# Intravesical sequential bacillus Calmette-Guérin (BCG)/Electromotive Drug Administration (EMDA®-Mitomycin) in patients with high-risk non-muscle-invasive bladder cancer: a prospective observational study

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# 1. Introduction

## Background

Bladder cancer is the sixth most commonly diagnosed cancer in the male population worldwide.

Risk factors for bladder cancer are tobacco smoking and occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons, and chlorinated hydrocarbons. (1).

Approximately 75%-80% of new bladder cancer cases present as non- muscle invasive bladder cancer. (2,4)

NMIBC comprises a heterogeneous group of patients with pathological stages: Ta (non-invasive tumours limited to mucosa), Cis (high grade flat tumours confined to the epithelium), and T1 (tumours invading lamina propria). (2,4)

NMIBC is characterised by a high risk of recurrence and a significant risk of progression to muscle-invasive disease after diagnosis. Standard therapy for NMIBC consists of the complete transurethral resection of all visible bladder tumours (TURBT), usually followed by an intravesical treatment with immunotherapy (e.g., BCG) or chemotherapy (e.g., Mitomycin).

TURBT is a crucial procedure in the diagnosis of NMIBC, in reducing the risk of recurrence and in the choice of the right clinical treatment. (3)

Risk groups (low-, intermediate- and high risk) have been developed to accurately predict recurrence and progression risk and to determine the best therapeutic management.

## Adjuvant therapy of high-risk NMIBC

Complete eradication of bladder tumour by careful transurethral resection (TURBT) is an important initial step in reducing the risk of recurrence. (3) Eradication may be enhanced by single immediate instillation of chemotherapeutic agent, which results in death of circulating and residual tumour cells after TURBT. For low-risk disease, TUR-BT followed by a single immediate instillation is considered sufficient treatment.

TURBT and a single immediate instillation is less effective against high grade and does not reduce the risk of progression, which is a major concern in high-risk NMIBC. Thus, TURBT and a single immediate instillation is inadequate in the optimal management of high-risk disease and further adjuvant therapy should be initiated. (4)

## BCG Treatment

Intravesical instillation of BCG results in multiple immunological reactions. BCG is attached and internalized in the urothelial cells and bladder cancer cells via binding of fibronectin on the surface molecules of mycobacterium bovis inducing inflammation and production of interleukines and interferones. (5-8) By cytokine secretion, macrophages, cytotoxic T-lymphocytes, natural killer cells (NKs) and neutrophils are recruited, with these cells involved in the cell mediated antitumour effect of BCG. (9-12)

BCG treatment includes an induction period of 6 weekly instillations followed by a maintenance period of 1-3 years. Currently, maintenance schedule introduced by Southwest Oncology Group (SWOG) applying three weekly maintenance instillations at 3 and 6 months, and every 6 months up to 3 years, is referred to as “the gold standard” and recommended by Guidelines. (4,13) However, treatment withdrawals are common due to toxicity or treatment failure, as in the SWOG trial only 16 % of patients in the maintenance arm were able to receive all intended instillations. In addition, maintenance therapy beyond 1 year is associated with further decrease in the risk of recurrence but not of progression or improvement of survival. (14) Although BCG treatment is considered generally safe, 40-71 % of patients suffer from local side effects such as cystitis, hematuria and urinary frequency. (15) Side effects usually resolve spontaneously and may be eased with anti-inflammatory medication. However, occurrence of side effects may result in discontinuation of treatment in approximately 7-49 % of patients. (14,15) Actual BCG-induced infectious complications are rare (0.1 % - 2.9 % of treated patients). (15) They may present with local infections of genitourinary tract such as epididymitis or mycobacterial cystitis, but occasionally as disseminated infections such as spondylitis, hepatitis, miliary tuberculosis and mycobacterial sepsis. (15,16)

BCG treatment is effective in preventing recurrence of NMIBC. However, a considerably large proportion of patients experience treatment failure. Approximately 33-44 % of patients receiving BCG experience recurrence and approximately 10% may develop muscle invasive disease.

## Intravesical chemotherapy

Due to the inferior efficacy in reducing recurrences in high-risk patients and lack of efficacy in reducing the risk of progression, intravesical chemotherapy as monotherapy is suboptimal in management of high-risk NMIBC. (17,18,19) Furthermore, passively administered intravesical Mytomicin has been demonstrated to penetrate poorly in subepithelial tissues underlying the lamina propria in ex vivo bladder model, which may be suggestive for inadequate effect against T1 tumours. (20) However, providing a better side-effect profile, intravesical chemotherapy is considered a feasible option in the treatment of patients with high risk of recurrence and low risk of progression (i.e., recurrent, multiple or large low-grade tumours). (21) Mitomycin is the most studied intravesical chemotherapeutic agent. (18) Mitomycin is an antibiotic, alkylating chemotherapeutic agent, which inhibits DNA synthesis. Most often Mitomycin treatment includes an induction course of 4-6 weekly instillations followed by maintenance therapy up to 1-3 years. (17) The absorption of Mitomycin may be increased by optimization of the conditions in the bladder during the instillation: reduction of urine production during treatment by voluntary dehydration and alkalinization of the urine to reduce the degradation of Mytomicin.

Alternating Mitomycin and BCG instillation therapy is the most studied intravesical combination treatment regimen in NMIBC.

## Device-assisted therapies

As NMIBC incidence has increased in several countries and availability of BCG has become an issue, it is essential to search for new more effective therapeutic options or strategies to improve the efficacy of existing drugs and to potentially preserve the patient's bladder. There is currently a growing interest in device-assisted techniques: the aim is improving the intravesical administration of chemotherapeutic agents and therefore increasing their effectiveness. The enhancement of the effect of the drug through device-assisted is a practice consolidated by the Guidelines.

## EMDA® ElectroMotive Drug Administration

Electrootive Drug Administration (EMDA®) is a method that combines intravesical chemotherapy with electric field conducted to the bladder. The mechanism of EMDA® in increasing the transportation of Mitomycin into the bladder wall is a phenomenon called electro-osmosis, also referred to as "solvent drag". (22)

Electro-osmosis is developed in the bladder as current of positive polarity is applied to intravesically administered solution containing $Na^+$, $Cl^-$ ions and Mytomicin

molecules. That results in iontophoretic migration of $Na^+$ ions covered by water molecules as well as free water influx into the underlying tissues, which creates osmotic drag (electro-osmosis) of non-ionized Mitomycin molecules into the bladder wall.

Di Stasi et al has been extensively studying EMDA- Mitomycin treatment. In 1999, Di Stasi demonstrated 4-7 times increased concentrations of Mitomycin in deeper layers of the bladder wall induced by electro- osmosis in ex vivo model. (20)

Intravesical EMDA®-Mitomycin is administered using a battery-powered generator to deliver a controlled electric current. The electrical current passes between the intravesical active electrode at the tip of a catheter to a dispersive ground electrode positioned on the lower abdomen. The specialized 16-Fr catheter is inserted, and the bladder is washed with water, then 40 mg Mitomycin in 100 ml is instilled with the operating current maintained at 23 mA pulsed electrical current. Treatment time is 20 minutes per session.

**Sequential BCG/EMDA® -Mytomicin therapy**

BCG may work synergistic in favor of Mitomycin by increasing the permeability of bladder mucosa and increasing the absorption of Mitomycin. In addition, Mitomycin might attack the cells refractory to BCG.

According to this hypothesis, Di Stasi et al conducted a RCT allocating 212 high-risk NMIBC patients to receive either BCG instillations followed by sequential EMDA®-Mitomycin instillations or conventional BCG monotherapy with 6 weekly instillations followed by monthly instillations up to 1 year. (23) The exceptionally good results demonstrated a 48-month longer disease-free interval (69 mo. vs. 21 mo., p=0,0012), 12.6 % lower risk of progression (9.3 % vs. 21.9 %, p=0,0047) and 10.9% higher overall survival rate (78.5 % vs. 67.6 %, p=0,045) in the sequential BCG/EMDA®- Mitomycin arm. Side effect profiles were similar, and treatment was terminated due to side effects in 3 % in both arms.

More recently, Gan et al reported results of single arm trial evaluating the effectiveness of sequential EMDA®- Mitomycin and BCG treatment in high-risk patients aiming to replicate the BCG/EMDA®- Mitomycin treatment arm demonstrated by Di Stasi et al. (24) The results were similar with 24 % risk of recurrence and 4,6 % risk of progression during the 2 years of follow up supporting the evidence by original BCG/EMDA®- Mitomycin trial.

A recent study (March 2019) conducted by researchers at Guy's Hospital in London (25) showed that sequential therapy (Mitomycin administered with EMDA® in combination with BCG) is twice as effective as standard monotherapy with BCG

alone: more than two-thirds of patients treated with sequential therapy were relapse-free for all 54 months of follow-up.

Sequential BCG/EMDA®- Mitomycin treatment is the first treatment regimen to succeed in demonstrating its superiority over BCG monotherapy in terms of recurrence, progression and survival.

## 2. Rational of the current study

High-risk BC is initially treated with TURBT and single perioperative instillation of intravesical chemotherapy. As there is the high-risk of recurrence and progression, adjuvant treatment with BCG is recommended. BCG treatment includes induction period (typically 6 instillations) followed by maintenance for at least one year.

BCG treatment has some challenges and limitations, e.g., treatment associated side-effects, lack of efficacy in some patients and also recently there have been global difficulties in obtaining BCG and in particular high-quality BCG.

Di Stasi et al, Gan et al, demonstrated the superiority of sequential BCG/EMDA®-Mytomicin in treatment of high-risk BC in terms of risk of recurrence and progression and confirmatory studies are important.

## 3. Endpoint of the study

The objective of the study is to demostrate the efficacy of sequential BCG/EMDA®-Mitomycin in preventing recurrences in patients with high-risk NMIBC.

Specifically, the objectives include the following:

**Primary objectives**

To determine the rate of treatment success (% of Complete Response) in patients who undergo BCG/EMDA®-Mitomycin three months after treatment.

Complete response (CR) rate defined as an absence of any tumor following chemoresection and will be assessed visually at 3- month check cystoscopy by patients' urologists.

**Secondary objectives**

To evaluate tolerability of BCG/EMDA®-Mitomycin.

For tolerability, treatment cessation will be recorded.

# 4. Patient selection

**Inclusion criteria**

The following criteria are needed for the patient to be eligible for inclusion in the study:

Histologically proven non-muscle-invasive tumour types confined to the urinary bladder:

1. Primary, multifocal
2. Ta, T1 HG
3. G2 HG
4. Any G3
5. Expected survival times more than two years

**Exclusion criteria**

1. Ta low grade tumour(s)
2. Carcinoma in situ with or without a papillary tumour(s)
3. Muscle invasive (pT≥2) tumors
4. Urothelial cancer involving the prostatic urethra or upper urinary tract
5. Non-urothelial bladder cancer
6. Prior BCG failure
7. Prior or concurrent immunotherapy
8. Known allergy or intolerance to Mitomycin or BCG and any medication or condition considered as contraindication to BCG or Mytomicin (as judged by the treating physician)
9. Urethral stricture, stone disease, chronic urinary tract infection or any other urological condition that may comprise study participation (as judged by the treating physician)
10. Bladder capacity less than 200 ml
11. Cardiac pacemaker or another active implantable medical device

12. Severe systemic infections (sepsis)
13. Age < 18 years
14. Pregnancy or lactating patient
15. Perforation of the urinary bladder wall after intraperitoneal surgery
16. Expected survival time less than two year
17. Other untreated or unstable malignancy in risk of recurrence/progression (as judged by the treating physician)
18. Expected poor compliance

## 5. Study design

The study is a prospective observational study on 10 patients with the aim to demonstrate the efficacy of BCG/EMDA®-Mitomycin in the preventing recurrent of high-risk NMIBC patients and to corroborate previously obtained results regarding the tolerability of the EMDA®- Mytomicin treatment.

Within 2-4 weeks after the endoscopic resection start the induction therapy: Electromotive Administration of Mitomycin (EMDA®-Mitomycin) is given sequentially with BCG instillations. The induction therapy includes weekly BCG and EMDA®-Mitomycin instillations (BCG, BCG and EMDA®- Mitomycin x three times) up to 9 weeks.

INDUCTION CYCLE

| WEEK | TREATMENT |
|---|---|
| 1° | BCG |
| 2° | BCG |
| 3° | EMDA®/ Mitomycin |
| 4° | BCG |
| 5° | BCG |
| 6° | EMDA®/ Mitomycin |
| 7° | BCG |
| 8° | BCG |
| 9° | EMDA®/ Mitomycin |

## 6. Treatment and follow-up

**TURBT**

Standard TURBT with the equipment used in normal clinical practice.

## Screening for eligibility

Screening for eligibility is performed as soon as the pathology report from TURBT is received. Adjuvant instillations should be initiated as soon as possible after TURBT (within 2-3 weeks after TURBT)

## BCG instillations

BCG instillations are administered according to normal clinical practice by the instructions provided by the manufacturer.

One BCG instillation includes approximately 2 x 10^8 - 3 x 10^9 colony form units of live, attenuated mycobacterium bovis BCG dissolved in 50 ml of saline, which is infused intravesically in the bladder via catheter and retained for 2 hours.

## EMDA®-Mitomycin instillations

The Electromotive Administration of Mitomycin (EMDA®-Mitomycin) is given sequentially with BCG instillations. The induction therapy includes weekly BCG and EMDA-MMC instillations (BCG, BCG and EMDA®-Mitomycin x three times) up to 9 weeks. It is followed by maintenance therapy with monthly BCG and EMDA-Mitomycin instillations (EMDA®-Mitomycin, EMDA®-Mitomycin and BCG x three times) up to 9 months.

EMDA®-Mitomycin treatment instruction

1. Urine is alkalized by instructing the patient to take 2 gr of sodium bicarbonate dissolved in 30 ml of water the night before instillation and two hours before the treatment. The patient is also instructed to minimize the amount of liquids and to avoid coffee, tea and alcohol from the night before the treatment.
2. Have the patient lie comfortably supine: do not place in lithotomy position.
3. Test the catheter-balloon twice at 5 ml with air before catheterisation, following the instructions for use of the CE-DAS® UROGENICS®.
4. Insert the CE-DAS® UROGENICS® into the bladder by using conventional gel lubricants preferably lidocaine based, water soluble and inflate balloon at 3 ml with air.
5. Wet the 2 dispersive electrodes with saline solution 0.9% or tap water. Spread an abundant layer of conductive ecg gel of 1-1.5 cm thickness on the chosen area on the sides of the navel. Spread a 1 cm layer on each of the electrodes (including corners). The gel must be evenly distributed, paying attention that there are no uncovered parts of the skin in this area. Do not press the gel. Place the electrodes on the sides of the navel, one on the right and one on the left, over the layer of gel that has been spread, taking care not to press the electrodes.

6. After flushing with distilled sterile water and draining the bladder, instil the drug solution into the bladder: 40 mg of Mytomicin diluted in 100 ml bidistilled water if the excipient is sodium chloride or in 100 ml of sodium chloride if the excipient is urea or mannitol
7. Connect the red wire of the PHYSIONIZER® to the catheter CE-DAS® UROGENICS® and the black wire to the dispersive electrodes. Follow the instructions of the PHYSIONIZER® and set all values as indicated: (current strenght 23 mA/pulsed, rise-rate 40 μA/sec, polarity positive)
8. Push "START" to run the treatment
9. After 20 minutes, the PHYSIONIZER® signals the end of the treatment with a beep.
10. Bladder is emptied and catheter and electrodes are removed

**Follow-up**

Patients undergo 3 months follow-up. At the time of follow-up visit, cystoscopy and urine citology are performed.

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