International Journal of Basic & Clinical Pharmacology
Sharma I et al. Int J Basic Clin Pharmacol. 2025 Sep;14(5):833-838
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20252584

Original Research Article

Study of adverse drug reaction of intravesical onco-BCG in non-muscle-invasive bladder cancer: a retrospective study

Ira Sharma[1]*, Kulbhushan Sharma[2], Atal Sood[1]

[1]Department of Pharmacology, Dr. Rajendra Prasad Government Medical College, Kangra at Tanda, Himachal Pradesh, India
[2]Department of Urology, Dr. Rajendra Prasad Government Medical College, Kangra at Tanda, Himachal Pradesh, India

Received: 12 June 2025
Revised: 16 July 2025
Accepted: 17 July 2025

***Correspondence:**
Dr. Ira Sharma,
Email: sharmaira724@gmail.com

ABSTRACT

Background: Intravesical onco-BCG is mainstay therapy for intermediate and high-risk NMIBC to reduce disease recurrence and progression. In India Danish 1331 strain was used till middle of last decade after that Moscow (Russia) strain is used.
Methods: Retrospective study was conducted in intermediate and high risk NMIBC patients. Patients receiving were interviewed for ADR's and were recorded as grade 1, grade 2, grade 3 symptoms (as per Cleveland clinic approach to management of BCG toxicity). The patients with NMIBC (Ta or T1 diseases as per TNM staging AJCC 8th edition) in intermediate and high-risk group were enrolled in the study. The diseases classified in low risk, intermediate risk and high risk as per EAU guidelines.
Results: Sixty patients were enrolled in the study. Mean age of the patients is 62.75 years with male: female ratio 20:1. 46.6% of patients had intermediate and 53.4% had high risk disease. Mean follow-up period in the study was 32.27 weeks. 93.4% of patients had grade 1 symptoms and 6.6% had grade 2 symptoms. None of the patients had grade 3 serious complications.
Conclusions: Intravesical OncoBCG (Moscow strain) is safe and well tolerated in study population.

Keywords: Adverse drug reactions, European Association of Urology, Non-muscle invasive bladder cancer, OncoBCG Moscow strain

INTRODUCTION

The Bacillus Calmette-Guérin (BCG) vaccine was first created in 1921 by Albert Calmette and Camille Guérin at the Pasteur Institute in Lille, France. They achieved this by repeatedly subculturing *Mycobacterium bovis*, ultimately producing a live attenuated and non-virulent bacterial strain. In 1976, Alvaro Morales from Queen's University in Canada was the first to use BCG intravesically for the treatment of non-muscle-invasive bladder cancer (NMIBC), demonstrating a substantial reduction in tumor recurrence.[1] This breakthrough led to subsequent trials, including those by Donald Lamm in the 1980s, which confirmed BCG's therapeutic efficacy. The treatment received approval from the US FDA for use in NMIBC by 1990.[2]

Today, intravesical BCG therapy is regarded as the standard adjuvant treatment for intermediate- and high-risk NMIBC, known for its role in minimizing recurrence and delaying progression.[3] Indian data indicate that approximately 50% to 66% of patients undergoing BCG therapy experience moderate to severe adverse drug reactions (ADRs).[4] Initially, the Danish 1331 strain was

predominantly used in India, but its availability declined around the mid-2010s, leading to the widespread use of the Moscow (Russia) strain. Currently, the Serum Institute of India is the sole domestic producer of the formulation.

This study was designed to evaluate the nature and intensity of ADRs associated with intravesical administration of the Moscow strain in patients with intermediate- and high-risk NMIBC. Genetically, mycobacteria contain segments known as regions of difference (RD). The wild-type *M. bovis* lacks RD4 through RD11, regions found in *M. tuberculosis*. Additionally, the BCG strain developed through 230 passages between 1908 and 1921 also lost RD1, setting it apart from its wild-type ancestor. Present-day BCG strains, all derived from wild-type *M. bovis*, remain resistant to pyrazinamide due to these RD deletions.

Over time, the BCG strain was distributed globally and cultivated into various substrains, named according to their geographic or manufacturing origins- such as Danish 1331, Connaught, Moscow, TICE, and Tokyo.[5] Prior to the advent of freeze-drying (lyophilization) around 1960, these strains were maintained through continuous subculturing, which further contributed to genetic divergence.[6]

The BCG phylogenetic "family tree" includes four principal strain groups. Group 1 contains the early strains, while groups 2 to 4 include the later strains. The Danish 1331 strain, previously used in India and isolated in 1954 after 1331 serial passages, belongs to group 3. In contrast, the Moscow strain currently in use is classified as an early strain, dating back to 1924.

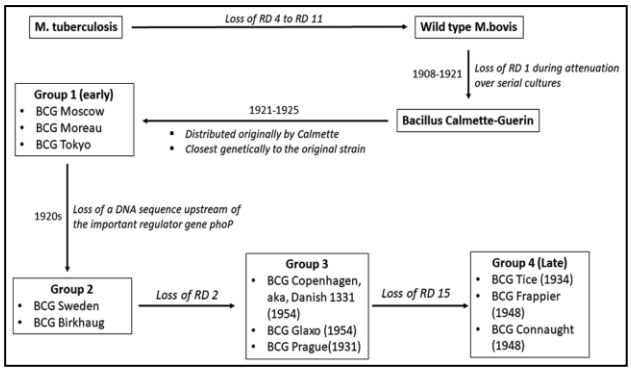

Figure 1: BCG phylogenetic "family tree".

Onco-BCG is a live bacterial vaccine, and its dosing is based on the number of colony-forming units (CFUs). CFU counts vary not only by strain but also by manufacturer and batch number, accounting for the differences in milligram-based dose recommendations.

India initially used the Danish 1331 strain for intravesical treatment of NMIBC, with early clinical data coming from Kamat et al. in 1994 at Tata Memorial Hospital, Mumbai[7]. Their study utilized a 120 mg dose, although earlier research suggests that 40-80 mg may be sufficient in CFU content. Later, the Danish 1331 formulation became available in India as 40 mg vials, each containing 1-8 × 10^8 CFU, and three vials were used per instillation, delivering 3 × 10^8 to 2.4 × 10^9 CFU. A 2017 systematic review identified only two other Indian studies involving this strain.[8] However, Danish 1331 was discontinued in India midway through the last decade.

In India, a 120 mg dose is commonly used for Onco-BCG. Vijjan et al, from Lucknow, conducted a randomized controlled trial comparing this standard dose to reduced doses of 40 mg and 80 mg using the Danish 1331 strain.[9] Their results showed similar recurrence and progression rates across all three arms, but significantly fewer side effects in the 40 mg group. One limitation of their study was the use of only induction therapy. A subsequent study by Agrawal et al from Agra involved a similar trial design using the same strain.[10] Their study included both induction and one-year maintenance therapy. Like the prior study, recurrence and progression did not differ significantly between groups, but toxicity- both local and systemic- was notably lower in the 40 mg arm.[10]

METHODS

Study design and setting

The study was a retrospective study. The study was conducted in the Department of Pharmacology and Department of Urology at Dr. RPGMC Kangra at Tanda, which is a multispecialty tertiary health care centre, situated in the foothills of Dhauladhar mountain range, at latitude of 32.0986360N and longitude of 76.3003390 E, amidst Kangra valley of Himachal Pradesh in India. The study was conducted after the due permissions from the protocol review committee, institutional ethics committee.

Study population

The patients with NMIBC (Ta or T1 diseases as per TNM staging AJCC 8th edition) in intermediate and high risk group were enrolled in the study. The disease was classified in low risk, intermediate risk and high risk as per EAU guidelines. Patients with intermediate and high risk who received intravesical Onco-BCG 80 mg will Moscow strain as six weekly instillations for induction and twelve monthly intravesical instillation as maintenance therapy were included in study. These patients were interviewed for adverse drug reactions and recorded as mild, moderate and severe as per Cleveland clinic approach to management of BCG toxicity (given in Annexure 1).

Inclusion criteria

Age more than 18 years, of either gender. Patients whose diagnosis is proven on histopathology as urothelial carcinoma. Patients with intermediate and high-risk diseases as per EAU guidelines. Patients giving written informed consent to participate in the study.

Exclusion criteria

Patients not willing to give written informed consent. Patients whose diagnosis is not proven in histopathologically. Patients with low-risk diseases category as per EAU guidelines.

Study duration

All the patients diagnosed as urothelial carcinoma from 1 October 2022 to 31 December 2024 received/receiving intravesical Onco BCG after fulfilling inclusion criteria were interviewed and information was recorded as per Annexure 2.

Statistical analysis

The data was collected, tabulated and analysed for various parameters and compared using appropriate statistical analysis tests. The data collected was tabulated in Microsoft Excel and analysed for various parameters and compared using appropriate statistical analysis tests using online 'social science statistics' software. Pie-chart was used for graphical representation of data

RESULTS

A total of 60 patients with non-muscle invasive bladder cancer (NMIBC) were included in the study. The mean age of the study population was 62.75 years, with a predominant male representation (male:female ratio =20:1), reflecting the gender distribution commonly observed in bladder cancer demographics.

Table 1: Demographic status of patients.

Total patients (N)	**60**
Mean age	62.75 years
M:F ratio	20:1
Intermediate risk	46.6%
High risk	53.4%
Mean exposure	32.27 weeks

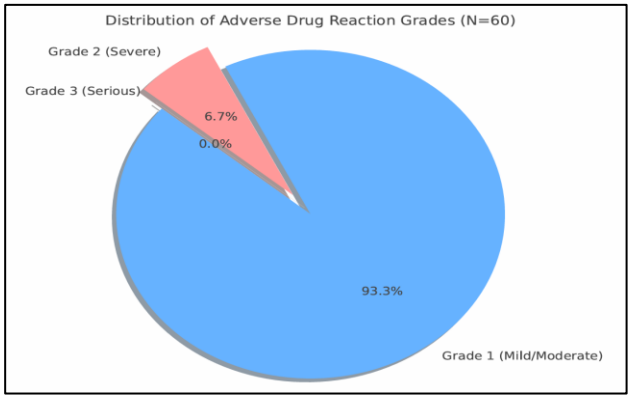

Figure 2: Distribution of adverse drug reaction grades (n=60).

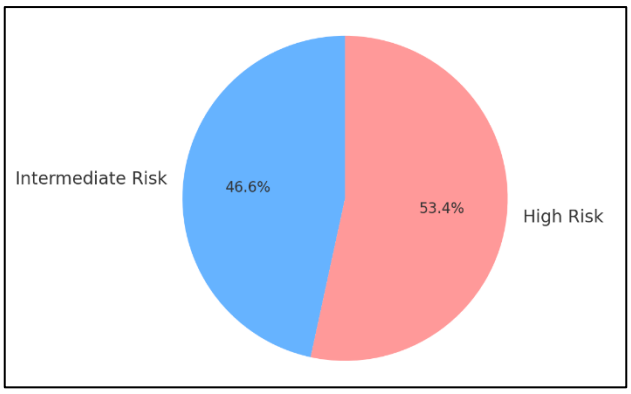

Figure 3: Risk group distribution among patients.

As per the EAU risk stratification, 46.6% (n=28) of patients belonged to the intermediate-risk group, while 53.4% (n=32) were classified as high-risk. All patients received intravesical Onco-BCG therapy (Moscow strain, 80 mg) according to the prescribed induction and maintenance protocol. The mean duration of BCG exposure was 32.27 weeks.

During follow-up, patients were assessed for adverse drug reactions (ADRs). Based on the Cleveland Clinic toxicity grading system, ADRs were documented and categorized as follows: moderate, severe, serious, as given in Annexure 1.

The frequency and severity of ADRs correlated with the duration of therapy and patient risk group, with a relatively higher incidence of moderate to severe ADRs observed in the high-risk group, likely due to longer exposure and repeated instillations.

Distribution of Adverse drug reactions by severity grade among NMIBC patients (n=60)

Grade 1 symptoms (mild/moderate, <48 hours): 93.4% of 60 patients =56 patients. Grade 2 symptoms (severe or lasting >48 hours): 6.6% of 60 patients =4 patients. Grade 3 symptoms (serious complications): 0 patients (none were observed).

DISCUSSION

Intravesical Bacillus Calmette-Guérin (BCG) immunotherapy continues to be the cornerstone in the treatment of intermediate- and high-risk non-muscle-invasive bladder cancer (NMIBC), offering substantial benefits in reducing tumor recurrence and progression.[3] Despite its widespread use, BCG therapy is associated with a broad spectrum of adverse drug reactions (ADRs), ranging from mild localized symptoms to severe systemic manifestations. The present retrospective analysis aimed to assess the ADR profile associated with the Moscow strain of Onco-BCG, which is now predominantly used in India following the unavailability of the Danish 1331 strain.[4]

Among the 60 patients enrolled in our study, 93.4% experienced grade 1 ADRs, while 6.6% reported grade 2 symptoms. Notably, no grade 3 complications were observed. These findings are consistent with prior research conducted by Thyavihally et al, who reported a significantly higher incidence of ADRs with the Moscow strain (67.4%) compared to the Danish 1331 strain (48.5%).[4] While our study reflects a lower overall incidence of moderate-to-severe toxicity, this could be attributed to differences in patient characteristics, improved clinical monitoring, or regional variation in strain handling.

Genetic divergence among BCG strains is one of the key factors influencing immunogenicity and tolerability. The Moscow strain belongs to the "early" group of BCG strains, whereas the Danish 1331 is a "late" strain.[5] Early strains retain more genetic elements such as RD1, which may contribute to heightened immune responses and possibly more side effects. Additionally, variations in colony-forming unit (CFU) counts due to batch, manufacturer, and strain differences can significantly influence clinical outcomes.[6]

In India, the standard dose for intravesical BCG instillation is 120 mg. However, multiple studies have investigated the potential for dose reduction without compromising efficacy. Kamat et al first reported on the use of the Danish 1331 strain in Indian patients using a 120 mg dose, but subsequent analysis suggested that even lower doses (40-80 mg) could be sufficient based on CFU content.[7] A 2017 meta-analysis by Quan et al reinforced the importance of considering dose and strain variability in optimizing BCG therapy.[8]

Notably, two Indian randomized trials- by Vijjan et al and Agrawal et al explored dose de-escalation using the Danish 1331 strain. Vijjan et al demonstrated that patients receiving 40 mg had similar outcomes in terms of recurrence and progression compared to those on 80 mg and 120 mg, but with significantly fewer side effects.[9] Agrawal et al, who also included maintenance therapy in their study design, confirmed these findings, showing that the 40 mg dose resulted in lower toxicity while maintaining comparable efficacy.[10] Although our study did not explore multiple dosing regimens, these findings support the potential benefit of dose reduction, especially for patients prone to ADRs.

Despite its retrospective nature and inherent limitations such as possible recall bias and incomplete documentation, our study offers important insights into the safety profile of the Moscow strain in real-world Indian settings. The uniformity of clinical protocols and a mean treatment exposure of 32.27 weeks enhance the reliability of our findings.

In conclusion, our study reinforces the tolerability of the Moscow strain of Onco-BCG in intermediate- and high-risk NMIBC patients. The predominance of mild adverse effects supports its continued use; however, further prospective studies are essential to evaluate the efficacy and safety of strain-specific and dose-adjusted BCG regimens in the Indian population.

CONCLUSION

This study supports the safety and tolerability of intravesical Onco-BCG therapy using the Moscow strain in patients with intermediate- and high-risk NMIBC. Although no severe complications were observed, the occurrence of low-to-moderate ADRs emphasizes the importance of routine monitoring. There is an urgent need to strengthen pharmacovigilance efforts, educate patients on possible adverse effects, and explore adjusted dosing strategies to enhance the therapeutic balance of BCG treatment in the Indian clinical context.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee vide letter no. HFW-HDRPGMC/Ethics/2024/007 IEC no.IEC/146/2023

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Cite this article as: Sharma I, Sharma K, Sood A. Study of adverse drug reaction of intravesical onco-BCG in Non-muscle-invasive bladder cancer: a retrospective study. Int J Basic Clin Pharmacol 2025;14:833-8.

ANNEXURE 1

Table 1: Cleveland clinic approach to management of BCG toxicity

Cleveland clinic approach to management of BCG toxicity	
Grade 1 Moderate Symptoms <48 hours	Mild or moderate irritative voiding symptoms, mild hematureia, fever <38.5 degree C
Grade 2 Severe symptoms and/or >48 hours	Severe irritative voiding symptoms, hematuria or symptoms lasting >48 hours.
Grade 3 Serious complications	Hemodynamic changes, persistent high grade fever. Allergic reactions, joint pain, rash solid organ involvement (epididymis, liver, lung, kidney, bone, joints, prostate)

ANNEXURE 2

Case recording form

Name:

Age:

Sex:

C.R No.:

Contact number:

Contact number of attendant/Care taker:

Address:

Risk stratification of non muscle invasive bladder cancer- Intermediate risk/High risk

History of present illness:

Medication:

Past history:

Personal history:

Family history:

History of drug allergy: