

# THE SIDE EFFECTS OF THE ADJUVANT INSTILLATIONAL TREATMENT WITH BCG FOR NON-MUSCLE INVASIVE BLADDER CANCER

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**Abstract:** *In addition to the benefits it confers intravesical immunotherapy with BCG, a negative aspect of this treatment is the side effects. They can be local or systemic, minor or major. This article is aimed at evaluating the frequency and severity of complications of adjuvant therapy with BCG for non-muscle invasive bladder cancer.*

**Key words:** *non-muscle invasive bladder cancer, side effects.*

## 1. Introduction

Treatment of non-muscle invasive bladder cancer by transurethral resection (TURBT) is followed by the appearance of tumor recurrence or progression in many cases. The low absorption capacity of the bladder, and relatively easy access into the endovesical cavity, was the triggering factor in the development of adjuvant instillational therapy, and it will become a key component in the treatment of non-muscle invasive tumors, having a role in reducing tumor recurrence and progression.

The most common substances used for endovesical instillational are chemotherapy (epirubicin, doxorubicin, mitomycin C, gemcitabine, Valrubicin, EOquin<sup>TM</sup>, taxanes) and Bacillus Calmette-Guérin (BCG) [6, 8, 10, 12].

The basis of immunotherapy is, firstly,

that the immune system is extremely important in the mechanism of recognition and elimination of tumor cells. It seems that tumor cells have the ability to escape immune recognition (as their survival mechanism), but may become liable by modulating the immune system. BCG is a suspension containing live attenuated bacteria. Instillational BCG therapy in bladder tumors in humans was founded in 1976 by A. Morales, and collaborators, having a strong impact. At this point, treatment with BCG is considered the most successful of all immunotherapy treatment applied to humans. With all the advances made in laboratory techniques and immunology, the way that the BCG exercises antitumor activity is not yet well known [1, 2, 6]. Numerous surveys conducted recently have shown multiple benefits, local and systemic from the

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immunological point of view after treatment with BCG, the most important being the antitumor effects mediated by T cells [6, 9, 10].

Table 1

CLASS I A GENERAL SYMPTOMS	CLASS II A GENERAL SYMPTOMS	CLASS III A GENERAL SYMPTOMS	CLASS IV
Flu syndrome >2h and 48h, Fever T $\geq$ 38 <sup>0</sup> C and <38,5 <sup>0</sup> C Muscular pain Asthenia  <b>CLASS I B</b> <b>LOCAL SIGNS</b> >12h and <48h Cystitis Nocturnal frequency > 2 and < 5 episodes /night Diurnal frequency > 6 and < 20 episodes/day Mictional imperiosity <G3 Grade 1 = Minim or moderate Grade 2 = Severe, but without urine loss Grade 3 = Severe, with uncontrolled urine loss Haematuria <G3 Grade 1 = without clots Grade 2 = with clots Grade 3 = obstruction or transfusion Uncontrolled loss of urine at the end of micturition<G3 Uncontrolled loss of urine at effort<G3 Dysuria <G3	Flu syndrome G1 or G2 $\geq$ from 48 hours and $\geq$ 7 days Fever T $\geq$ from 38,5 <sup>0</sup> C < 48 hours $\geq$ from 39,5 <sup>0</sup> C < 12 hours Muscular pain = G3 Asthenia = G3 Artralgias Grade 1 = Minor Grade 2 = Moderate Grade 3 = Severe  <b>CLASS I B</b> <b>LOCAL SIGNS</b> G1 or G2 ~ from 48 hours < 7 days with clinical severe signs ~G3 Cystitis Nocturnal frequency $\geq$ 5 episodes/night Diurnal frequency $\geq$ 20 episodes/day Haematuria = G3 Uncontrolled loss of urine at the end of micturition = G3 Uncontrolled loss of urine at effort = G3 Dysuria = G3	<ul style="list-style-type: none"> <li>• Flu syndrome <math>\geq</math>7days</li> <li>• Fever T <math>\geq</math>39,5<sup>0</sup>C &gt; 12 hours <math>\geq</math>38,5<sup>0</sup>C &gt; 48 hours</li> <li>✓ Alergic reaction</li> <li>Grade 1 = edema</li> <li>Grade 2 = bronchospasm</li> <li>Grade 3 = bronchospasm that regres with oral treatment</li> <li>Grade 4 = anaphylactic shock</li> <li>✓ Skin rash</li> <li>Grade 1 = erythema</li> <li>Grade 2 = dry desquamation, vesiculas</li> <li>Grade 3 = desquamation and ulceration</li> <li>Grade 4 = exfoliative dermatitis with skin necrosis</li> <li>✓ Arthritis</li> <li>✓ Uveitis, iridociclitis</li> </ul> <b>CLASS III B</b> <b>LOCAL SIGNS</b> <ul style="list-style-type: none"> <li>• Cystitis <math>\geq</math>7 days</li> </ul>	<ul style="list-style-type: none"> <li>• Cardiovascular collapse</li> <li>• Respiratory depression</li> <li>• CIVD</li> <li>• Hepatitis</li> <li>Grade 1 – Transaminases: 1,2-2,5 x N</li> <li>Grade 2 – Transaminases: 2,6-5 x N</li> <li>Grade 3 – Transaminases: 5,1-10 x N</li> <li>Grade 4 – Transaminases: 10 x N</li> <li>• Septicemia:               <ul style="list-style-type: none"> <li>- miliaris</li> <li>- vascular infection</li> <li>- prosthesis infection</li> </ul> </li> </ul>
REGIONAL SIGNS	REGIONAL SIGNS	REGIONAL SIGNS	
Isolate suprapubic pain<G3 Isolate renal pain <G3 Perianal pain <G3 Constipation <G3	<ul style="list-style-type: none"> <li>▪ Isolate suprapubic pain = G3</li> <li>▪ Isolate renal pain = G3</li> <li>▪ Perianal pain = G3</li> <li>▪ Constipation = G3</li> </ul>	<ul style="list-style-type: none"> <li>• Prostatitis</li> <li>• Epididymitis</li> <li>• Orchitis</li> <li>• Renal abscess</li> <li>• Urethral stenosis</li> </ul>	

There are many strains of BCG, all derived from the originally strain of Pasteur Institute, produced by different companies with very small differences in the concentrations of colony forming units and antitumor effects.

In addition to the benefits of intravesical immunotherapy confers as evidenced by numerous meta-analysis, a negative aspect (maybe the only) is the side effects of BCG. They are quite common, which prompted some clinicians to be reluctant to use BCG. It is estimated however that the vast majority of side effects can be treated successfully (even very serious ones) and that the rate of severe complications is quite low (less than 5% of cases). It was also found that adverse reactions frequency increases during BCG therapy [3, 4, 5, 7, 9, 12, 13].

Side effects can be classified into local and systemic adverse reactions. According to World Health Organization, these are resumed in the table above [12].

## 2. Purpose

The purpose of this study was to evaluate the side effects of adjuvant instillational treatment with BCG, used to prevent relapses and progression of non-muscle invasive bladder cancer.

## 3. Material and Method

We conducted a study during 2006-2010 in the Clinic of Urology Brasov where we seized a total of 53 patients diagnosed with non-muscle invasive bladder cancer (by transurethral resection of bladder tumors), who received instillational treatment postoperative (adjuvant) with BCG. Age of patients was between 42 and 74 years and distribution of patients according to sex showed a predominance of men (ratio 2.2/1).

Patients have been evaluated every 3

months during the first year, every 6 months of the second and third year and once per year afterwards with abdominal echography, urethrocytostcopy and suplimentary tests depending on the situation.

## 4. Results

After analyzing the data reported by patients treated with adjuvant instillational BCG, we could highlight the numerous side effects, but the vast majority of low intensity:

### 1. General and local side effects of Class I

- Class I A:
  - fever between 38 and 38.5°C and chills: 23 patients (43.39%)
  - minor muscle pain: 8 patients (15.09%)

Most of these patients has not necessitated any treatment, but occasionally, some patients have taken aspirin or paracetamol. Symptoms occurred 2-6 hours after instillation and disappeared within 24 hours.

- Class I B:
  - night and daytime urinary frequency: 42 patients (79.24%)
  - dysuria: 39 patients (73.58%)
  - minimum mictional imperiosity: 18 patients (33.96%)
  - macroscopic haematuria with mild intensity: 41 patients (77.35%)
  - isolated suprapubic pain, minor: 6 patients (11.32%)
  - isolated perianal pain, minor: 2 patients (3.77%)

Most did not require medication. Isolated cases where anti-inflammatory drugs were administered (diclofenac 100 mg, especially in the form of suppositories, or 200 or 400 mg ibuprofen) or minor analgesics. Side effects occurred at 2-4 hours after instillation and were resolved in 12-48 hours.

### 2. General and local side effects of Class II:

- Class II B:
  - fever over 38.5°C (less than 48 hours) or above 39.5°C (less than 12 hours): 2 patients (3.77%). Urine culture was performed to rule out a possible urinary tract infection and they received antibiotic treatment, anti-inflammatory and painkiller drugs, with subsequent disappearance of symptoms.
- Class II B:
  - large suprapubic pain: 1 patient (1.88%). Symptoms disappeared after administration of anti-inflammatory form of suppositories (diclofenac 100 mg), antispasmodic and antibiotic.
  - high intensity perianal pain: 1 patient (1.88%). Symptoms disappeared after administration of anti-inflammatory (suppositories) and antibiotics
  - increased urinary frequency and dysuria lasting more than 48 hours: 3 patients (5.66%). The symptoms disappeared after administration of antibiotic medication, anti-inflammatory and anticholinergic.

In all these cases urine culture was performed to rule out a possible urinary infection.
- 3. General and local side effects of Class III:
  - Class III A:
    - fever above 38.5°C (more than 48 hours) or above 39.5 ° C (more than 12 hours): one patient (1.88%). Because the symptoms did not yield to anti inflammatory drugs, antipyretics and fluoroquinolone (ofloxacin 400 mg), the patient was guided to the Pneumoftiziologie Department, where he received treatment for tuberculosis and the symptoms disappear. This patient discontinued BCG treatment and epirubicin therapy was performed.
  - skin redness with different locations: one patient. She presented erythematous plaques with different sizes located in different parts of the body, and not accompanied by itching or other symptoms. The onset of erythematous plaques was 2-3 hours post instillation and lasted about 10-12 days. The side effect doesn't occurred in the first instillations made, but from the 8th month of treatment. Did not require specific treatment and disappeared spontaneously after a maximum of 12 days.
- Class III B:
  - persistent cystitis (more than 7-8 days after instillation): 1 patient (1.88%). The patient experienced these events after the first 4 instillations during the second course of BCG (for tumor recurrence). Symptoms were not resolved after anti-inflammatory and antibiotic treatment and she was guided to the Pneumoftiziologie Department, where he treated for tuberculosis (BCG was discontinued). Current, patient is without tumor recurrence, but had developed a sarcoma of the thigh (without regard to endovesical instillations with BCG).
  - acute epididymitis: 2 patients (3.77%). In one case, the antibiotic and anti-inflammatory treatment was sufficient to reverse the signs and symptoms. In the second case epididymectomy was required.
  - stricture of the urethra: 3 patients (5.55%). Have been solved by making internal optical urethrotomy.
  - histopathologically confirmed granulomatous prostatitis (by puncture biopsy): 1 patient (1.88%). Symptomatology was resolved by antibiotics and anti-inflammatory drugs.

No side effects were registered in class IV.



Fig. 1. *Erythematous-violaceous lesions, slightly infiltrated, edema, round-oval shape, diameter and location range*



Fig. 2. *Erythematous-violaceous lesions, slightly infiltrated, edema, round-oval shape, diameter and location range*



Fig. 3. *Erythematous-violaceous lesions, slightly infiltrated, edema, round-oval shape, diameter and location range*

## 5. Discussion

The first thing that attracts attention after exposure of these data is that instillational adjuvant treatment with BCG is accompanied by relatively frequent side effects. However, side effects that have occurred have been easily treated and most of them have brought particular problems to patients. From this point of view, comparing the frequency of side effects with the benefits of this treatment, in terms of relapse rate and tumor progression, most patients can move easily over the unpleasant events. Two patients did not receive complete treatment due to side effects of the instillational BCG.

We tried a careful observation of any differences between different strains of BCG used, in terms of frequency or severity of side effects. We found only minor differences, as reported side effects in patients who were treated with different strains. The emergence of possible side effects can thus be explained less by the type of strain used, is particularly important status of specific and nonspecific immune response of the patient. In terms of favorable response rate to treatment we found no differences regardless of the strain used for instillation.

It is obvious that, before start the treatment, a severe BCG infection should be considered. Traumatic instillation may facilitate BCG-induced septicaemia, with possible septic shock and possibly death. Before each instillation with BCG we should exclude bacterial urinary tract infection, because bladder inflammation may increase risk of haematologic dissemination. If during therapy with BCG a urinary tract infection is diagnosed, treatment should be discontinued until normalization of urinalysis and antibiotic treatment completion [9, 10, 11, 14].

There are studies showing that the side effects of immunotherapy are the main cause of treatment withdrawal, but the same authors argue that an education in making the correct instillations, prevention of side effects and open and honest communication

between doctor and patient, should be the key to the compliance of patients for this treatment [10].

## 6. Conclusions

Adjuvant instillational treatment with BCG, although shows clear benefits in reducing relapse rate and progression of non-muscle invasive bladder tumors, it is accompanied by numerous side effects. However, they are in most cases, local side effects, light and easy to treat. Treatment can be performed successfully and with minimal side effects by strictly respecting the terms of the instillational protocols, a fair and honest communication of the urologist with the patient regarding the possible occurrence of side effects, the treatment of their potential dangers and the major benefits BCG therapy.

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