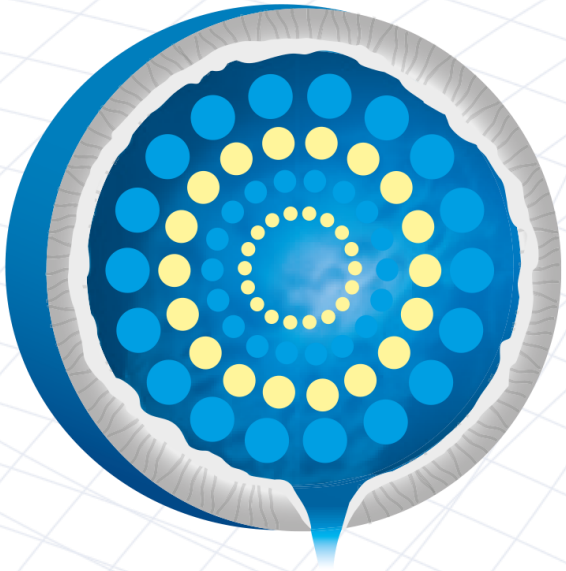


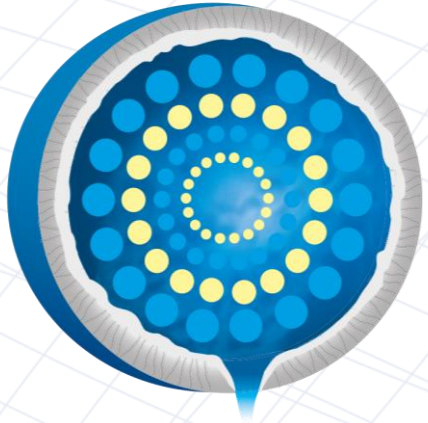
EMDA®

Electromotive Drug Administration

PHYSION®

What is EMDA?

EMDA is a device-assisted therapy that increases drug transport across biological membranes under the influence of an electric field.



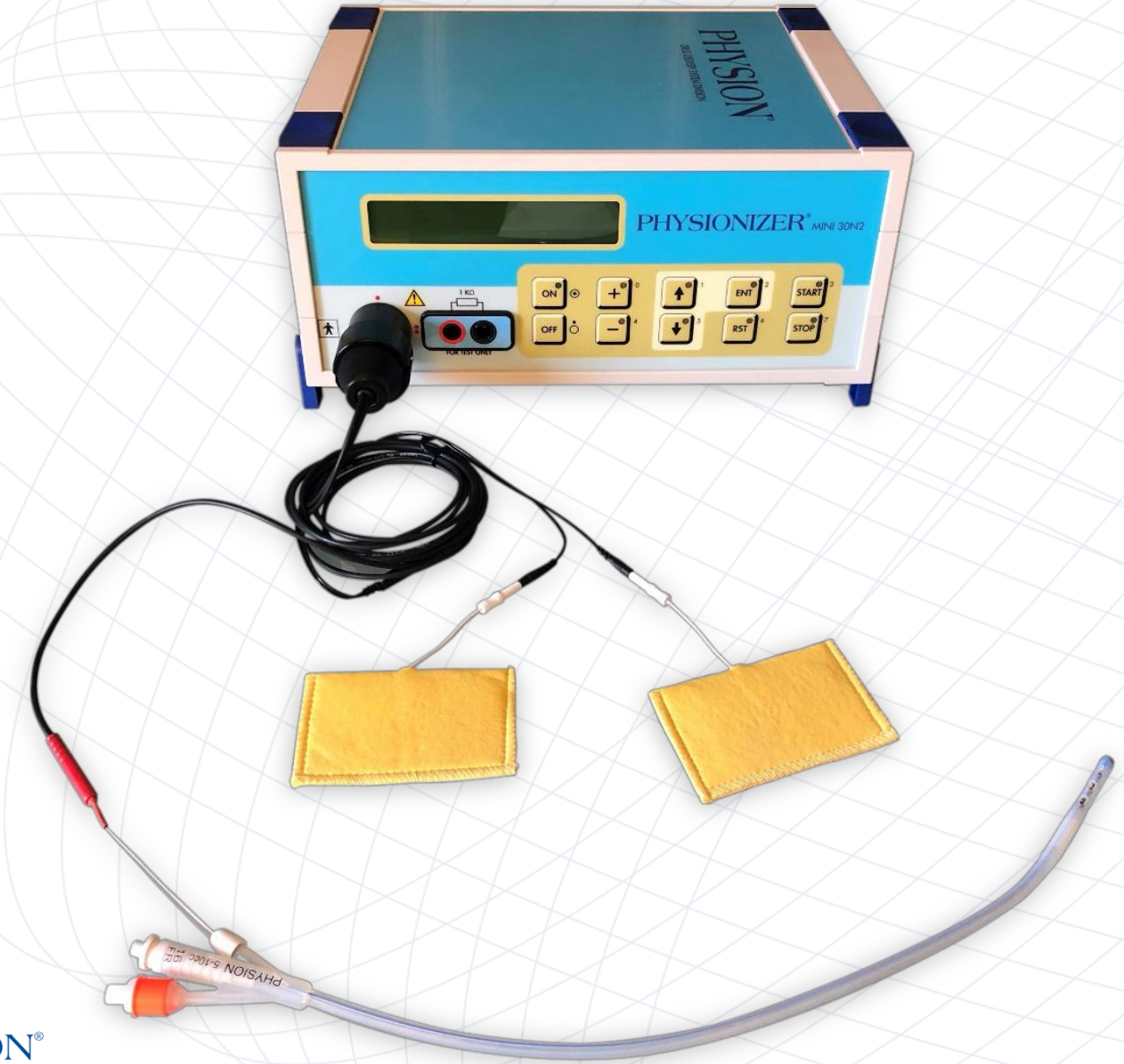
EMDA is characterized by a combination of different electromolecular interactions that **improves drug absorption from 4 to 7 times**:

- Iontophoresis
- Electrophoresis/Electrosmosis
- Electroporetion

The deeper drug penetration and the greater drug bioavailability result in an increased clinical effectiveness.

PHYSION®

Device Components



Micro-source current

Physionizer Mini 30N2, 12V battery operated current generator. Easy to use and reliable.

Active electrode

CE-DAS Urogenics silicone 16 F electrode-catheter placed in the bladder. Soft and easy to place.

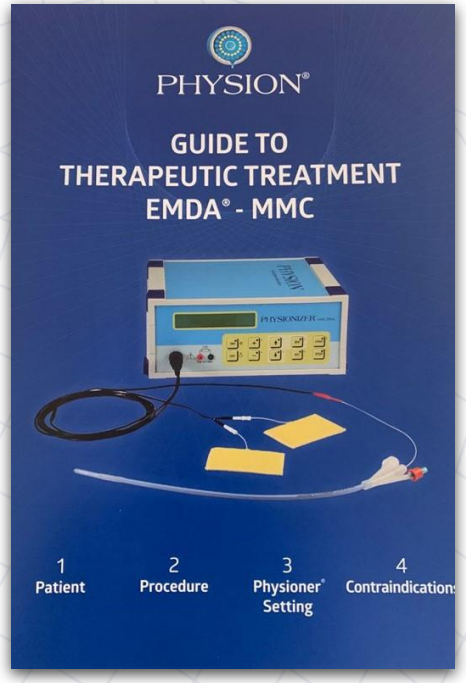
Dispersive electrode

Two dispersive sponge ground electrodes (cathode) placed on the skin of the abdomen to create a low-current circuit between the catheter tip (anode) and the current generator.

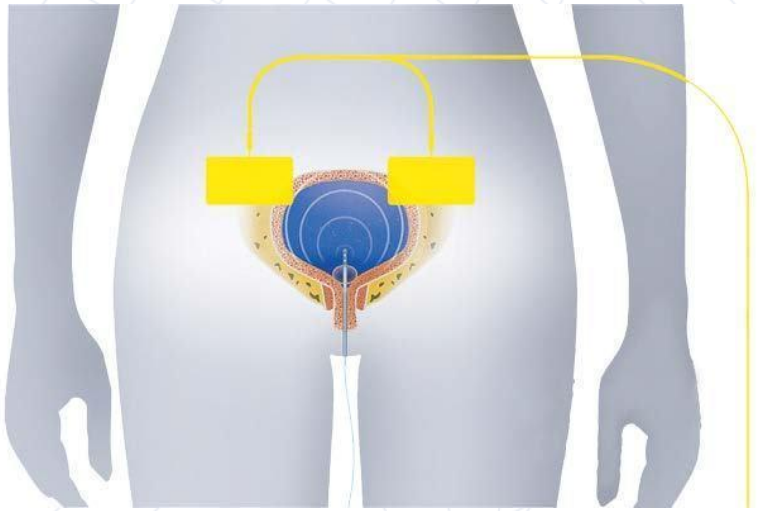
PHYSION®

EMDA IS EASY TO USE, SAFE AND THE TREATMENT IS QUICK

Treatment modality



- A urogenic 16F electrode-catheter is inserted into the bladder
- The bladder is drained to remove residual electrolytes
- The drug solution is administered
- Two dispersive electrodes are placed on the sides of the navel with an abundante layer of conductive gel
- A micro-current of 23 mA is applied for **20 minutes**



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EMDA FIELDS OF APPLICATION

- **URO-ONCOLOGY**

Non Muscle Invasive Bladder Cancer

- HIGH-RISK
- INTERMEDIATE RISK
- BCG FAILURE

- **FUNCTIONAL UROLOGY**

Interstitial Cystitis

Bladder pain

Recurrent Bacterial Cystitis

Overactive Bladder

Local Bladder Anesthesia

Peyronie Disease

PHYSION®

EMDA CAN BE USE WITH SEVERAL DRUGS

URO-ONCOLOGY

ALL TYPE OF MITOMYCIN

If the excipient is sodium chloride Mitomycin is diluted in 100 ml bidistilled water; if the excipient is urea or mannitol it is diluted in 100 ml sodium chloride 0.9%

MITOMYCIN COMBINED WITH BCG

Sequential administration of BCG and electromotive administration of Mitomycin in cases of high risk NMIBC

FUNCTIONAL UROLOGY

Dexamethasone	Scopolamine butylbromide	Epinephrine
Naropin	Lidocaine	Oxybutynin
Netilmicin	Gentamicin	Amikacin
Ialuronic Acid	Verapamil	Bethanecol
	Botulinum Toxin	

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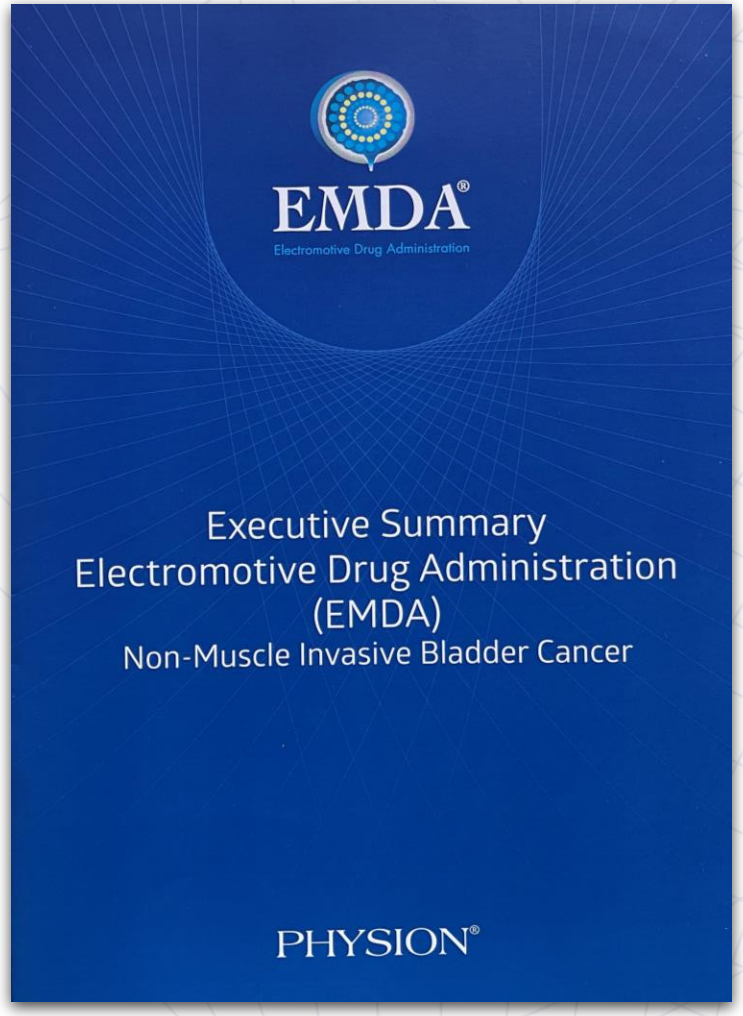
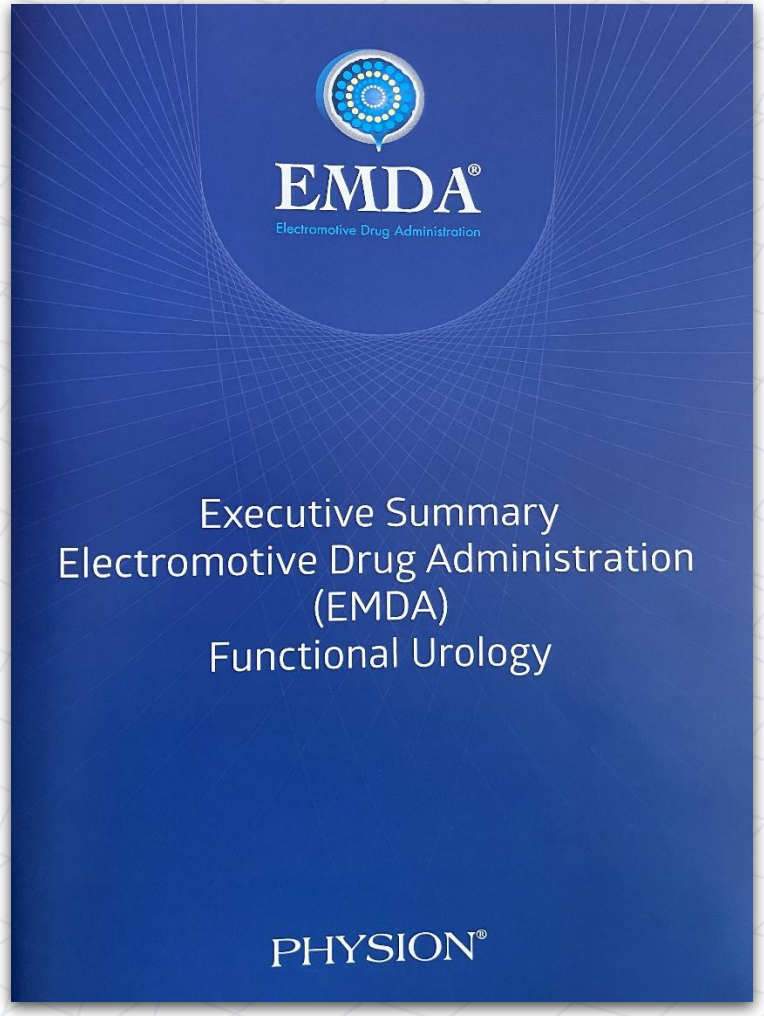
Clinical Trials Executive Summary





To join the EMDA community users gives the possibility to open up new lines of research and to publish research data

PHYSION®

EMDA FOR NON MUSCLE INVASIVE BLADDER CANCER

HIGH RISK

- T1
- G3
- Ta G1-G2 > 3 cm + multiple +recurrent
- CIS (primary or T1G3 associated)

Protocol: Sequential Treatment
BCG + EMDA-MMC

Twice as efficace as «golden standard» BCG monoterapy to reduce recurrence and progression

INTERMEDIATE RISK

- Ta-T1 G2 > 3 + unifocal
- Ta-T1 G2 multifocal + primary
- Ta G1 multifocal + recurrent

Protocol: Intermediate risk
8 EMDA-MMC instillations

EMDA reduces recurence rate almost twice as much as passive diffusion

BCG FAILURE

- BCG Failure
- BCG Intolerance

Protocol: BCG Failure
6 EMDA-MMC instillations

At 3 years follow up 61,5 % avoid cystectomy

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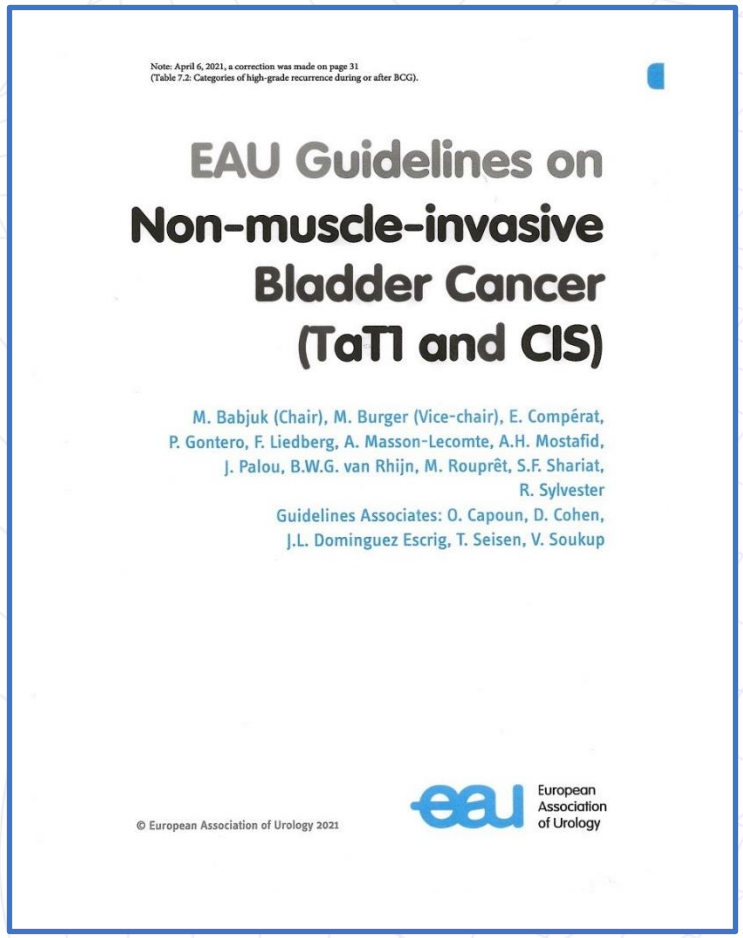
EAU Guidelines NMIBC 2021



7.2.1.3 Options to improving efficacy of intravesical chemotherapy

7.2.1.3.2 Device- assisted intravesical chemotherapy

Electromotive Drug Administration

«The efficacy of MMC using EMDA sequentially combined with BCG in patients with high-risk tumours has been demostrated in one small RCT *(Di Stasi, 2006)*» page 25

7.2.3 Combination therapy

7.2.3.1. Intravesical BCG + chemotherapy vs BCG alone

«In a RCT *(Di Stasi, 2006)* using MMC with EMDA, a combination of BCG and MMC with EMDA showed an improved recurrence-free interval and reduced progression rate compared to BCG monotherapy» page 28

7.4.3 Treatment of BCG unresponsive tumours and patients with BCG intolerance

«Currently, several bladder preservations strategies are being investigated such…device assisted instillations *(Racioppi, 2018)*» page 31

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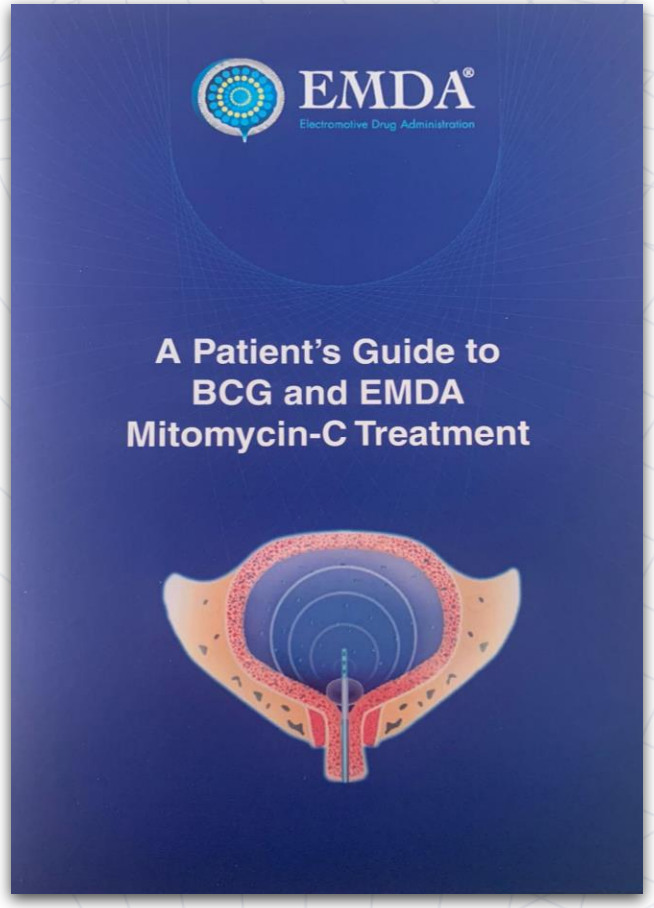
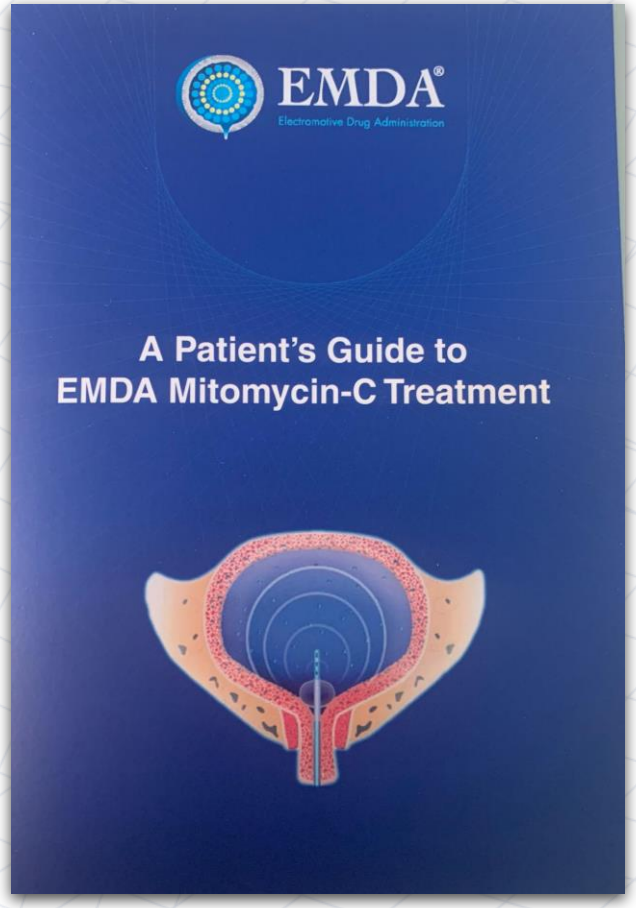
Patient Support Guidebooks

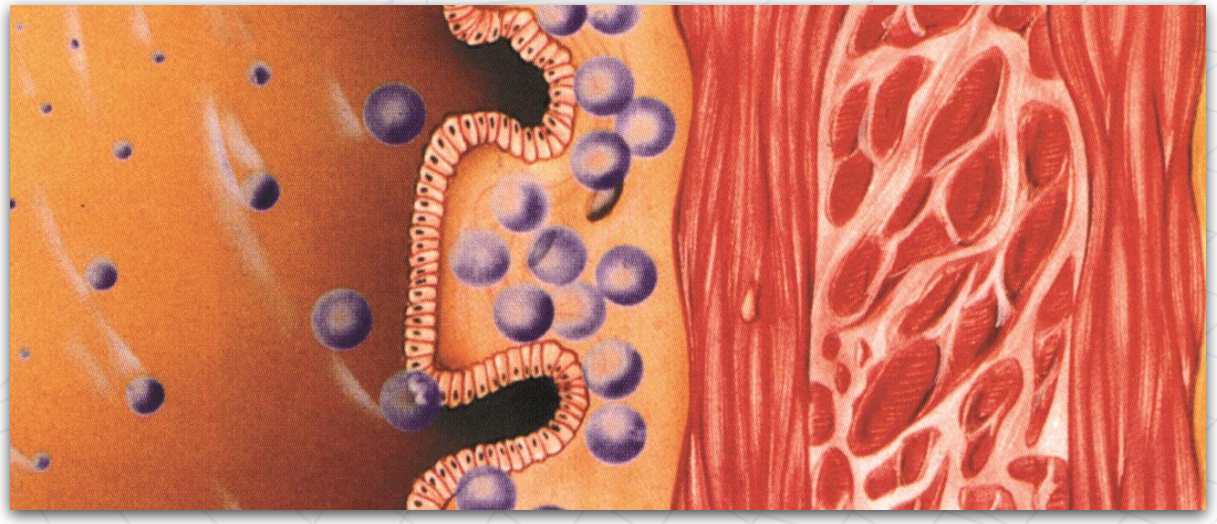




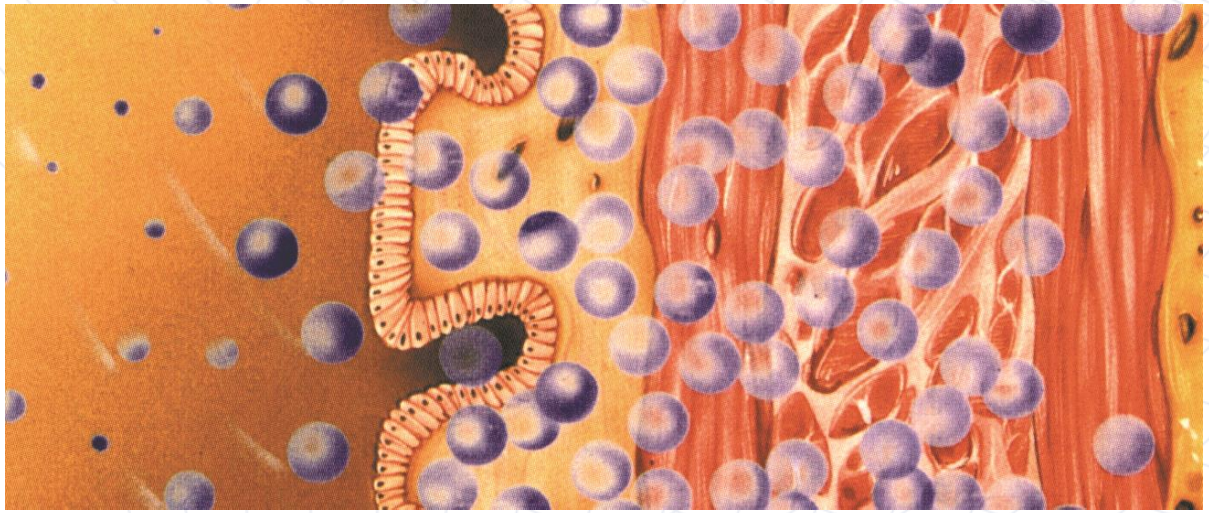
Recognizing the imperative to center on the patient, we designed these Guides so that patients and their families are active participants in the experience of care, improving their knowledge and awereness of treatment.

PHYSION®

EMDA versus Passive Diffusion

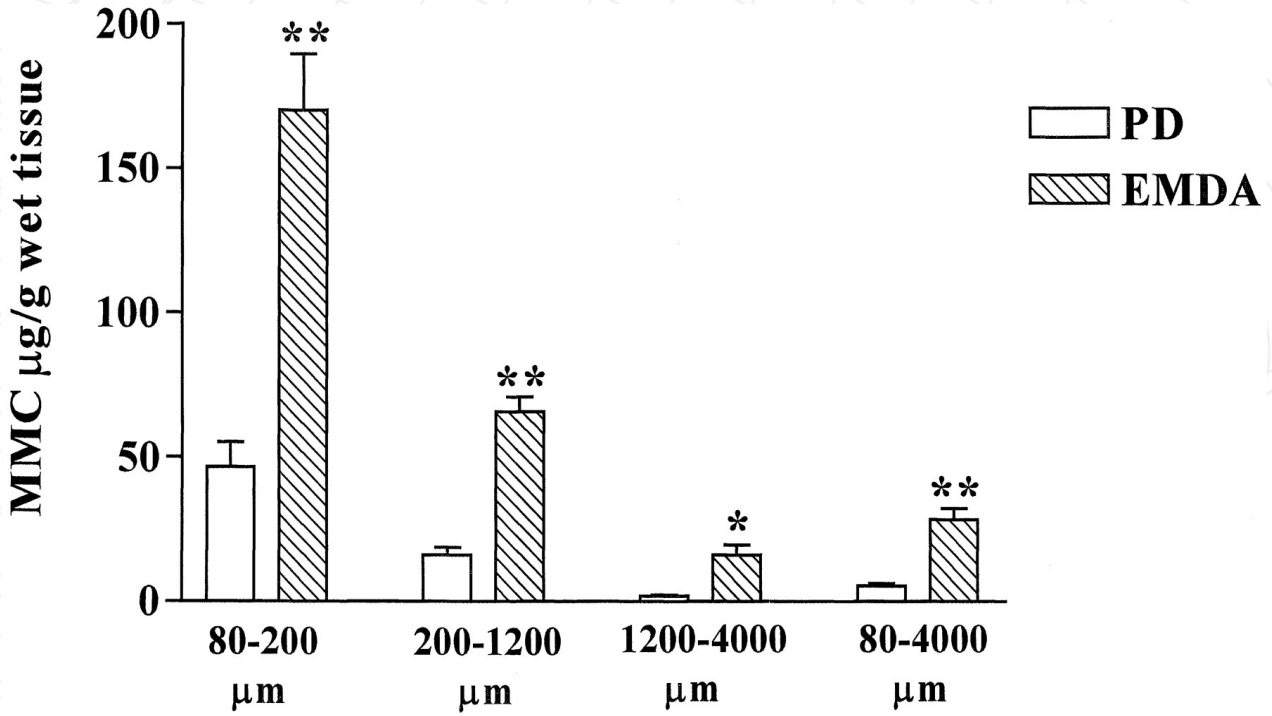


PASSIVE DIFFUSION



EMDA ENHANCED

With EMDA, MMC concentration is increased from 4 to 7 times and plasma levels remains well below toxic levels.



Di Stasi et al, Cancer Research 1999

PHYSION®

EMDA versus Passive Diffusion

Section	Administration	Concentration	Results
Urothelium P<0.0001	Passive diffusion	46,6	3.7
	EMDA	170.0	
Lamina propria P<0.0001	Passive diffusion	16.1	4.1
	EMDA	65.6	
Muscularis P<0.0001	Passive diffusion	1.9	8.4
	EMDA	15.9	

EMDA significantly enhances MMC transport into all of the layers of the bladder wall.

The applied electric current causes no biological damage to tissue and no chemical modification of drug.

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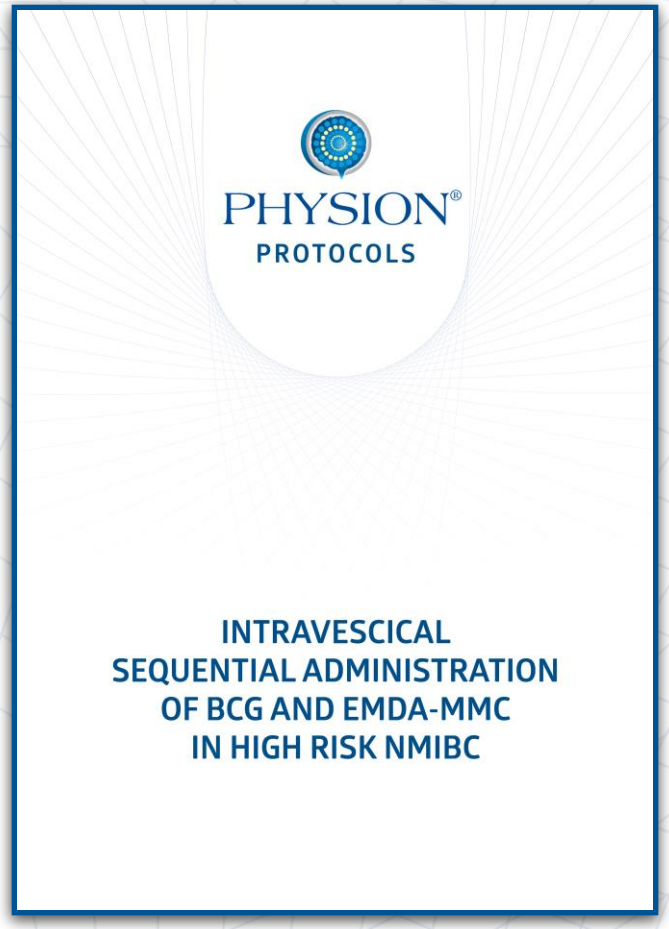
Di Stasi et al, Cancer Research 1999

Treatment of High-risk NMIBC alternative to BCG alone: Sequential treatment BCG + EMDA-MMC



The rationale to combining immunotherapeutic and chemiotherapeutic drugs is based on the need to increase efficacy and reduce emergence of resistant malignant cells: BCG-induced inflammation makes the bladder mucosa more permeable so that mitomycin reaches the target tissue more easily.

The number of BCG doses is the same as monotherapy: 6 BCG doses.

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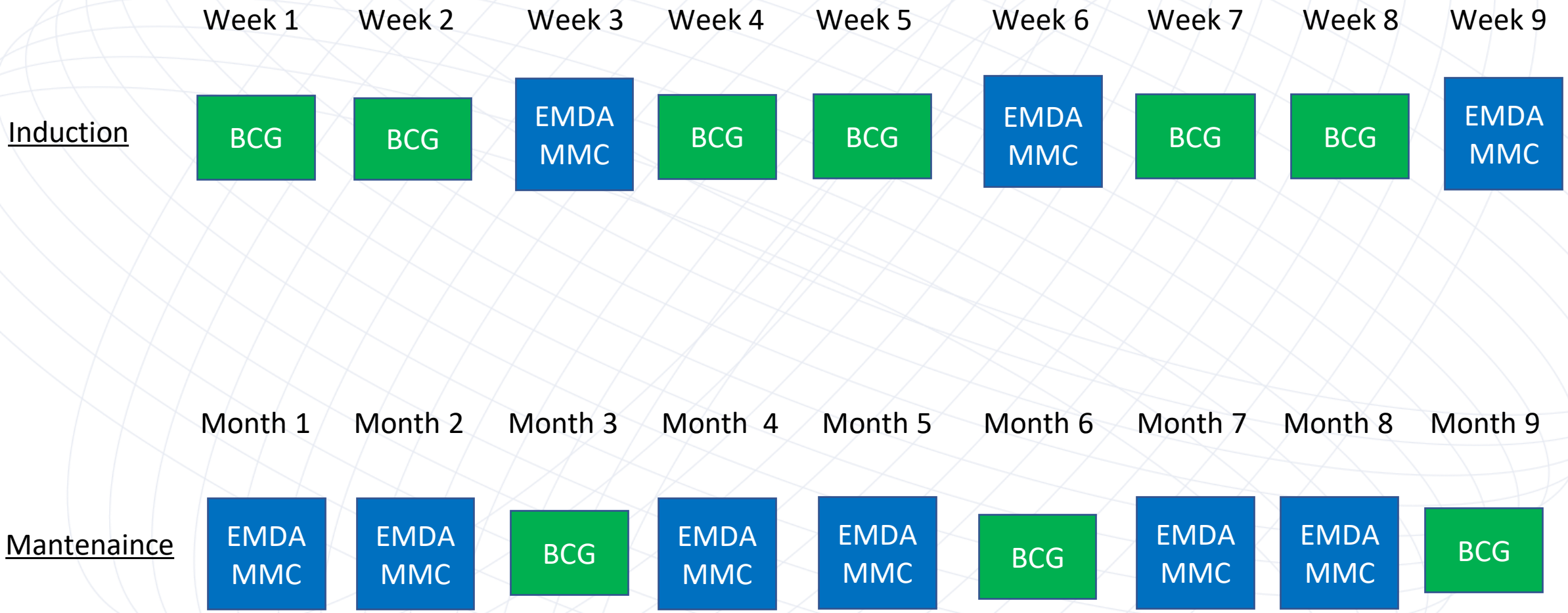
Treatment protocol



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Clinical Studies

Articles

Sequential BCG and electromotive mitomycin versus BCG alone for high-risk superficial bladder cancer: a randomised controlled trial

Savino M Di Stasi, Antonella Giannantoni, Arcangelo Giurioli, Marco Valenti, Germano Zampa, Luigi Storti, Francesco Attisani, Andrea De Carolis, Giovanni Capelli, Giuseppe Vespasiani, Robert L Stephen*

Summary

Background The rationale for combining anticancer drugs has not been applied consistently to use of intravesical agents for treatment of superficial bladder cancer, for which immunotherapeutic BCG and chemotherapeutic mitomycin seem to be a potentially effective combination. We aimed to do a prospective, randomised comparison of BCG alone with that of sequential BCG and electromotive mitomycin in patients with stage pT1 bladder cancer.

Methods After transurethral resection and multiple biopsies, 212 patients with stage pT1 bladder cancer were randomly assigned to: 81 mg BCG infused over 120 min once a week for 6 weeks (n=105); or to 81 mg BCG infused over 120 min once a week for 2 weeks, followed by 40 mg electromotive mitomycin (intravesical electric current 20 mA for 30 min) once a week as one cycle for three cycles (n=107). Complete responders underwent maintenance treatment: those assigned BCG alone had one infusion of 81 mg BCG once a month for 10 months, and those assigned BCG and mitomycin had 40 mg electromotive mitomycin once a month for 2 months, followed by 81 mg BCG once a month as one cycle for three cycles. The primary endpoint was disease-free interval; secondary endpoints were time to progression; overall survival; and disease-specific survival. Analyses were done by intention to treat. This trial has been submitted for registration at the US National Cancer Institute website http://clinicaltrials.gov.

Findings Median follow-up was 88 months (IQR 63–110). Patients assigned sequential BCG and electromotive mitomycin had higher disease-free interval than did those assigned BCG alone (69 months [95% CI 55–86] *vs* 21 months [15–54]; difference between groups 48 months [42–54], log-rank p=0·0012). Patients assigned sequential BCG and electromotive mitomycin also had lower recurrence (41·9% [32·7–51·5] *vs* 57·9% [48·7–67·5]; difference between groups 16·0% [2·7–29·3], log-rank p=0·0012); progression (9·3% [3·8–14·8] *vs* 21·9% [17·9–25·9]; difference between groups 12·6% [3·0–22·2], log-rank p=0·004); overall mortality (21·5% [13·5–29·5] *vs* 32·4% [23·4–41·4], difference between groups 10·9% [0·6–21·2], log-rank p=0·045); and disease-specific mortality (5·6% [1·2–10·0] *vs* 16·2% [6·1–23·3], difference between groups 10·6% [2·5–18·7], log-rank p=0·01). Side-effects were mainly localised to the bladder.

Interpretation BCG-induced inflammation might increase the permeability of the bladder mucosa such that mitomycin can reach the target tissue more easily and exert its anticancer effect.

Lancet Oncol 2006; 7: 43–51
Published online December 16, 2005
DOI: 10.1016/S1470-2045(05)70472-1

See Reflection and Reaction page 6

*R L Stephen died in July, 2004
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Correspondence to: Prof Savino M Di Stasi, Via Torrice n 4, 00186 Rome, Italy
sdistas@tin.it

Introduction

Intravesical treatment for superficial bladder cancer has been used for the past 4–5 decades. Most early reports of such treatment were anecdotal, and the effects were not clarified until the early to mid 1990s.[1] Intravesical chemotherapy is beneficial in terms of frequency of recurrence and time to recurrence in grade 1–2 stage Ta tumours, which are usually non-invasive. By contrast, intravesical chemotherapy has negligible effect on disease progression in high-risk superficial bladder cancer—ie, grade 3, stage T1, and carcinoma in situ. However, BCG as induction and maintenance treatment effectively delays progression.[2]

Mitomycin for treatment of bladder cancer has been studied widely, with various doses, concentrations, infusion volumes, and residence times in the bladder—usually in non-selected groups of patients. Studies[3,4] have recorded an incomplete and variable clinical response to intravesical mitomycin, partly as a result of the insensitivity of highly malignant tumours and inadequate drug delivery to tumour cells. Wientjes and colleagues[4] combined data for laboratory, animal, and human studies with those from computer simulations to derive a mitomycin regimen that would keep diffusion down concentration gradients to an optimum (ie, **Fick's first law of diffusion**). In a phase III trial,[3] patients with stage Ta grade 1–2 bladder cancer who were allocated this regimen (40 mg mitomycin, pharmacokinetic manipulation to increase drug concentration by decreasing urine volume, and urine alkalinisation to stabilise the drug) had better time to recurrence and less recurrence than did those with the same stage and grade of cancer allocated standard treatment (20 mg mitomycin). However, data for patients with carcinoma in situ, stage T1, or grade 3 disease were less definitive, although a trend of improved time to recurrence was noted.[3]

Fick's first law of diffusion
The rate of diffusion or transport of a drug across a biological membrane is directly proportional to the surface area of the membrane and to the concentration gradient, and is inversely proportional to the thickness of the membrane.

(*) 81 mg BCG x 2hrs 1/wks x 6 wks

Di Stasi et al, Lancet Oncology 2006

- Prospective, randomized, multicenter comparative study
- 221 pts with primary or recurrent T1G2 (all multifocal) +/- Cis or T1G3 (unifocal or multifocal) +/- Cis randomised in 2 group:
  - Control Group: 105 pts → BCG standard monotherapy (*)
  - Group EMDA/MMC: 107 pts → cycle BCG+BCG+EMDA-MMC repeated 3 times for a total of 9 weekly treatment
- Complete responders underwent maintenance treatment
  - Control Group → BCG 1/months x 10 months
  - Group EMDA/MMC → cycle EMDA-MMC+EMDA-MMC+BCG repeated 3 times for a total of 9 monthly treatment
- Follow-up (median): 88 months

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	DISEASE-FREE INTERVAL (months)	RECURRENCE RATE	PROGRESSION RATE	OVERALL MORTALITY	DISEASE-SPECIFIC MORTALITY
BCG	21	57.9 %	21.9 %	32.4 %	16.2 %
BCG + EMDA-MMC	69	41.9 %	9.3 %	21.5 %	5.6 %

The sequential administration of BCG and MMC with EMDA determined a lower RR, a longer DFI and a reduced PR compared to BCG alone. This translated in better OAM and DSM rate compared to BCG alone

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Subgroups T1HG(G3) + CIS results

T1G3 + Tis	BCG	BCG-EMDA/MMC
RECURRANCE RATE	68.3 %	50 %
DISEASE-FREE INTERVAL (months)	11	53
PROGRESSION RATE	41.5 %	16.7 %
OVERALL MORTALITY	53.7 %	23.8 %
DISEASE SPECIFIC MORTALITY	36.6 %	11.9 %

There was a statitistically significant difference in favour of the sequential therapy BCG+EMDA-MMC in RR, DFI, PR, OAM, DSM in this subgroup.

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LANCET Oncology 2006; 7(1):43-51	BCG (%) (n=105)	Seq BCG and EMDA mitomycin C (%) (n=107)
Dysuria	51 (48.5%)	54 (50.5%)
Bacterial cystitis	14 (13.3%)	16 (14.9%)
Drug-induced cystitis	46 (43.8%)	49 (45.8%)
Macroscopic haematuria Prostatitis	61 (58.1%)	64 (59.8%)
Protatitis	1 (1%)	0
Fever	24 (22.8%)	21 (19.6%)
Influenza-like symptoms	34 (32.4%)	33 (30.8%)
Fatigue	32 (30.5%)	32 (29.9%)

Groups did not differ in the frequency and severity of side effects.
Toxic effects associated with BCG+EMDA-MMC are no worse than those associated with BCG alone and were mainly localised to the bladder.
3 pts stopped treatment in both groups.

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« Intravesical sequential bacillus Calmette-Guérin and electromotive MMC vs bacillus Calmette-Guérin alone for stage pT1 urothelium bladder cancer «
(Di Stasi AUA 2012)

	BCG-EMDA/MMC	BCG
DISEASE-FREE INTERVAL (months)	79	26
RECURRENCE RATE	45 %	62 %
PROGRESSION RATE	12 %	28 %
OVERALL MORTALITY	44 %	59 %
DISEASE SPECIFIC MORTALITY	9 %	23 %

A further follow-up (median) at 121 months was conducted.
BCG+EMDA-MMC provided better results than BCG alone in terms of higher response rate and longer remission time.

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Clinical Studies

Sequential bacillus Calmette-Guérin/Electromotive Drug Administration of Mitomycin C as the Standard Intravesical Regimen in High Risk Nonmuscle Invasive Bladder Cancer: 2-Year Outcomes

Christine Gan,* Suzanne Amery, Kathryn Chatterton, Muhammad Shamim Khan, Kay Thomas and Tim O'Brien

From the Urology Centre, Guy's and St. Thomas' National Health Service Trust, London, United Kingdom

Purpose: Sequential bacillus Calmette-Guérin/electromotive drug administration of mitomycin C is reported to be superior to bacillus Calmette-Guérin alone but it has not been widely adopted. We aimed to determine the efficacy and tolerability of sequential bacillus Calmette-Guérin/electromotive drug administration of mitomycin C in high risk, nonmuscle invasive bladder cancer.

Materials and Methods: Starting in 2009 bacillus Calmette-Guérin/electromotive drug administration of mitomycin C was introduced as the standard induction regime in patients with high risk, nonmuscle invasive bladder cancer undergoing bladder conservation. As induction bacillus Calmette-Guérin was administered in weeks 1 and 2. Mitomycin C was administered in electromotive fashion (40 mg and 20 mA current for 30 minutes) in week 3 and repeated thrice for a total of 9 weeks. As maintenance 3 doses of bacillus Calmette-Guérin were given 3 months after induction and then every 6 months for 3 years. Outcome measures were disease recurrence at first check, 1 and 2-year cystoscopy, and treatment tolerability.

Results: Of the 151 patients with high risk, nonmuscle invasive bladder cancer treated between June 2009 and 2013, 44 underwent primary cystectomy and 107 received sequential bacillus Calmette-Guérin/electromotive drug administration of mitomycin C. Disease was high grade Ta/T1 in 86 patients (80%), of whom 34 (32%) also had carcinoma in situ. A total of 19 patients (18%) had primary carcinoma in situ and 2 had recurrent large volume, low grade disease. Of 107 patients 104 underwent first check cystoscopy, including 90 (87%) who were clear. Of the 90 complete responders 86 underwent 1-year cystoscopy, including 74 (86%) who were recurrence-free. Of the 74 patients 71 underwent 2-year cystoscopy, of whom 66 (93%) remained recurrence-free. The full induction schedule was not completed in 30 patients (28%), including 16 and 14 with minor and major schedule alterations, respectively. There was no difference in recurrence between patients who received a full vs a reduced induction schedule.

Conclusions: This study confirms the excellent oncologic efficacy of sequential bacillus Calmette-Guérin/electromotive drug administration of mitomycin C in cases of high risk, nonmuscle invasive bladder cancer. Tolerability is a challenge but alterations to the 9-week schedule appeared to have a negligible impact on outcomes.

Abbreviations and Acronyms

BCG = bacillus Calmette-Guérin
CIS = carcinoma in situ
EMDA = electromotive drug administration
HR = high risk
MIBC = muscle invasive bladder cancer
MMC = mitomycin C
NMIBC = nonMIBC
PD = passive diffusion
TURBT = transurethral resection of bladder tumor

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The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

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For another article on a related topic see page 1903.

Key Words: urinary bladder neoplasms, Mycobacterium bovis, mitomycin, drug delivery systems, treatment outcome

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Vol. 195, 1697-1703, June 2016
Printed in U.S.A.

Gan, O'Brien et al, Journal of Urology 2016

- Prospective, cohort study
- 107 pts with HG NMIBC:
  - 86 pts Ta-T1 HG (80%) of whom 34 with CIS (32%)
  - 19 pts primary CIS (18%)
  - 2 pts recurrent, large volume, LG disease (2%)
- 9-week induction sequential treatment with the cycle BCG+BCG+EMDA-MMC ripeated 3 times for a total of 9 treatments.
- First check cistoscopy was performed in 104 pts
- Pts who were recurrence free proceded to maintenance treatment
- Tolerability: the full 9-week treatment was not completed in 30/107 pts (28%): 16/30 had minor alterations and received 7 or 8 doses, 14 had major alterations
- Follow-up (median): 24 months

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DISEASE FREE AT	COMPLETE RESPONSE RATE (*)	N° PATIENTS
FISRT CHECK CYSTOSCOPY	87 %	90/104
1-YEAR CYSTOSCOPY	86 %	74/86
1-YEAR CYSTOSCOPY	93 %	66/71

PROGRESSION RATE AT 2 YEARS	3 %

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(*) Recurrence-free

Conclusion

This study confirms the excellent oncology efficacy of sequential BCG + EMDA-MMC administration in case of High Risk NMIBC. The response rate and DFI exceeds the previously published results by Di Stasi et al.

Since 2009 Guy's Hospital introduced sequential treatment as standard induction regimen in High Risk NMIBC.

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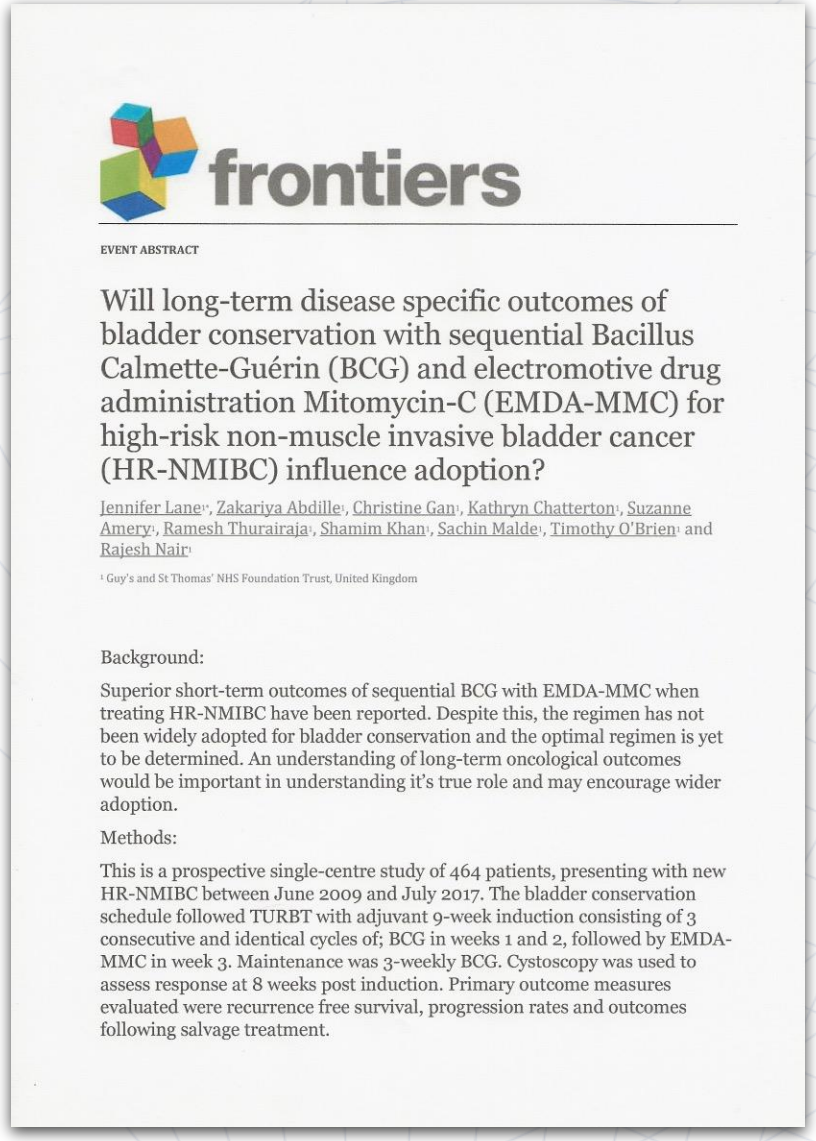


frontiers

EVENT ABSTRACT

Will long-term disease specific outcomes of bladder conservation with sequential Bacillus Calmette-Guérin (BCG) and electromotive drug administration Mitomycin-C (EMDA-MMC) for high-risk non-muscle invasive bladder cancer (HR-NMIBC) influence adoption?

Jennifer Lane[1], Zakariya Abdille[1], Christine Gan[1], Kathryn Chatterton[1], Suzanne Amery[1], Ramesh Thurairaja[1], Shamim Khan[1], Sachin Malde[1], Timothy O'Brien[1] and Rajesh Nair[1]

[1] Guy's and St Thomas' NHS Foundation Trust, United Kingdom

Background:

Superior short-term outcomes of sequential BCG with EMDA-MMC when treating HR-NMIBC have been reported. Despite this, the regimen has not been widely adopted for bladder conservation and the optimal regimen is yet to be determined. An understanding of long-term oncological outcomes would be important in understanding it's true role and may encourage wider adoption.

Methods:

This is a prospective single-centre study of 464 patients, presenting with new HR-NMIBC between June 2009 and July 2017. The bladder conservation schedule followed TURBT with adjuvant 9-week induction consisting of 3 consecutive and identical cycles of; BCG in weeks 1 and 2, followed by EMDA-MMC in week 3. Maintenance was 3-weekly BCG. Cystoscopy was used to assess response at 8 weeks post induction. Primary outcome measures evaluated were recurrence free survival, progression rates and outcomes following salvage treatment.

Clinical Studies

Gan, O'Brien et al, Guy's and St. Thomas' NHS Foundation Trust (Bladder Cancer Translational Research Meeting, King's College, 2019)

- Prospective, cohort study
- 249 pts with HG NMIBC:
  -206 pts Ta-T1 HG (83 %)
  - 13 pts primary CIS (5 %)
  - 30 pts recurrent, large volume, LG disease (12%)
- 9-week induction sequential treatment with the cycle BCG+BCG+EMDA-MMC ripeated 3 times
- 196/249 (79 %) completed the induction treatment
- Follow-up (median): 54 months

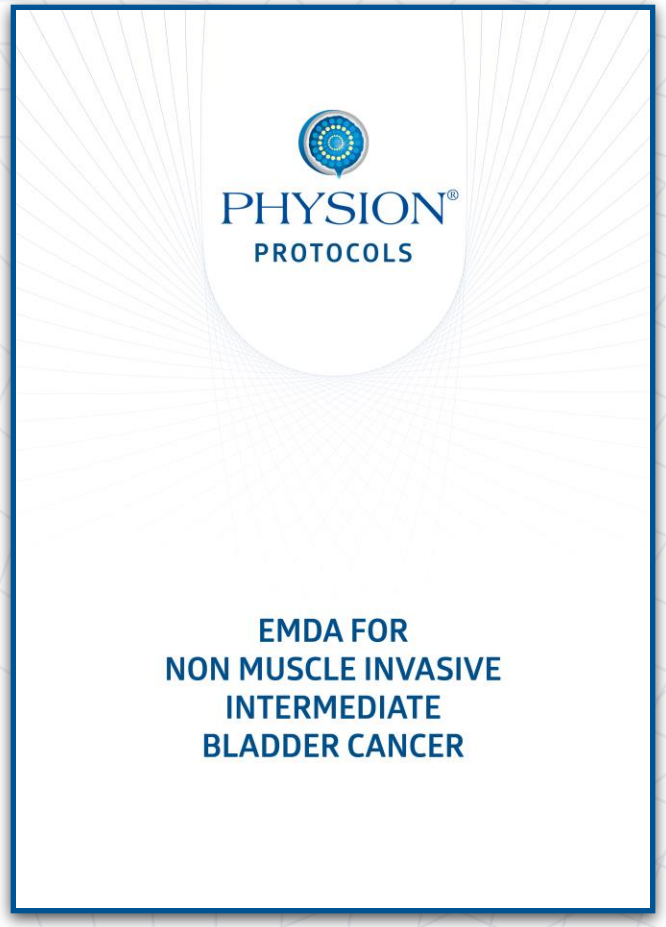
PHYSION®

DISEASE FREE AT	COMPLETE RESPONSE RATE CR%	N° PATIENTS
54 MONTHS	63 %	123/196

If BCG/EMDA-MMC treatment is completed, over two-thirds of patients remain disease free during long term follow-up: this is twice the efficacy quoted for BCG alone and adds further weight to the adoption of this sequential regimen in bladder preservation for HR-NMIBC.

PHYSION®

Treatment of Intermediate-risk NMIBC with EMDA-MMC: PASSIVE DIFFUSION vs EMDA-MMC



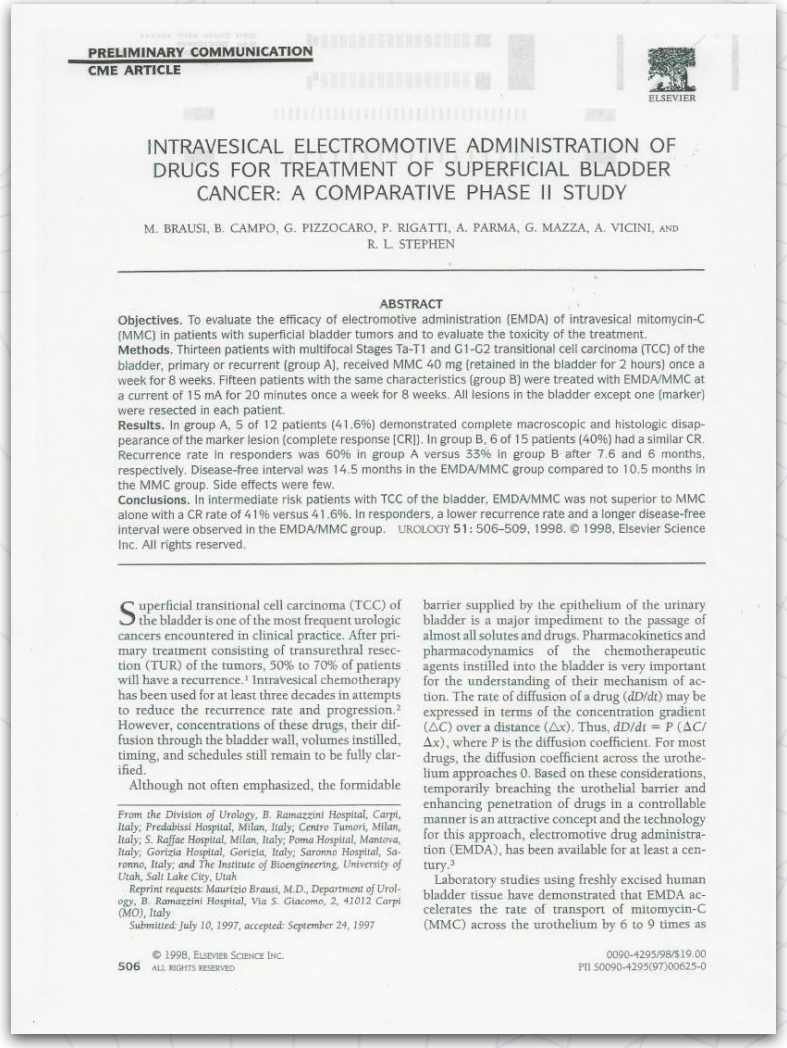
Treatment Protocol

Induction: 1 instillation of MMC with EMDA per week for 8 weeks for a total of 8 instillations

Maintenance: 1 instillation of MMC with EMDA per month for 3 months, cycle repeated 2 times for a total of 8 instillations

PHYSION®

Clinical Studies: PD vs EMDA-MMC



PRELIMINARY COMMUNICATION
CME ARTICLE

ELSEVIER

INTRAVESICAL ELECTROMOTIVE ADMINISTRATION OF DRUGS FOR TREATMENT OF SUPERFICIAL BLADDER CANCER: A COMPARATIVE PHASE II STUDY

M. BRAUSI, B. CAMPO, G. PIZZOCARO, P. RIGATTI, A. PARMA, G. MAZZA, A. VICINI, AND R. L. STEPHEN

ABSTRACT

Objectives. To evaluate the efficacy of electromotive administration (EMDA) of intravesical mitomycin-C (MMC) in patients with superficial bladder tumors and to evaluate the toxicity of the treatment.
Methods. Thirteen patients with multifocal Stages Ta-T1 and G1-G2 transitional cell carcinoma (TCC) of the bladder, primary or recurrent (group A), received MMC 40 mg (retained in the bladder for 2 hours) once a week for 8 weeks. Fifteen patients with the same characteristics (group B) were treated with EMDA/MMC at a current of 15 mA for 20 minutes once a week for 8 weeks. All lesions in the bladder except one (marker) were resected in each patient.
Results. In group A, 5 of 12 patients (41.6%) demonstrated complete macroscopic and histologic disappearance of the marker lesion (complete response [CR]). In group B, 6 of 15 patients (40%) had a similar CR. Recurrence rate in responders was 60% in group A versus 33% in group B after 7.6 and 6 months, respectively. Disease-free interval was 14.5 months in the EMDA/MMC group compared to 10.5 months in the MMC group. Side effects were few.
Conclusions. In intermediate risk patients with TCC of the bladder, EMDA/MMC was not superior to MMC alone with a CR rate of 41% versus 41.6%. In responders, a lower recurrence rate and a longer disease-free interval were observed in the EMDA/MMC group. UROLOGY 51: 506–509, 1998. © 1998, Elsevier Science Inc. All rights reserved.

Superficial transitional cell carcinoma (TCC) of the bladder is one of the most frequent urologic cancers encountered in clinical practice. After primary treatment consisting of transurethral resection (TUR) of the tumors, 50% to 70% of patients will have a recurrence.[1] Intravesical chemotherapy has been used for at least three decades in attempts to reduce the recurrence rate and progression.[2] However, concentrations of these drugs, their diffusion through the bladder wall, volumes instilled, timing, and schedules still remain to be fully clarified.

Although not often emphasized, the formidable barrier supplied by the epithelium of the urinary bladder is a major impediment to the passage of almost all solutes and drugs. Pharmacokinetics and pharmacodynamics of the chemotherapeutic agents instilled into the bladder is very important for the understanding of their mechanism of action. The rate of diffusion of a drug (dD/dt) may be expressed in terms of the concentration gradient (ΔC) over a distance (Δx). Thus, $dD/dt = P\ (\Delta C/\Delta x)$, where P is the diffusion coefficient. For most drugs, the diffusion coefficient across the urothelium approaches 0. Based on these considerations, temporarily breaching the urothelial barrier and enhancing penetration of drugs in a controllable manner is an attractive concept and the technology for this approach, electromotive drug administration (EMDA), has been available for at least a century.[3]

Laboratory studies using freshly excised human bladder tissue have demonstrated that EMDA accelerates the rate of transport of mitomycin-C (MMC) across the urothelium by 6 to 9 times as

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Submitted: July 10, 1997, accepted: September 24, 1997

0090-4295/98/$19.00
PII S0090-4295(97)00625-0

Brausi et al Urology 1998

- Multicenter, non-randomized, comparative, phase II study
- 28 pts : Ta-T1, G1-G2, primary multifocal or recurrent, with marker lesion (≤ 1,5 cm)
- EMDA-MMC Group: pts 13 → EMDA-MMC weekly for 8 weeks
- Control Group : pts 15 → PD-MMC weekly for 8 weeks
- Complete response: complete macroscopic and histological disappereance of the marker lesion with negative citology.
- Follow-up (median): 16,3 months

PHYSION®

	RATE OF RECURRENCE	DISEASE-FREE INTERVAL (months)
PD-MMC	60 %	10.5
EMDA-MMC	33 %	14.5

CR was 40% in both arms: the ablative effect of 20 minute-treatment of EMDA-MMC on marker lesions was effective as 2-hour treatment of MMC alone .

A lower recurrence-rate and a longer disease-free interval were observed in the EMDA-MMC group.

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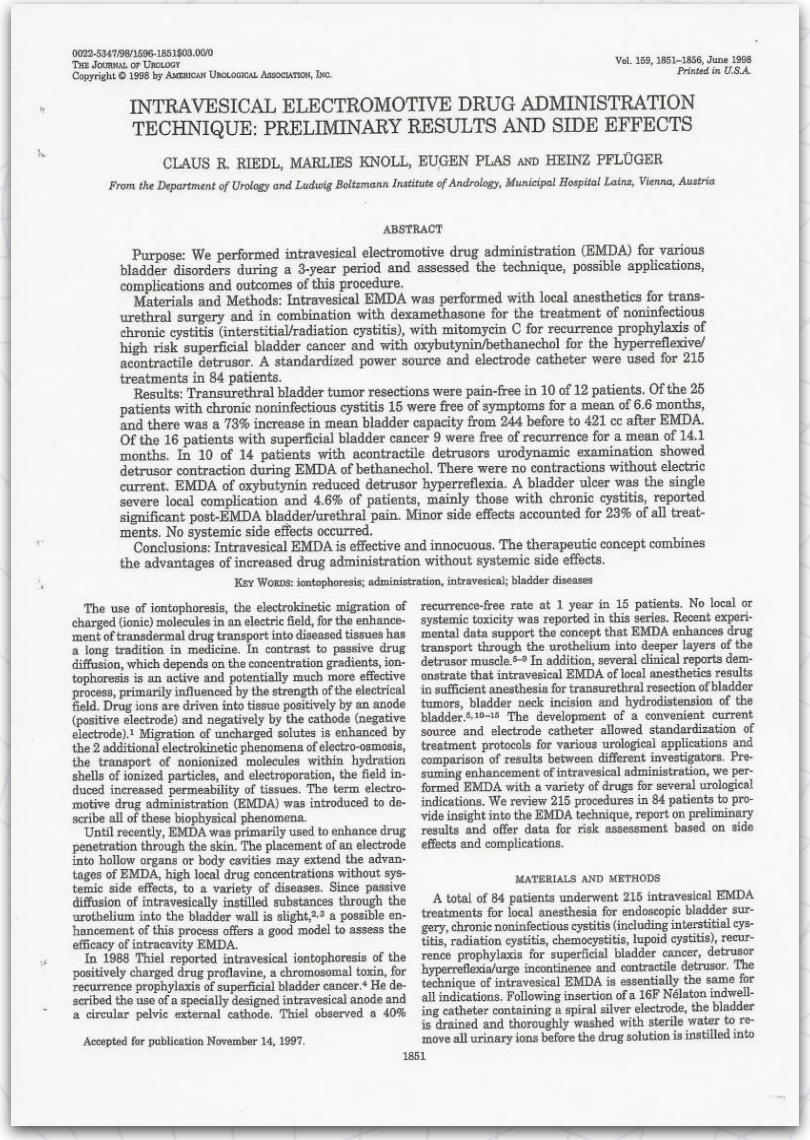

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INTRAVESICAL ELECTROMOTIVE DRUG ADMINISTRATION TECHNIQUE: PRELIMINARY RESULTS AND SIDE EFFECTS

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From the Department of Urology and Ludwig Boltzmann Institute of Andrology, Municipal Hospital Lainz, Vienna, Austria

ABSTRACT

Purpose: We performed intravesical electromotive drug administration (EMDA) for various bladder disorders during a 3-year period and assessed the technique, possible applications, complications and outcomes of this procedure.

Materials and Methods: Intravesical EMDA was performed with local anesthetics for transurethral surgery and in combination with dexamethasone for the treatment of noninfectious chronic cystitis (interstitial/radiation cystitis), with mitomycin C for recurrence prophylaxis of high risk superficial bladder cancer and with oxybutynin/bethanechol for the hyperreflexive/acontractile detrusor. A standardized power source and electrode catheter were used for 215 treatments in 84 patients.

Results: Transurethral bladder tumor resections were pain-free in 10 of 12 patients. Of the 25 patients with chronic noninfectious cystitis 15 were free of symptoms for a mean of 6.6 months, and there was a 73% increase in mean bladder capacity from 244 before to 421 cc after EMDA. Of the 16 patients with superficial bladder cancer 9 were free of recurrence for a mean of 14.1 months. In 10 of 14 patients with acontractile detrusors urodynamic examination showed detrusor contraction during EMDA of bethanechol. There were no contractions without electric current. EMDA of oxybutynin reduced detrusor hyperreflexia. A bladder ulcer was the single severe local complication and 4.6% of patients, mainly those with chronic cystitis, reported significant post-EMDA bladder/urethral pain. Minor side effects accounted for 23% of all treatments. No systemic side effects occurred.

Conclusions: Intravesical EMDA is effective and innocuous. The therapeutic concept combines the advantages of increased drug administration without systemic side effects.

KEY WORDS: iontophoresis; administration, intravesical; bladder diseases

The use of iontophoresis, the electrokinetic migration of charged (ionic) molecules in an electric field, for the enhancement of transdermal drug transport into diseased tissues has a long tradition in medicine. In contrast to passive drug diffusion, which depends on the concentration gradients, iontophoresis is an active and potentially much more effective process, primarily influenced by the strength of the electrical field. Drug ions are driven into tissue positively by an anode (positive electrode) and negatively by the cathode (negative electrode).[1] Migration of uncharged solutes is enhanced by the 2 additional electrokinetic phenomena of electro-osmosis, the transport of nonionized molecules within hydration shells of ionized particles, and electroporation, the field induced increased permeability of tissues. The term electromotive drug administration (EMDA) was introduced to describe all of these biophysical phenomena.

Until recently, EMDA was primarily used to enhance drug penetration through the skin. The placement of an electrode into hollow organs or body cavities may extend the advantages of EMDA, high local drug concentrations without systemic side effects, to a variety of diseases. Since passive diffusion of intravesically instilled substances through the urothelium into the bladder wall is slight,[2,3] a possible enhancement of this process offers a good model to assess the efficacy of intracavity EMDA.

In 1988 Thiel reported intravesical iontophoresis of the positively charged drug proflavine, a chromosomal toxin, for recurrence prophylaxis of superficial bladder cancer.[4] He described the use of a specially designed intravesical anode and a circular pelvic external cathode. Thiel observed a 40% recurrence-free rate at 1 year in 15 patients. No local or systemic toxicity was reported in this series. Recent experimental data support the concept that EMDA enhances drug transport through the urothelium into deeper layers of the detrusor muscle.[5–9] In addition, several clinical reports demonstrate that intravesical EMDA of local anesthetics results in sufficient anesthesia for transurethral resection of bladder tumors, bladder neck incision and hydrodistension of the bladder.[5,10–15] The development of a convenient current source and electrode catheter allowed standardization of treatment protocols for various urological applications and comparison of results between different investigators. Presuming enhancement of intravesical administration, we performed EMDA with a variety of drugs for several urological indications. We review 215 procedures in 84 patients to provide insight into the EMDA technique, report on preliminary results and offer data for risk assessment based on side effects and complications.

MATERIALS AND METHODS

A total of 84 patients underwent 215 intravesical EMDA treatments for local anesthesia for endoscopic bladder surgery, chronic noninfectious cystitis (including interstitial cystitis, radiation cystitis, chemocystitis, lupoid cystitis), recurrence prophylaxis for superficial bladder cancer, detrusor hyperreflexia/urge incontinence and contractile detrusor. The technique of intravesical EMDA is essentially the same for all indications. Following insertion of a 16F Nélaton indwelling catheter containing a spiral silver electrode, the bladder is drained and thoroughly washed with sterile water to remove all urinary ions before the drug solution is instilled into

Accepted for publication November 14, 1997.

Riedl et al Journal of Urology, 1998

- Prospective, cohort study
- 22 pts NMIBC:
  - TaG2 (14)
  - TaG1 (1)
  - T1G2 (2)
  - T1G3 (3)
  - Cis G3 (2)
- 4 weekly treatment EMDA-MMC
- Follow-up (median) 14.1 months
- Complete Remission Rate : 56.6 % at 14.1 months (included Tis and 2/3 T1G3)
- Treatment well tolerated

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«Intravesical adjuvant electromotive MMC in patients with primary intermediate-risk urothelial non muscle invasive bladder cancer: a randomized controlled trial»

(Di Stasi et al European Urology Supplements 2019)

225 pts with primary intermediate risk were randomly assigned to:

75 TURBT alone

77 pts → PD-MMC weekly for 6 weeks → Responders Maintenance → PD-MMC monthly for 10 months

73 pts → EMDA-MMC weekly for 6 weeks → Responders Maintenance → EMDA-MMC monthly for 10 months

Medium follow-up: 86 months

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	TURBT	PD-MMC	EMDA-MMC
RECURRENCE RATE	63 %	60 %	36 %
DISEASE-FREE INTERVAL (month)	10	10.5	19

	PD-MMC	EMDA-MMC
LOCAL SIDE EFFECTS AND SYPTOMS	25 % (19/77)	26 % (19/73)
TREATMENT STOP FOR CHEMICAL CYSTITIS SIDE-EFFECTS	4 % (3/77)	1 % (1/73)

EMDA-MMC reduces recurrence rates and enhances the disease-free interval in pts with intermediate-risk disease.

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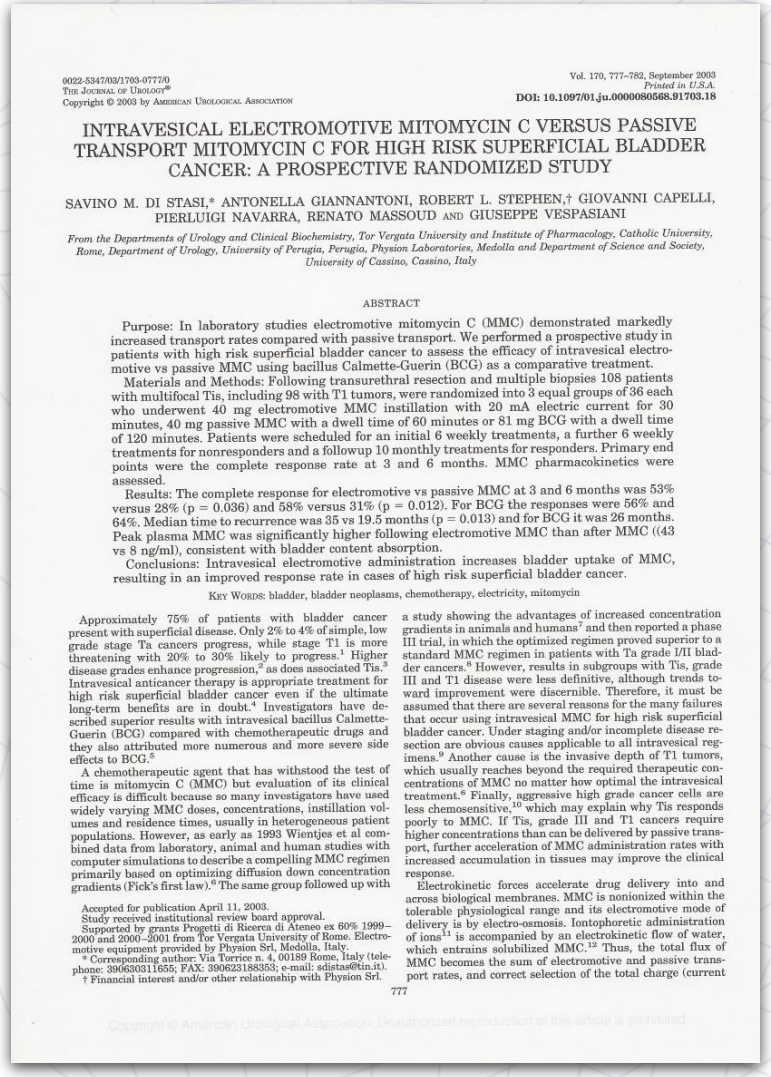
Clinical Studies: EMDA-MMC vs PD-MMC



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INTRAVESICAL ELECTROMOTIVE MITOMYCIN C VERSUS PASSIVE TRANSPORT MITOMYCIN C FOR HIGH RISK SUPERFICIAL BLADDER CANCER: A PROSPECTIVE RANDOMIZED STUDY

SAVINO M. DI STASI,* ANTONELLA GIANNANTONI, ROBERT L. STEPHEN,† GIOVANNI CAPELLI, PIERLUIGI NAVARRA, RENATO MASSOUD AND GIUSEPPE VESPASIANI

From the Departments of Urology and Clinical Biochemistry, Tor Vergata University and Institute of Pharmacology, Catholic University, Rome, Department of Urology, University of Perugia, Perugia, Physion Laboratories, Medolla and Department of Science and Society, University of Cassino, Cassino, Italy

ABSTRACT

Purpose: In laboratory studies electromotive mitomycin C (MMC) demonstrated markedly increased transport rates compared with passive transport. We performed a prospective study in patients with high risk superficial bladder cancer to assess the efficacy of intravesical electromotive vs passive MMC using bacillus Calmette-Guerin (BCG) as a comparative treatment.

Materials and Methods: Following transurethral resection and multiple biopsies 108 patients with multifocal Tis, including 98 with T1 tumors, were randomized into 3 equal groups of 36 each who underwent 40 mg electromotive MMC instillation with 20 mA electric current for 30 minutes, 40 mg passive MMC with a dwell time of 60 minutes or 81 mg BCG with a dwell time of 120 minutes. Patients were scheduled for an initial 6 weekly treatments, a further 6 weekly treatments for nonresponders and a followup 10 monthly treatments for responders. Primary end points were the complete response rate at 3 and 6 months. MMC pharmacokinetics were assessed.

Results: The complete response for electromotive vs passive MMC at 3 and 6 months was 53% versus 28% ($p = 0.036$) and 58% versus 31% ($p = 0.012$). For BCG the responses were 56% and 64%. Median time to recurrence was 35 vs 19.5 months ($p = 0.013$) and for BCG it was 26 months. Peak plasma MMC was significantly higher following electromotive MMC than after MMC ((43 vs 8 ng/ml), consistent with bladder content absorption.

Conclusions: Intravesical electromotive administration increases bladder uptake of MMC, resulting in an improved response rate in cases of high risk superficial bladder cancer.

KEY WORDS: bladder, bladder neoplasms, chemotherapy, electricity, mitomycin

Approximately 75% of patients with bladder cancer present with superficial disease. Only 2% to 4% of simple, low grade stage Ta cancers progress, while stage T1 is more threatening with 20% to 30% likely to progress.[1] Higher disease grades enhance progression,[2] as does associated Tis.[3] Intravesical anticancer therapy is appropriate treatment for high risk superficial bladder cancer even if the ultimate long-term benefits are in doubt.[4] Investigators have described superior results with intravesical bacillus Calmette-Guerin (BCG) compared with chemotherapeutic drugs and they also attributed more numerous and more severe side effects to BCG.[5]

A chemotherapeutic agent that has withstood the test of time is mitomycin C (MMC) but evaluation of its clinical efficacy is difficult because so many investigators have used widely varying MMC doses, concentrations, instillation volumes and residence times, usually in heterogeneous patient populations. However, as early as 1993 Wientjes et al combined data from laboratory, animal and human studies with computer simulations to describe a compelling MMC regimen primarily based on optimizing diffusion down concentration gradients (Fick's first law).[6] The same group followed up with a study showing the advantages of increased concentration gradients in animals and humans[7] and then reported a phase III trial, in which the optimized regimen proved superior to a standard MMC regimen in patients with Ta grade I/II bladder cancers.[8] However, results in subgroups with Tis, grade III and T1 disease were less definitive, although trends toward improvement were discernible. Therefore, it must be assumed that there are several reasons for the many failures that occur using intravesical MMC for high risk superficial bladder cancer. Under staging and/or incomplete disease resection are obvious causes applicable to all intravesical regimens.[9] Another cause is the invasive depth of T1 tumors, which usually reaches beyond the required therapeutic concentrations of MMC no matter how optimal the intravesical treatment.[6] Finally, aggressive high grade cancer cells are less chemosensitive,[10] which may explain why Tis responds poorly to MMC. If Tis, grade III and T1 cancers require higher concentrations than can be delivered by passive transport, further acceleration of MMC administration rates with increased accumulation in tissues may improve the clinical response.

Electrokinetic forces accelerate drug delivery into and across biological membranes. MMC is nonionized within the tolerable physiological range and its electromotive mode of delivery is by electro-osmosis. Iontophoretic administration of ions[11] is accompanied by an electrokinetic flow of water, which entrains solubilized MMC.[12] Thus, the total flux of MMC becomes the sum of electromotive and passive transport rates, and correct selection of the total charge (current

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Study received institutional review board approval.
Supported by grants Progetti di Ricerca di Ateneo ex 60% 1999–2000 and 2000–2001 from Tor Vergata University of Rome. Electromotive equipment provided by Physion Srl, Medolla, Italy.
* Corresponding author: Via Torrice n. 4, 00189 Rome, Italy (telephone: 390630311655; FAX: 390623188353; e-mail: sdistas@tin.it).
† Financial interest and/or other relationship with Physion Srl.

Di Stasi et al, The Journal of Urology 2003

- Multicenter, prospective, randomized, comparative, phase III study
- 108 pts randomized in 3 groups:
  - 98 T1 with concurrent multifocal Cis
  - 10 multifocal Cis
- EMDA-MMC Group: pts 36 → EMDA-MMC weekly for 6 week
- PD-MMC Group : pts 36 → PD-MMC weekly for 6 weeks
- Control Group : pts 36 → BCG weekly for 6 weeks
- Primary endpoint were CR rate at 3 and 6 months
- Follow-up (median): 45 months

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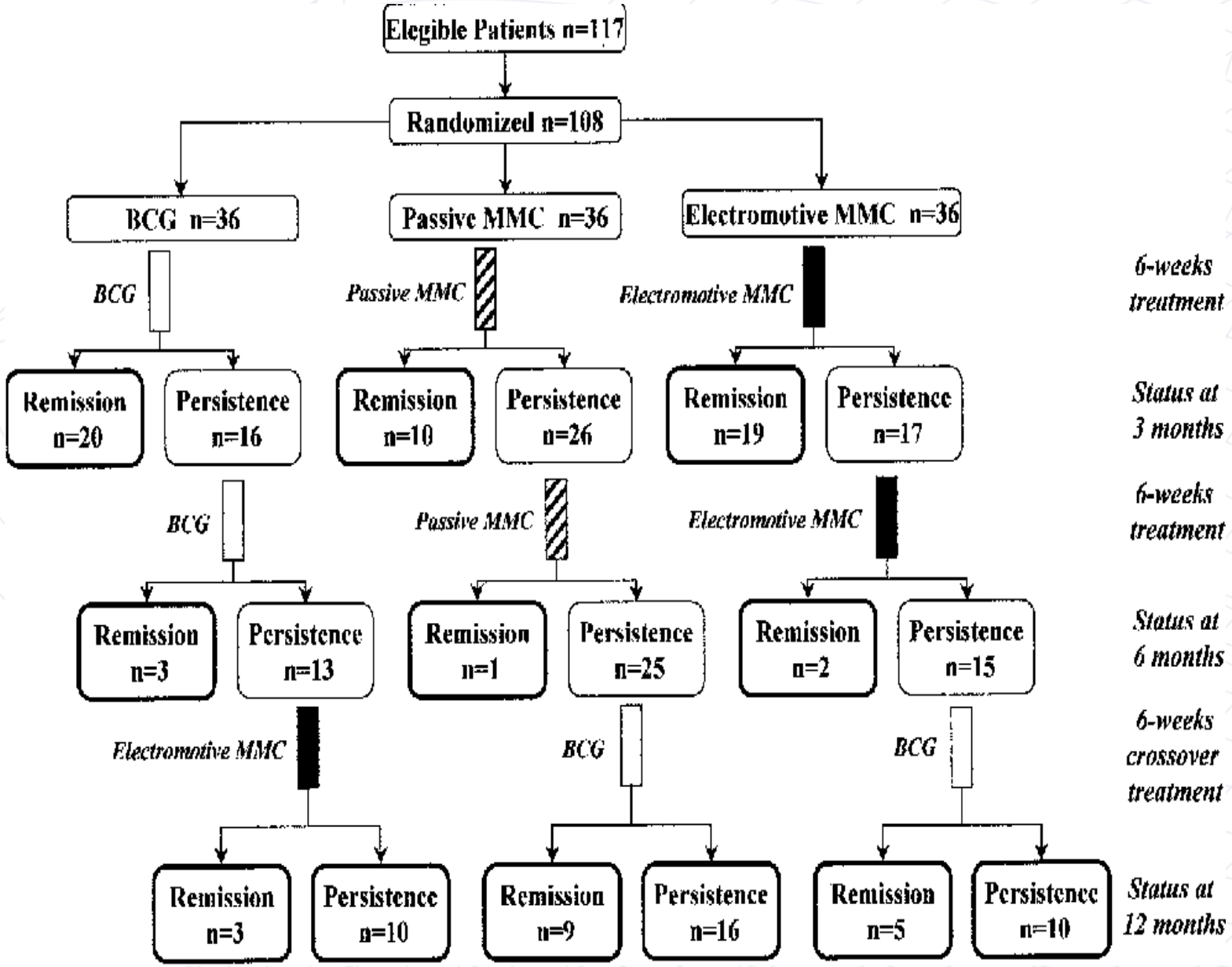

At 3 months: a further 6 weekly treatment for non-responders and mainteneince treatment for responders.

At 6 months: 6-weeks crossover treatment for non responders

PD-MMC Group /EMDA-MMC Group

↓

Crossover to 6-week BCG

BCG Group

↓

Crossover to 6-week EMDA-MMC

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	PD	EMDA-MMC	BCG
CR RATE AT 3 MONTHS	28 %	53 %	56 %
CR RATE AT 6 MONTHS	31 %	58 %	64 %
CR % CROSSOVER	-	23 %	35 %
TIME TO RECURRENCE (months)	19.5	35	26

Intravesical electromotive administration (EMDA) increases bladder uptake of MMC resulting in a superior response rate in pts with High-risk NMIBC compared with passive MMC transport. Response rate of EMDA-MMC matchs those induced by BCG.

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Adverse Effect	No. BCG (%)	No. Passive MMC (%)	No. Electromotive MMC (%)	p Value (Fisher exact test)
Urinary frequency	21 (58.3)	6 (16.7)	7 (19.4)	0.001
Bacterial cystitis	9 (25.0)	7 (19.4)	7 (19.4)	0.874
Drug induced cystitis	24 (66.7)	9 (25.0)	13 (36.1)	0.001
Visible hematuria	26 (72.2)	6 (16.7)	8 (22.2)	0.001
Prostatitis	1 (2.8)	0	0	1.000
Epididymitis	1 (2.8)	0	0	1.000
Fever	7 (19.4)	0	0	0.001
General malaise	11 (30.5)	1 (2.8)	0	0.001
Fatigue	16 (44.4)	0	1 (2.8)	0.001
Allergic reactions	0	2 (5.6)	3 (8.3)	1.000
Treatment modified:				
No	10 (27.8)	26 (72.2)	21 (58.4)	
Yes, continued	22 (61.1)	8 (22.2)	12 (33.3)	0.003
Yes, stopped	4 (11.1)	2 (5.6)	3 (8.3)	

Local and systemic effects were significantly more prominent in the BCG arm than in EMDA-MMC and PD-MMC arms. There were no statistical differences between the 2 MMC arms.
A total of 32 pts on BCG, 34 on PD-MMC and 33 on EMDA-MMC completed the treatment.
During EMDA-MMC plasma MMC at all time points was higher than after passive transport (always below toxic concentration 400 ng/ml)
Peak plasma MMC was significantly higher following EMDA-MMC than after MMC : 43 vs 8 ng/ml

PHYSION®

«Carcinoma in situ of the bladder: long-term results of a randomized prospective study comparing intravesical electromotive MMC C, PD MMC C and BCG «
(Di Stasi European Urology 2008)

	PD-MMC	EMDA-MMC	BCG
CR%	19.4%	33.3%	36.1%
TIME TO RECURRENCE	9.1	15.0	17.8
PROGRESSION RATE	44.4%	30.6%	27.8%
TIME TO PROGRESSION (month)	21.5	26.9	27.8
OVERALL MORTALITY	52.7%	47.2%	52.7%
DISEASE-SPECIFIC MORTALITY	30.5%	22.2%	22.2%

A further follow-up (median) at 82.5 months was conducted

EMDA-MMC provides a better response rate and disease-free interval than PD-MMC.

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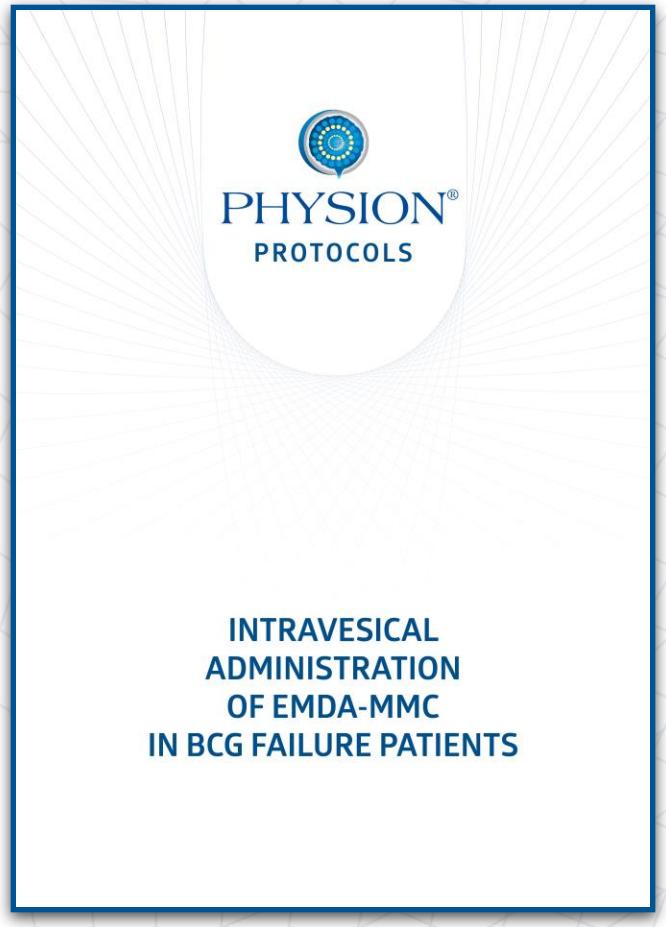
Treatment of High-risk NMIBC unresponsive to BCG: a viable option to offer patients than radical cystectomy



Treatment Protocol

Induction: 1 instillation of MMC with EMDA per week for 6 weeks for a total of 6 instillations

Maintenance: 1 instillation of MMC with EMDA per month for 3 months, cycle repeated 2 times for a total of 6 instillations

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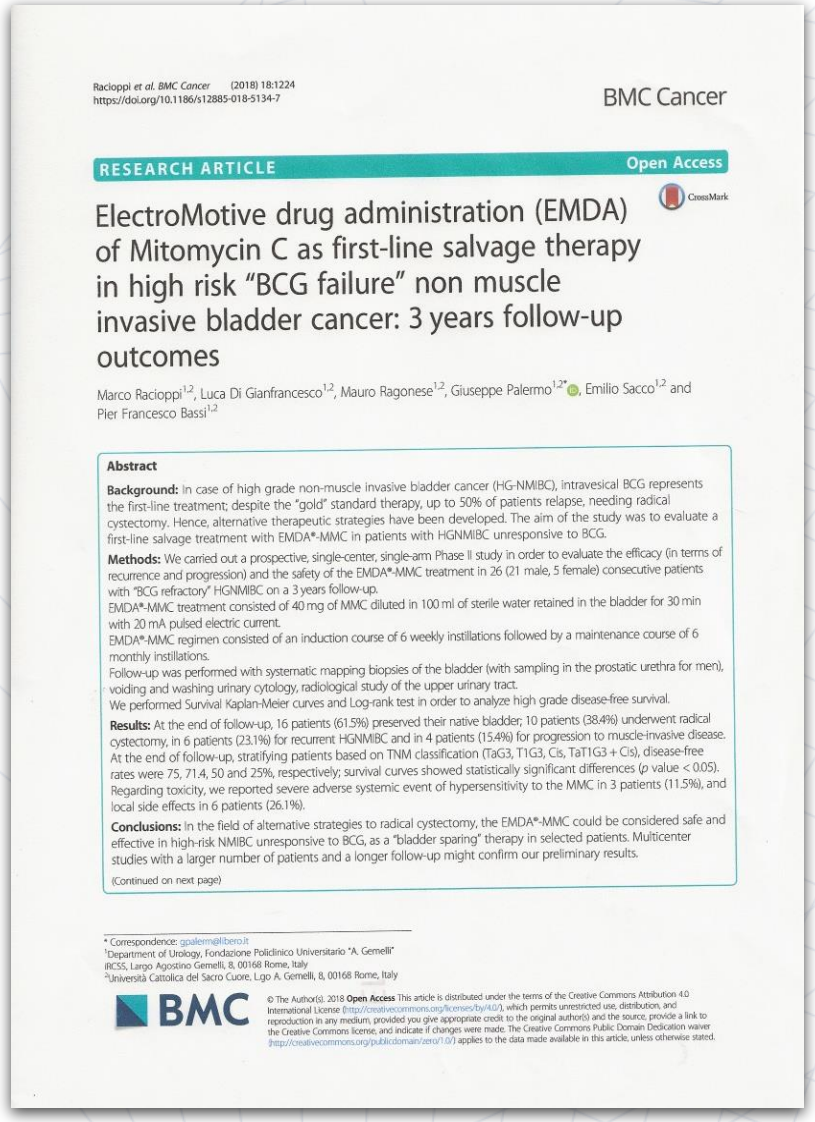

Racioppi et al. BMC Cancer (2018) 18:1224
https://doi.org/10.1186/s12885-018-5134-7

BMC Cancer

RESEARCH ARTICLE Open Access

ElectroMotive drug administration (EMDA) of Mitomycin C as first-line salvage therapy in high risk "BCG failure" non muscle invasive bladder cancer: 3 years follow-up outcomes

Marco Racioppi[1,2], Luca Di Gianfrancesco[1,2], Mauro Ragonese[1,2], Giuseppe Palermo[1,2*], Emilio Sacco[1,2] and Pier Francesco Bassi[1,2]

Abstract

Background: In case of high grade non-muscle invasive bladder cancer (HG-NMIBC), intravesical BCG represents the first-line treatment; despite the "gold" standard therapy, up to 50% of patients relapse, needing radical cystectomy. Hence, alternative therapeutic strategies have been developed. The aim of the study was to evaluate a first-line salvage treatment with EMDA®-MMC in patients with HGNMIBC unresponsive to BCG.

Methods: We carried out a prospective, single-center, single-arm Phase II study in order to evaluate the efficacy (in terms of recurrence and progression) and the safety of the EMDA®-MMC treatment in 26 (21 male, 5 female) consecutive patients with "BCG refractory" HGNMIBC on a 3 years follow-up.
EMDA®-MMC treatment consisted of 40 mg of MMC diluted in 100 ml of sterile water retained in the bladder for 30 min with 20 mA pulsed electric current.
EMDA®-MMC regimen consisted of an induction course of 6 weekly instillations followed by a maintenance course of 6 monthly instillations.
Follow-up was performed with systematic mapping biopsies of the bladder (with sampling in the prostatic urethra for men), voiding and washing urinary cytology, radiological study of the upper urinary tract.
We performed Survival Kaplan-Meier curves and Log-rank test in order to analyze high grade disease-free survival.

Results: At the end of follow-up, 16 patients (61.5%) preserved their native bladder; 10 patients (38.4%) underwent radical cystectomy, in 6 patients (23.1%) for recurrent HGNMIBC and in 4 patients (15.4%) for progression to muscle-invasive disease. At the end of follow-up, stratifying patients based on TNM classification (TaG3, T1G3, Cis, TaT1G3 + Cis), disease-free rates were 75, 71.4, 50 and 25%, respectively; survival curves showed statistically significant differences (p value < 0.05). Regarding toxicity, we reported severe adverse systemic event of hypersensitivity to the MMC in 3 patients (11.5%), and local side effects in 6 patients (26.1%).

Conclusions: In the field of alternative strategies to radical cystectomy, the EMDA®-MMC could be considered safe and effective in high-risk NMIBC unresponsive to BCG, as a "bladder sparing" therapy in selected patients. Multicenter studies with a larger number of patients and a longer follow-up might confirm our preliminary results.

(Continued on next page)

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Clinical Studies

Racioppi et al, BMC Cancer 2018

- Prospective cohort, single- center, single arm, phase II study
- 26 pts BCG Refractory HG NMIBC undergone at least an induction course of BCG:

  - 4 TaG3 (15.4 %)

  - 14 T1G3 (53.8 %)

  - 4 Cis (15.4 %)

  - 4 Ta-T1 G3 + Cis (15.4 %)

- Induction: 6 weekly instillation
- Maintenance: 6 monthly instillation

- Follow-up (median): 3 years

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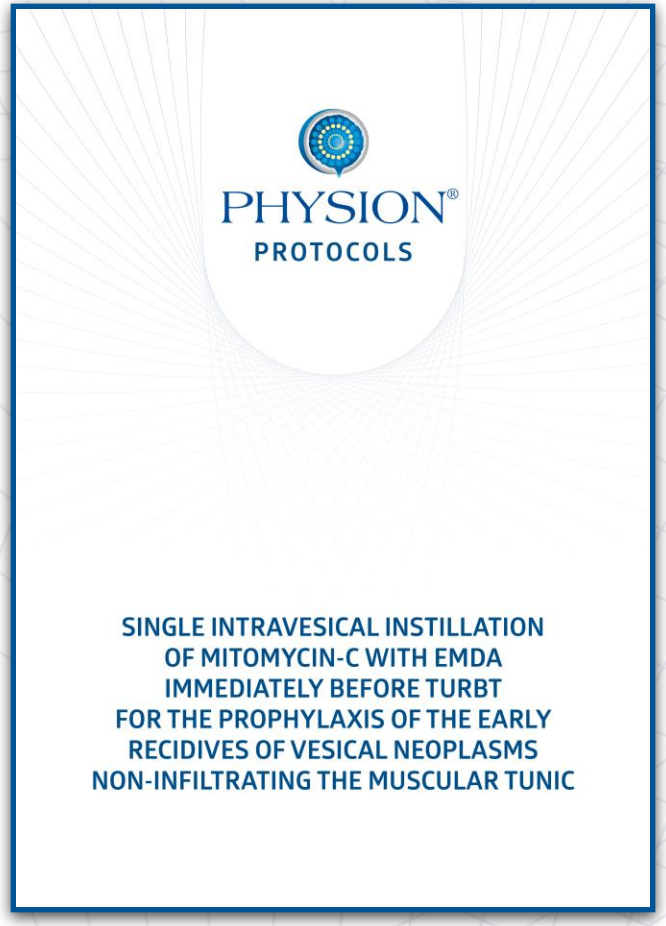
At 3-year follow up 61.5 % preserved their bladders with disease free-rates highest for papillary Ta-T1 tumors.

	DISEASE-FREE RATES AT 3 YEARS
TaG3	75 %
T1G3	71,4 %
Tis	50 %
TaT1G3 + Tis	25 %

EMDA-MMC treatment is an efficacy tool in the long term conservative strategy of High-Risk NMIBC unresponsive to BCG.

PHYSION®

A new approach to preoperative relapse prophylaxis: a single instillation of EMDA / MMC immediately before TURBT



High MMC concentrations in bladder tissue destroy or inhibit implantation of viable cancer cells that could have been released during TURBT and thus the recurrence rate of NMIBC is reduced.

Patient Selection

Pts with established endoscopic diagnosis of urotheliam carcinoma of the bladder, primary and non-infiltrating the muscolaris tunic

Treatment Protocol

Single MMC instillation with EMDA 30/60 minutes before spinal or general anesthesia for endoscopic resection of bladder cancer

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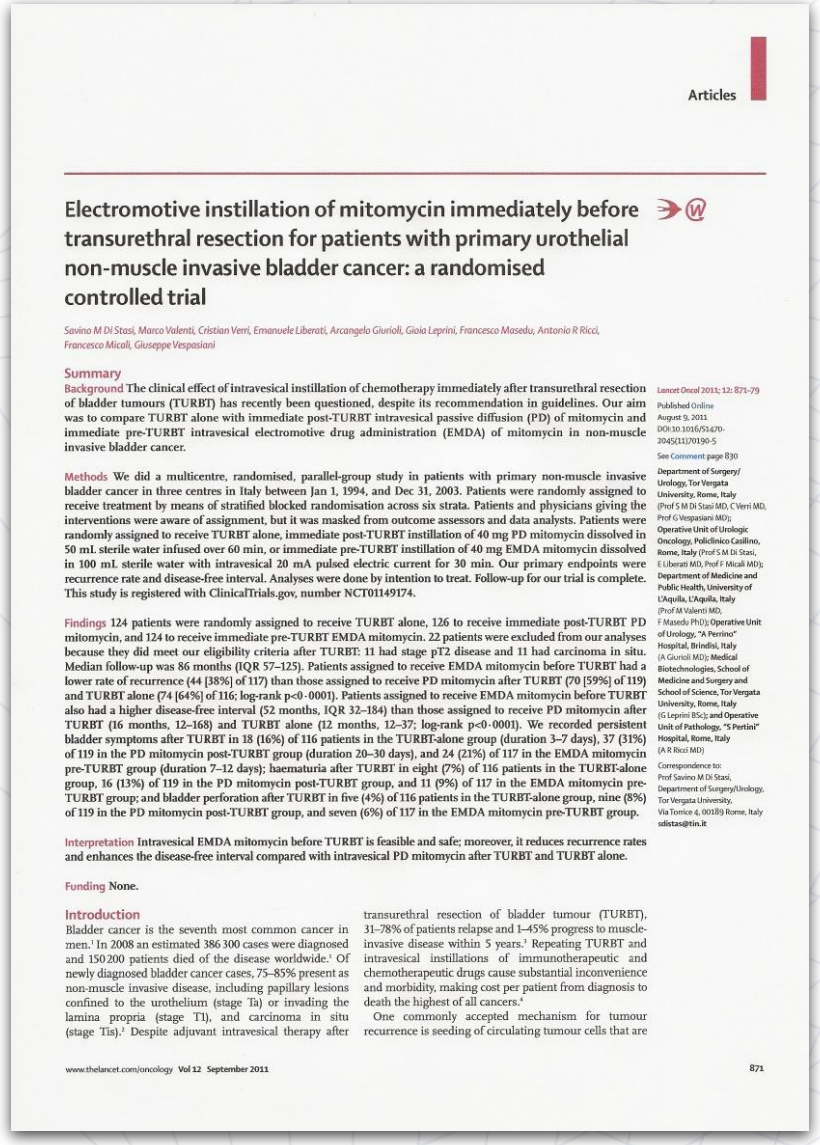

Articles

Electromotive instillation of mitomycin immediately before transurethral resection for patients with primary urothelial non-muscle invasive bladder cancer: a randomised controlled trial

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Summary

Background The clinical effect of intravesical instillation of chemotherapy immediately after transurethral resection of bladder tumours (TURBT) has recently been questioned, despite its recommendation in guidelines. Our aim was to compare TURBT alone with immediate post-TURBT intravesical passive diffusion (PD) of mitomycin and immediate pre-TURBT intravesical electromotive drug administration (EMDA) of mitomycin in non-muscle invasive bladder cancer.

Methods We did a multicentre, randomised, parallel-group study in patients with primary non-muscle invasive bladder cancer in three centres in Italy between Jan 1, 1994, and Dec 31, 2003. Patients were randomly assigned to receive treatment by means of stratified blocked randomisation across six strata. Patients and physicians giving the interventions were aware of assignment, but it was masked from outcome assessors and data analysts. Patients were randomly assigned to receive TURBT alone, immediate post-TURBT instillation of 40 mg PD mitomycin dissolved in 50 mL sterile water infused over 60 min, or immediate pre-TURBT instillation of 40 mg EMDA mitomycin dissolved in 100 mL sterile water with intravesical 20 mA pulsed electric current for 30 min. Our primary endpoints were recurrence rate and disease-free interval. Analyses were done by intention to treat. Follow-up for our trial is complete. This study is registered with ClinicalTrials.gov, number NCT01149174.

Findings 124 patients were randomly assigned to receive TURBT alone, 126 to receive immediate post-TURBT PD mitomycin, and 124 to receive immediate pre-TURBT EMDA mitomycin. 22 patients were excluded from our analyses because they did meet our eligibility criteria after TURBT: 11 had stage pT2 disease and 11 had carcinoma in situ. Median follow-up was 86 months (IQR 57–125). Patients assigned to receive EMDA mitomycin before TURBT had a lower rate of recurrence (44 [38%] of 117) than those assigned to receive PD mitomycin after TURBT (70 [59%] of 119) and TURBT alone (74 [64%] of 116; log-rank p<0·0001). Patients assigned to receive EMDA mitomycin before TURBT also had a higher disease-free interval (52 months, IQR 32–184) than those assigned to receive PD mitomycin after TURBT (16 months, 12–168) and TURBT alone (12 months, 12–37; log-rank p<0·0001). We recorded persistent bladder symptoms after TURBT in 18 (16%) of 116 patients in the TURBT-alone group (duration 3–7 days), 37 (31%) of 119 in the PD mitomycin post-TURBT group (duration 20–30 days), and 24 (21%) of 117 in the EMDA mitomycin pre-TURBT group (duration 7–12 days); haematuria after TURBT in eight (7%) of 116 patients in the TURBT-alone group, 16 (13%) of 119 in the PD mitomycin post-TURBT group, and 11 (9%) of 117 in the EMDA mitomycin pre-TURBT group; and bladder perforation after TURBT in five (4%) of 116 patients in the TURBT-alone group, nine (8%) of 119 in the PD mitomycin post-TURBT group, and seven (6%) of 117 in the EMDA mitomycin pre-TURBT group.

Interpretation Intravesical EMDA mitomycin before TURBT is feasible and safe; moreover, it reduces recurrence rates and enhances the disease-free interval compared with intravesical PD mitomycin after TURBT and TURBT alone.

Funding None.

Introduction

Bladder cancer is the seventh most common cancer in men.[1] In 2008 an estimated 386 300 cases were diagnosed and 150 200 patients died of the disease worldwide.[2] Of newly diagnosed bladder cancer cases, 75–85% present as non-muscle invasive disease, including papillary lesions confined to the urothelium (stage Ta) or invading the lamina propria (stage T1), and carcinoma in situ (stage Tis).[3] Despite adjuvant intravesical therapy after transurethral resection of bladder tumour (TURBT), 31–78% of patients relapse and 1–45% progress to muscle-invasive disease within 5 years.[3] Repeating TURBT and intravesical instillations of immunotherapeutic and chemotherapeutic drugs cause substantial inconvenience and morbidity, making cost per patient from diagnosis to death the highest of all cancers.[4]

One commonly accepted mechanism for tumour recurrence is seeding of circulating tumour cells that are

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Clinical Studies

Di Stasi et al, The Lancet Oncology 2011

- Prospective, multicenter, randomized, parallel-group study

- All categories of risk are included in the trial:
  - Primary Ta-T1
  - G1, G2, G3
  - Unifocal and Multifocal

- 374 pts randomized in 3 groups:

  - EMDA Group: pts 124 → EMDA-MMC pre-TURBT instillation

  - Control 1 Group: pts 124 → TURBT alone

  - Control 2 Group: pts 126 → immediate post-TURBT passive MMC

- Follow-up (median): 86 months

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	TURBT	PD-MMC POST-TURBT	EMDA-MMC PRE-TURBT
N° pts excluding those inelegible (T2 or Cis)	116	119	117
DISEASE-FREE INTERVAL (months)	12	16	52
RATE OF RECURRENCE	64 %	59 %	38 %
PROGRESSION RATE TO MIBC	21 %	19 %	16%

EMDA-MMC pre-TURBT reduces recurrences rates and enhanches the disese-free interval compared with TURBT alone and intravesical passive diffusion MMC post-TURBT.

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SIDE EFFECTS AND SYMPTOMS	PD-MMC POST-TURBT	EMDA-MMC PRE -TURBT
Treatment not administered	21 % (bladder perforation, gross hematuria)	1 % (urethral stricture)
Overt bladder perforation after TURBT	8%	6 %
Gross hematuria after TURBT	13 %	9 %
Treatment stop	24 %: instillation was stopped after 10-15 min (pain, bladder spasm, leakage of drug solution)	_
Irritative bladder symptoms rate	31 %	21%
Lasting of irratitive bladder symptoms after resection	20-30 days	7-12 days

99% of the patients compleated EMDA-MMC pre-TURBT treatment.
It's a safe and well tolerated procedure.

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A recent study confirms safety of EMDA-assisted instillation (Rehme, Rubben et al, Der Urologe)

Originalien

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Redaktion
H. Rübben, Essen

Nicht muskelinvasives Urothelkarzinom der Harnblase

Verträglichkeit der postoperativen EMDA-unterstützten Mitomycin-Instillationsbehandlung

Hintergrund und Fragestellung

Die weltweit standardisierte Inzidenz des Harnblasenkarzinoms beträgt derzeit 10,1/100.000 für Männer und 2,5/100.000 für Frauen [7]. Das Robert-Koch-Institut schätzt anhand der Registerdaten aus dem Jahr 2006, dass in Deutschland jährlich ca. 30.000 Menschen einem Harnblasenkarzinom erkranken, von denen ca. 5400 karzinombedingt versterben. Der Anteil der nicht muskelinvasiven Urothelkarzinome bei Erstdiagnose liegt bei ca. 85%. Hiervon haben ca. 15% die Lamina propria durchbrochen. Trotz hoher Rezidivrate liegt das Progressionsrisiko eines oberflächlichen Urothelkarzinoms bei ca. 4% [9]. Im Spektrum der nicht muskelinvasiven Low-grade-Urothelkarzinome steht daher bei exzellentem tumorspezifischem Überleben nicht die Verhinderung der Progression, sondern die Verhinderung des Tumorrezidivs im Vordergrund.

Der Einfluss einer intravesikalen Chemotherapie auf das Rezidivverhalten nicht muskelinvasiver Harnblasenkarzinome ist gut untersucht. Im Jahr 2004 führte die Arbeitsgruppe der „European Organization for Research and Treatment of Cancer" (EORTC) um Richard Sylvester [10] eine Metaanalyse durch, in die die Daten aus 7 randomisierten Studien zu dieser Thematik eingingen. Es lagen Daten zu 1476 Patienten vor. 728 Patienten erhielten postoperativ eine einmalige intravesikale Instillation mit Epirubicin, Mitomycin C, Thiotepa oder Pirarubicin. Im Vergleich dazu wurden 748 Patienten ausschließlich mittels transurethraler Resektion ohne Instillation behandelt. Von 728 instillierten Patienten entwickelten 267 (36,7%) Patienten ein Rezidiv, im Vergleich zu 362 (48,4%), die mittels transurethraler Resektion (TUR) alleine therapiert wurden. Dies entspricht einer absoluten Reduktion um 12%. Ein Einfluss auf die Progressionsrate konnte nicht gezeigt werden.

Die Arbeitsgruppe um Di Stasi [5, 6] geht seit längerem der Frage nach, ob die Instillationsbehandlung mit Mitomycin C durch ein Zusammenwirken von Iontophorese und Elektrophorese, der elektromotiv getriggerten Medikamentenapplikation (EMDA), hinsichtlich der Effektivität gesteigert werden kann. Grundlage für diese Untersuchung ist die Überlegung, dass intravesikal appliziertes Mitomycin in nicht ausreichender Konzentration die Tumorzellen erreicht. In experimentellen und klinischen Studien konnte gezeigt werden, dass die Aufnahme von Mitomycin im Gewebe im Vergleich zur passiven Diffusion durch EMDA-getriggerte Verabreichung erhöht wird.

In einer Pilotstudie konnte gezeigt werden, dass Patienten mit EMDA-getriggert verabreichtem Mitomycin C weniger Rezidive und eine längere Remissionszeit aufwiesen als Patienten mit einer Mitomycin-Applikation und passiver Diffusion [2]. Di Stasi et al. [4] untersuchten 2006 die Effektivität einer sequentiellen Behandlung von Patienten mit High-risk-Blasenkarzinomen mit Bacillus Calmette-Guérin (BCG) und EMDA-getriggert verabreichtem Mitomycin C vs. BCG alleine. 212 Patienten gingen in die Studie ein. 105 Patienten erhielten BCG für eine Dauer von 6 Wochen, 107 Patienten erhielten in 3 Behandlungszyklen zwei wöchentliche BCG-Instillationen, gefolgt von einer wöchentlichen Behandlung mit 40 mg EMDA-getriggert verabreichtem Mitomycin C. Die Gruppe der sequentiell therapierten Patienten zeigte eine niedrigere Rezidivrate von 41,9% vs. 57,9% und eine verringerte Progressionsrate von 9,3% vs. 21,9% [4]. Die gleiche Arbeitsgruppe publizierte 2011 eine multizentrische randomisierte Studie zum Vergleich der präoperativen EMDA-gestützten Mitomycin-Instillation vs. postoperativer Einmalins-

25 pts diagnosed with NMIBC underwent post-TURBT EMDA-MMC instillations.

Blood sample was taken before starting the procedure and 15, 30, 60 and 120 min after starting the procedure for quantification of MMC serum level.

In 24 pts the measured serum level of MMC was below 50 ng/ml

In 1 pts serum level was 155 ng/ml at 15 min and 65 ng/ml at 30 min

EMDA is a safe procedure: the measured MMC serum levels were always below the toxic concentration of 400 ng/ml

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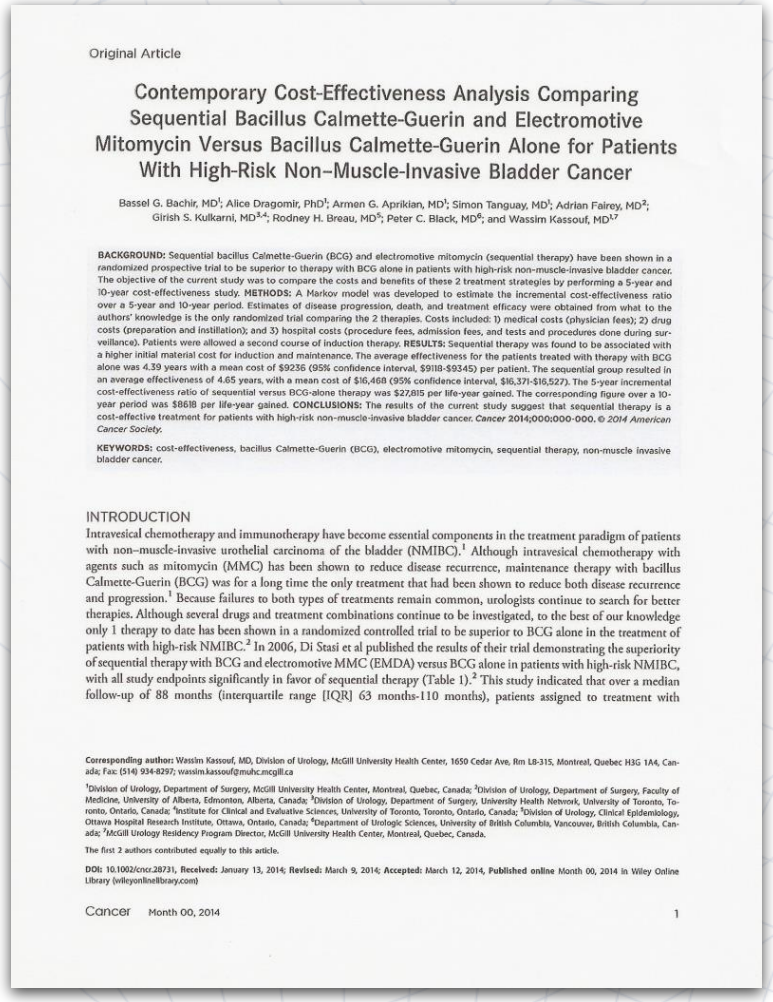
Cost-Effectiveness analysis comparing Sequential BCG+EMDA-MMC vs BCG alone in patients with High-risk NMIBC (Bachir et al, Cancer 2014)



Original Article

Contemporary Cost-Effectiveness Analysis Comparing Sequential Bacillus Calmette-Guerin and Electromotive Mitomycin Versus Bacillus Calmette-Guerin Alone for Patients With High-Risk Non–Muscle-Invasive Bladder Cancer

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BACKGROUND: Sequential bacillus Calmette-Guerin (BCG) and electromotive mitomycin (sequential therapy) have been shown in a randomized prospective trial to be superior to therapy with BCG alone in patients with high-risk non-muscle-invasive bladder cancer. The objective of the current study was to compare the costs and benefits of these 2 treatment strategies by performing a 5-year and 10-year cost-effectiveness study. **METHODS:** A Markov model was developed to estimate the incremental cost-effectiveness ratio over a 5-year and 10-year period. Estimates of disease progression, death, and treatment efficacy were obtained from what to the authors' knowledge is the only randomized trial comparing the 2 therapies. Costs included: 1) medical costs (physician fees); 2) drug costs (preparation and instillation); and 3) hospital costs (procedure fees, admission fees, and tests and procedures done during surveillance). Patients were allowed a second course of induction therapy. **RESULTS:** Sequential therapy was found to be associated with a higher initial material cost for induction and maintenance. The average effectiveness for the patients treated with therapy with BCG alone was 4.39 years with a mean cost of $9236 (95% confidence interval, $9118-$9345) per patient. The sequential group resulted in an average effectiveness of 4.65 years, with a mean cost of $16,468 (95% confidence interval, $16,371-$16,527). The 5-year incremental cost-effectiveness ratio of sequential versus BCG-alone therapy was $27,815 per life-year gained. The corresponding figure over a 10-year period was $8618 per life-year gained. **CONCLUSIONS:** The results of the current study suggest that sequential therapy is a cost-effective treatment for patients with high-risk non–muscle-invasive bladder cancer. *Cancer* 2014;000:000-000. © *2014 American Cancer Society.*

KEYWORDS: cost-effectiveness, bacillus Calmette-Guerin (BCG), electromotive mitomycin, sequential therapy, non-muscle invasive bladder cancer.

INTRODUCTION

Intravesical chemotherapy and immunotherapy have become essential components in the treatment paradigm of patients with non–muscle-invasive urothelial carcinoma of the bladder (NMIBC).[1] Although intravesical chemotherapy with agents such as mitomycin (MMC) has been shown to reduce disease recurrence, maintenance therapy with bacillus Calmette-Guerin (BCG) was for a long time the only treatment that had been shown to reduce both disease recurrence and progression.[1] Because failures to both types of treatments remain common, urologists continue to search for better therapies. Although several drugs and treatment combinations continue to be investigated, to the best of our knowledge only 1 therapy to date has been shown in a randomized controlled trial to be superior to BCG alone in the treatment of patients with high-risk NMIBC.[2] In 2006, Di Stasi et al published the results of their trial demonstrating the superiority of sequential therapy with BCG and electromotive MMC (EMDA) versus BCG alone in patients with high-risk NMIBC, with all study endpoints significantly in favor of sequential therapy (Table 1).[2] This study indicated that over a median follow-up of 88 months (interquartile range [IQR] 63 months-110 months), patients assigned to treatment with

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Objective: to compare costs and benefits of BCG+EMDA-MMC and BCG alone by performing a 5-year and 10-year cost-effectiveness study.

Methods: a Markov model was developed to estimate the incremental cost-effectiveness ratio over a 5 and 10-year period, using the data from Di Stasi et al, Lancet 2006 study (RR,PR, mortality).

Cost included:

1. Medical costs (physician fees)
2. Drug costs (preparation and instillation)
3. Hospital costs (procedure fees, admissiom fees, test and procedures done during surveillance)

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Even if sequential therapy is associated with higher material initial cost, considering recurrence rate, progression rate and survival at 5 and 10 years this therapy results a cost-effective treatment for patients with High-risk NMIBC and can be potentially integrated into hospital and health system as a standard care.

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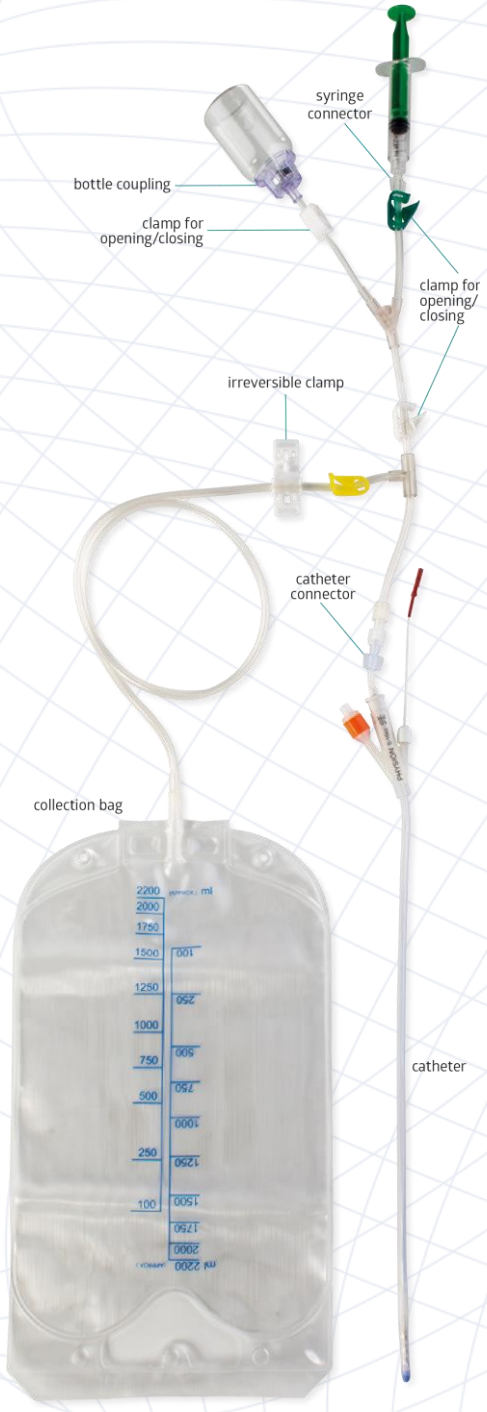

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Physion developed this closed system medical device for the reconstitution and intravesical administration of medication, both chemotherapy (Mitomycin), immunotherapeutic (BCG) and for the subsequenty recovery of urine and drug residual at the end of treatment.

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