



## Management of lower urinary tract symptoms during intravesical BCG therapy

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### **Introduction:**

Intravesical immunotherapy with Bacillus Calmette-Guerin (BCG) is commonly used as an adjuvant treatment following transurethral resection of high-risk non-muscle invasive bladder cancer (NMIBC). The completion of treatment maintenance schedules can often require a maximum of three years. Patients successfully complete the entire 3-year BCG maintenance, experience significant advantages, including a 27% decrease progression and a 32% reduction in recurrence risk as compared to intravesical treatment with mitomycin.[1]

However, a mere 16% of patients manage to complete the entire 36-month regimen of instillations. This is primarily due to adverse effects of BCG that manifest locally and systemically.[1]

### **Intravesical BCG Adverse Effects**

Adverse effects can be categorized into two types: local and systemic side effects. BCG cystitis is the most prevalent local side effect, affecting 75% of patients. It is characterized by frequency, urgency, and haematuria. It occurs even in the absence of a confirmed urinary tract infection.[2] Typically, it resolves on its own within 48 hours[3] . However, about 20 % of patients continue to have severe symptoms leading to discontinuation of treatment course[4].

### **How Intravesical BCG works**

The precise mechanism by which intravesical BCG influences bladder cancer cells remains largely unknown; however, it is certain that urothelial cells and the immune system are involved[5]. Upon internalization of BCG by the urothelium, several cytokines as IFN- $\gamma$ , IL-2, and IL-12 and chemokines as No and H<sub>2</sub>O<sub>2</sub> are secreted[6, 7]. These substances collaborate with immune cells, such as macrophages, granulocytes, lymphocytes, and natural killer cells, to induce direct cytotoxicity that kills bladder cancer cells.[7, 8]

**How to reduce BCG side effects**

Different strategies have been proposed to decrease BCG side effects:

a. *Prophylactic Measures:*

The International Bladder Cancer Group's (IBCG) recommends not administer BCG until at least two weeks have passed since a TURBT to permit the bladder mucosa to re-epithelialize.

Also, instruct healthcare personnel in the correct methods of catheterization to avoid urothelial injury.

Additionally, Urologists must be aware if there is gross haematuria, they must postpone the administration of BCG until it has been resolved.[9]

b. *Pharmacological methods:*

Many oral and intravesical medications have been used to alleviate Intravesical BCG cystitis.

I. Intravesical medications:

1. *Local instillation therapy:*

Local instillation therapy represents a viable option for treatment of various oncological and non-oncological bladder disorders diseases.[10]

For BCG cystitis, Topazio et al. investigated the value of intravesical instillation of a mixture of Tetracaine hydrochloride, six methylprednisolone, nitrofurantoin and distilled water. They reported that 94 % of patients experienced relief of symptoms[11]. Despite, the small number of patient tested, this solution could be used when other alternative treatments fail.

II. Oral medications:

a. Non-steroidals(NSAIDS):

There is a notion that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) like aspirin can impair the effectiveness of intravenous BCG as it could interfere with the fibrin-mediated binding of BCG, which in turn reduces the effectiveness of the intravenous BCG. However, Boorjian et al, did not find a decrease in the efficacy of BCG when compared to individuals who did not consume NSAIDs[12].

b. Anticholenergics:

Many anticholinergic medications have been used for treatment of BCG side effects. This includes: oxybutynin, tolterodine and Solifenacin. However, no drug was proved to be superior to another one. On the other hand, Johnson et al, indicated that the use of the anticholinergic oxybutynin was associated with worse outcome than placebo in form of increased fever, frequency and dysuria[13]. Till date, there is no specific recommendation on which drug to be used.

c. Pentosan Polysulphate(PPS):

It is a heparin analogue that enhances the glycosaminoglycan (GAG) layer which overlie the urothelium. Yadav et al, reported that oral dose of 100mg PPS three times a day was associated with marked improvement of in patients symptoms. Furthermore, an experimental study showed that PPS was associated with an enhanced immunological response suggesting an additional oncological benefit[14].

## d. Quinolone Antibiotics:

Many quinolone antibiotics were tested to evaluate their efficacy for management of BCG cystitis. Ofloxacin was investigated for its efficacy in decreasing BCG side effects and it showed promising results[3]. Moreover, levofloxacin was proved to improve BCG cystitis symptoms[15]. However, their effect on the long term oncological outcome is uncertain.

**Conclusion**

BCG cystitis is a major health concern for patients receiving intravesical BCG therapy for NMIBC and its responsible for a large percent of BCG discontinuation. Many management strategies are available, however non of them showed superiority or long term effects. Further studies are needed to explore new options for this emerging dilemma.

**References**

1. Babjuk, M., et al., *European Association of Urology guidelines on non-muscle-invasive bladder cancer (Ta, T1, and carcinoma in situ)*. 2022. **81**(1): p. 75-94.
2. Brausi, M., et al., *Side effects of Bacillus Calmette-Guerin (BCG) in the treatment of intermediate-and high-risk Ta, T1 papillary carcinoma of the bladder: results of the EORTC genito-urinary cancers group randomised phase 3 study comparing one-third dose with full dose and 1 year with 3 years of maintenance BCG*. 2014. **65**(1): p. 69-76.
3. Colombel, M., et al., *The effect of ofloxacin on bacillus calmette-guerin induced toxicity in patients with superficial bladder cancer: results of a randomized, prospective, double-blind, placebo controlled, multicenter study*. 2006. **176**(3): p. 935-939.
4. Sylvester, R.J., et al., *Long-term efficacy results of EORTC genito-urinary group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, bacillus Calmette-Guerin, and bacillus Calmette-Guerin plus isoniazid in patients with intermediate-and high-risk stage Ta T1 urothelial carcinoma of the bladder*. 2010. **57**(5): p. 766-773.
5. Rischmann, P., et al., *BCG intravesical instillations: recommendations for side-effects management*. 1999. **37**(Suppl. 1): p. 33-36.
6. Kawai, K., et al., *Bacillus Calmette-Guerin (BCG) immunotherapy for bladder cancer: Current understanding and perspectives on engineered BCG vaccine*. 2013. **104**(1): p. 22-27.
7. Shah, G., et al. *iNOS expression and NO production contribute to the direct effects of BCG on urothelial carcinoma cell biology*. in *Urologic Oncology: Seminars and Original Investigations*. 2014. Elsevier.
8. Shah, G., et al., *H<sub>2</sub>O<sub>2</sub> generation by BCG induces the cellular oxidative stress response required for BCG's direct effects on urothelial carcinoma tumor biology*. 2014. **192**(4): p. 1238.
9. Andius, P., M. Fehrling, and S.J.B.i. Holmäng, *Intravesical bacillus Calmette-Guèrin therapy: experience with a reduced dwell-time in patients with pronounced side-effects*. 2005. **96**(9): p. 1290-1293.
10. El Hefnawy, A.S., et al., *Intravesical instillation of platelet rich plasma for treatment of interstitial cystitis/bladder pain syndrome: A pilot study*. 2022: p. 10.1097.
11. Topazio, L., et al., *Could hyaluronic acid (HA) reduce Bacillus Calmette-Guèrin (BCG) local side effects? Results of a pilot study*. 2014. **14**: p. 1-6.
12. Boorjian, S.A., et al., *Fibrin clot inhibitor medication and efficacy of bacillus Calmette-Guerin for bladder urothelial cancer*. 2009. **182**(4): p. 1306-1312.

13. Johnson, M.H., et al., *Randomized controlled trial of oxybutynin extended release versus placebo for urinary symptoms during intravesical Bacillus Calmette-Guerin treatment*. 2013. **189**(4): p. 1268-1274.
14. Yadav, S., et al., *Role of oral pentosan polysulphate in the reduction of local side effects of BCG therapy in patients with non-muscle-invasive bladder cancer: a pilot study*. 2016. **118**(5): p. 758-762.
15. Numakura, K., et al., *Effect of Levofloxacin on the Efficacy and Adverse Events in Intravesical Bacillus Calmette-Guerin Treatment for Bladder Cancer: Results of a Randomized, Prospective, Multicenter Study*. 2022. **8**(6): p. 1666-1672.