 (48.8%) experienced complications during the induction phase, while 43 (51.2%) developed complications during the maintenance phase.

Regarding treatment completion, 133 patients (76%) actively continued treatment and were under regular follow-up during data analysis. Ten patients (6%) underwent radical cystectomy due to progression or recurrence of disease not amenable to further intravesical or endoscopic management. Twenty-one patients (12%) discontinued BCG therapy due to drug-related toxicities, while another 10 patients (6%) were lost to follow-up. Two patients (1%) developed muscle-invasive disease and were referred for systemic chemotherapy.

Among those who developed BCG-related complications (n=84), dysuria was the most frequently reported local adverse effect, observed in 41 patients (48.8%). Cystitis occurred in 23 patients (27.4%), while hematuria was documented in 8 patients during therapy. Other local complications included epididymoorchitis and granulomatous prostatitis. Systemic complications were less common but notable; three patients had persistent fever lasting more than 48 hours and required inpatient evaluation and management with the support of infectious disease specialists. One patient developed reactive arthritis, and another case of miliary tuberculosis was diagnosed and successfully managed with antitubercular therapy.

Table 1: General Characteristics of the study population

	Number	**%**
Age Group		
31-40	2	1.20
41-50	7	3.50
51-60	32	18.20
61-70	58	33
71-80	57	32.30
81-90	18	10.20
>91	2	1.20
Gender		
Male	159	90.40
Female	17	9.60
Presentation		
Hematuria	147	83.50
LUTS	14	7.90
Dysuria	5	2.80
Suprapubic pain	6	3.40
Abdominal pain	3	1.70
Incidental	2	1.10
Stage of the tumour		
T1G1	133	75.60
T1G3	35	19.80
CIS	8	4.50
Complication		
INDUCTION DOSE	41	48.80
MAINTENANCE DOSE	43	51.20
Complication		
Dysuria	41	48.80
Cystitis	23	27.40
Haematuria	8	9.50
Epididymoorchitis	4	4.80
Prostatitis	3	3.60
Persistent fever	3	3.60
Arthritis	1	1.20
Miliary tuberculosis	1	1.20

Table 2: Treatment details of the study subjects.

Treatment Status	**Weekly**	**Monthly**
Defaulter	4	6
Stopped BCG	10	11
Radical cystectomy	0	10
On treatment and follow-up	–	133
On chemotherapy	–	2

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DISCUSSION

This study assessed the incidence and severity of complications associated with intravesical Bacillus Calmette-Guérin (BCG) therapy in 176 patients diagnosed with superficial bladder cancer. Our findings confirm that while BCG remains a mainstay in the management of non-muscle-invasive bladder cancer (NMIBC),[1] it carries a significant risk of adverse events, with 47.7% of our patients experiencing treatment-related complications. This is consistent with literature indicating that approximately 8% of patients may need to discontinue BCG therapy due to its associated toxicities.[1,2,6,9]

The demographic profile of our cohort—predominantly male patients in the sixth and seventh decades of life—is in keeping with global epidemiological trends of bladder cancer, where urothelial carcinoma is more common in men and typically affects older individuals.[2,3] Clinically, painless hematuria was the most frequent presenting symptom (83.5%), often occurring alongside lower urinary tract symptoms (LUTS) or dysuria. This is congruent with established patterns of presentation for NMIBC.[1,6]

Our cohort's tumour characteristics reflect typical NMIBC distribution, with a majority classified into intermediate-risk (T1G1) and high-risk (T1G3 and CIS) groups. This mirrors the broader clinical landscape where NMIBC represents a substantial proportion of bladder cancer diagnoses.[1,2,10] These patients are ideal candidates for BCG therapy, which has demonstrated efficacy in reducing both recurrence and progression.[1,10,11]

Local complications were more prevalent than systemic ones, with dysuria (48.8%), cystitis (27.4%), and hematuria being the most common. These adverse effects are well-documented and often reflect chemical cystitis or BCG-induced local inflammatory responses.[7] Our results are in agreement with existing studies, including those by Sharma et al. (2020), which emphasize that while effective, intravesical BCG therapy can be hampered by treatment-related adverse effects, ultimately impacting compliance and efficacy.[2]

Systemic complications, although less common, were also identified and included persistent fever, reactive arthritis, and a case of miliary tuberculosis. These findings are critical, as they highlight the spectrum of rare but serious BCG-related infections that can occur post-instillation.[1,11-13] Notably, Pérez-JacoisteAsín et al. emphasized the paucity of systematic data on disseminated BCG infections, most of which have been reported in isolated case studies with variable management approaches.[9] Our observation of miliary tuberculosis, while rare, reinforces the necessity of vigilance for systemic involvement during and after BCG therapy.

In our study, 12% of patients discontinued BCG therapy due to toxicity, a clinically significant figure that underscores the need for pre-treatment risk stratification and ongoing patient monitoring. In cases of local toxicities, dose reduction and temporary treatment suspension were effective in enabling therapy continuation. However, 6% of patients required radical cystectomy due to disease progression or recurrence, a reminder that while BCG therapy can reduce progression, it is not universally effective. Literature reports that BCG may fail in up to 40% of patients, particularly in those with high-risk diseases.[9,14]

This study contributes valuable data to the growing body of literature on BCG-related complications in NMIBC management. It reinforces the importance of early identification and management of adverse events and the development of structured protocols for managing BCG-related toxicity. The absence of BCG sepsis in our cohort and only one case of miliary tuberculosis reflects the relative safety of the therapy when administered with appropriate safeguards. However, the occurrence of systemic side effects, even if infrequent, warrants careful consideration, particularly in older or immunocompromised patients.

Future research should focus on identifying predictive markers for severe toxicity and exploring alternative dosing regimens or novel intravesical agents with improved safety profiles. Stratifying patients based on their risk for complications may optimize outcomes and enhance the therapeutic index of BCG in NMIBC management.

CONCLUSION

Intravesical BCG therapy remains a cornerstone in the management of NMIBC but is associated with a significant incidence of both local and systemic complications. Nearly half of the patients in our cohort experienced adverse effects, with 12% discontinuing treatment and 6% requiring radical cystectomy. These findings underscore the importance of vigilant monitoring, early intervention, and individualized treatment strategies to optimize outcomes and minimize morbidity.

REFERENCES

1. Liu Y, Lu J, Huang Y, Ma L. Clinical spectrum of complications induced by intravesical immunotherapy of Bacillus Calmette-Guerin for bladder cancer. Journal of Oncology. 2019;2019(1):6230409
2. Sharma V, Thakur AP, Ramasamy V, Shukla PK, Solanki FS, Choudhary A, Patel P. Complications of intravesical BCG therapy in non-muscle invasive bladder cancer: our tertiary care centre experience. African Journal of Urology. 2020 Dec;26:1-9.
3. Böhle A, Bock PR. IntravesicalbacilleCalmette-Guerin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. Urology. 2004 Apr 1;63(4):682-6.
4. Pasin E, Josephson DY, Mitra AP, Cote RJ, Stein JP. Superficial bladder cancer: an update on etiology, molecular development, classification, and natural history. Reviews in urology. 2008;10(1):31

ISSN (O): 2687-5365; ISSN (P): 2753-6556

5. Miyake M, Nishimura N, Fujii T, Fujimoto K. Recent advancements in the diagnosis and treatment of non-muscle invasive bladder cancer: Evidence update of surgical concept, risk stratification, and BCG-treated disease. International Journal of Urology. 2023 Nov;30(11):944-57.
6. Alhunaidi O, Zlotta AR. The use of intravesical BCG in urothelial carcinoma of the bladder. Ecancermedicalscience. 2019 Feb 26;13:905.
7. Waked R, Choucair J, Chehata N, Haddad E, Saliba G. Intravesical Bacillus Calmette-Guérin (BCG) treatment's severe complications: a single institution review of incidence, presentation and treatment outcome. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases. 2020 May 1;19:100149.
8. Decaestecker K, Oosterlinck W. Managing the adverse events of intravesical bacillus Calmette–Guérin therapy. Research and reports in urology. 2015 Oct 23:157-63.
9. Asín MA, Fernández-Ruiz M, López-Medrano F, Lumbreras C, Tejido A, San Juan R, Arrebola-Pajares A, Lizasoain M, Prieto S, Aguado JM. Bacillus Calmette-Guérin (BCG) infection following intravesical BCG administration as adjunctive therapy for bladder cancer: incidence, risk factors, and outcome in a single-institution series and review of the literature. Medicine. 2014 Oct 1;93(17):236-54.
10. Chang SS, Boorjian SA, Chou R, Clark PE, Daneshmand S, Konety BR, Pruthi R, Quale DZ, Ritch CR, Seigne JD, Skinner EC. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. The Journal of urology. 2016 Oct;196(4):1021-9.
11. Herr HW, Pinsky CM, Whitmore Jr WF, Sogani PC, Oettgen HF, Melamed MR. Long-term effect of intravesical bacillus Calmette-Guerin on flat carcinoma in situ of the bladder. The Journal of urology. 1986 Feb 1;135(2):265-7.
12. Shore ND, Redorta JP, Robert G, Hutson TE, Cesari R, Hariharan S, Faba ÓR, Briganti A, Steinberg GD. Non-muscle-invasive bladder cancer: An overview of potential new treatment options. InUrologic Oncology: Seminars and Original Investigations 2021 Oct 1 (Vol. 39, No. 10, pp. 642-663). Elsevier.
13. Slovacek H, Zhuo J, Taylor JM. Approaches to non-muscle-invasive bladder cancer. Current Oncology Reports. 2021 Sep;23:1-1.
14. Holzbeierlein JM, Bixler BR, Buckley DI, Chang SS, Holmes R, James AC, Kirkby E, McKiernan JM, Schuckman AK. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline: 2024 amendment. The Journal of urology. 2024 Apr;211(4):533-8.

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