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TOPIC PAPER

Updates in intravesical electromotive drug administration® of mitomycin-C for non-muscle invasive bladder cancer

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Abstract Electromotive drug administration® (EMDA) increases the local drug efficacy by controlling and enhancing transmembranous transport into tissue. EMDA of intravesical mitomycin-C (MMC) has been used for treatment of non-muscle invasive bladder cancer (NMIBC) for about a decade on the basis of laboratory studies that demonstrated an enhanced administration rate of MMC into all bladder wall layers after EMDA compared to standard instillation/passive diffusion (PD). Higher MMC concentrations might have a clinical impact since EMDA was associated with lower recurrence rates than PD in randomized studies. Further data suggest that EMDA/MMC is at least equivalent to BCG in treatment of high-risk bladder tumours. In addition, BCG combined with EMDA/MMC as well as preoperative EMDA/MMC are new therapeutic strategies with promising preliminary results in terms of higher remission rates and longer remission times. In summary, these findings suggest that EMDA for MMC delivery in the bladder could be a major therapeutic breakthrough in the treatment of NMIBC.

Keywords Non-muscle invasive bladder cancer · Intravesical therapy · Electromotive drug administration · Mitomycin-C

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Introduction

Bladder cancer, accounting for 5–10% of all malignancies in males in Europe and the USA, with a growing incidence in females, has an annual estimate of 357,000 newly diagnosed cases and 145,000 deaths worldwide [1]. Most bladder tumours are non-muscle-invasive transitional cell carcinomas which include flat carcinoma in situ (stage Tis) as well as papillary lesions that may be confined to the mucosa (stage Ta) or invade the lamina propria (stage T1) [2]. Standard treatment for non-muscle invasive bladder cancer (NMIBC) is complete transurethral resection (TUR) followed by close cystoscopic surveillance and the major challenge is prevention of recurrence and disease progression. After TUR alone 5-year-recurrence rates vary with risk status—from 31% in low-risk to 78% in high-risk patients while progression rates range from 0.8 to 45% [2].

Standard prophylaxis for recurrence is intravesical instillations of cytotoxic or immunotherapeutic agents, which combines maximum local efficacy with negligible systemic drug uptake. Although mitomycin-C (MMC), doxorubicin and epirubicin, which have been tested in numerous randomized clinical trials, are the most common used cytotoxic agents [3, 4], they have little effect on recurrence and progression rates, although outcomes were better in low grade stage Ta than in high grade T1 and Tis tumours. As a meta-analysis demonstrated [5], a single instillation of MMC or epirubicin immediately after TUR reduced the recurrence risk by 39%, which led to standardization of this procedure [2]. In patients with high-risk NMIBC intravesical Bacillus Calmette-Guérin (BCG), although more toxic, is standard therapy, since recurrence rates are lower than after intravesical chemotherapy [6]. If, however, BCG therapy fails, cystectomy is the final, disabling option.

Even though MMC is the most popular drug for intravesical chemoprophylaxis, dosage/concentration, infusion volumes and indwelling times vary and lack standard definition [4]. Extensive investigations have attempted to determine optimum conditions for maximum MMC delivery to the bladder wall [7–11]. In a phase III trial Au et al. [12] demonstrated that an optimised regimen (40 mg MMC with pharmacokinetic manipulation, i.e. decreasing urine volume and urine alkalinisation for drug stabilization) was better than a standard MMC regimen (20 mg MMC). However, results in subgroups with Tis, grade 3, and T1 disease were less definitive, although trends toward improvement were discernible.

Mitomycin-C seems to reduce the risk of tumour recurrence and possibly progression of NMIBC. Failure may be due to stage T1 tumour invasion to a depth that MMC cannot penetrate by passive transport, or reduced chemosensitivity in high grade cancer cells. Both problems may be overcome by ensuring greater MMC accumulation in bladder tissues, as is achieved with electromotive administration.

The physical principle of intravesical electromotive drug administration® (EMDA) of MMC

"Electromotive drug administration®" is characterised by a combination of several different electro–molecular interactions: iontophoresis, electroosmosis/electrophoresis and electroporation are all responsible for electromotive transport of drug molecules in an electric field across biological membranes into underlying tissues. [13].

Iontophoresis refers to accelerated ion transport (into tissues) by means of an electric current that is passed through a solution containing the ions (i) and administered at a rate defined by Faraday's Law:

$$Ji\ (\mathrm{mol/s}) = I(\mathrm{tr})/zF \quad (1)$$

where I is the current (amperes), tr is the proportion of applied current carried by i, z the valency; and F is Faraday's constant [14, 15]. Iontophoresis usually increases water transport around the target molecules which will entrain any non-ionised solutes that are present. This form of "solvent drag" is termed electroosmosis [13].

Electroporation implies increasing biological membrane permeability under the influence of an electric field, which increases transport rates down concentration gradients [16].

The total drug transport rate includes both passive diffusion (PD) and EMDA. When a membrane is characterised by low permeability e.g. the urothelium, EMDA predominates so that, for all practical purposes, it may be considered as solely responsible for drug transport. EMDA rates are not only markedly increased but are also well controlled by variations in current intensity.

Since MMC is mostly non-ionised within the urinary pH range, electroosmosis is the predominant process for EMDA. The requisite ions come as a sodium chloride in MMC crystals. When a current with positive polarity is applied to a solution containing Na^+/Cl^-/MMC, sodium ions are transported via iontophoresis into underlying tissues, carrying along water that also contains MMC molecules in hydration shells [16, 17].

Mitomycin-C penetration of the urothelium was investigated in vitro in a two-cell diffusion chamber model. MMC concentrations in human bladder tissue sections were analysed by high-performance liquid chromatography.

An initial study showed that in all tissue samples exposed to electric current MMC concentrations were higher than after PD, the variability in drug delivery rate was reduced and the electric current caused no histological tissue damage and no chemical modification to MMC [18]. In a second study MMC concentration-depth profiles in the bladder wall after PD and EMDA were compared. While MMC concentrations after PD reached a plateau in all compartments after 15 min with no further increase, EMDA significantly enhanced MMC administration and reduced variability in drug delivery rate in all bladder wall layers, reaching IC90 levels in the urothelium and lamina propria [19].

These in vitro experiments were limited by lack of blood supply. Much more convincing are in vivo data from a clinical study that compared MMC administered by PD or EMDA in high-risk NMIBC [20]. Peak plasma MMC concentrations were significantly higher with EMDA (43 vs. 8 ng/ml), and the EMDA-induced increase in MMC tissue penetration resulted in a better clinical response rate. Estimates for MMC plasma concentration–time area under the curve values are three times higher for EMDA than for PD. Although EMDA markedly increased drug transport into the bladder wall, MMC plasma levels remained well below toxic concentrations (400 ng/ml).

Technique of intravesical EMDA/MMC

Intravesical EMDA is administered by a battery powered generator (Physionizer® 30, manufactured by Physion®, Medolla, Italy) that delivers a controlled electric current of 0–30 mA/0–55 V DC, which is passed between two electrodes: the active intravesical electrode, which is integrated into a specifically designed transurethral catheter, and the dispersive ground electrodes, which are placed on lower abdomen skin (Fig. 1). Active electrode polarity and current intensity are set on the current generator by the operator.

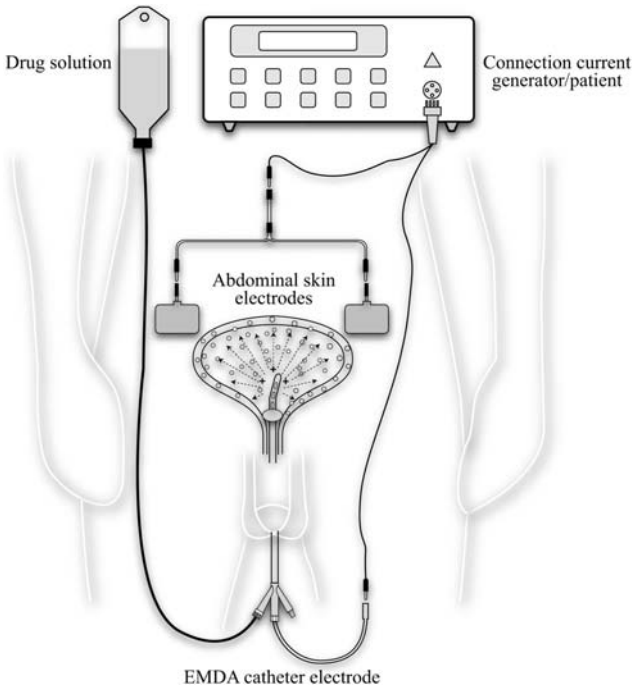

Fig. 1 Representation of an intravesical therapy with EMDA system

When applying intravesical EMDA for MMC chemotherapy of NMIBC, the special electrode catheter is inserted into the bladder using a standard sterile technique. The bladder must be carefully washed with distilled water to clear urinary solutes that would interfere with drug ions before instilling a solution of 40 mg MMC in 100 cc of water. This volume is needed for uniform bladder distension and homogenous distribution of the electric field and the drug. The catheter and ground electrodes are connected to the generator, and the active electrode is set to positive polarity. The generator gradually increases the current to the established level. When the maximum current of 23–25 mA is tolerated, the total treatment time is 30 min. Some patients report a tingling or burning sensation from the electric current.

Efficacy of intravesical EMDA/MMC

MMC-EMDA delivery rates in vitro showed a fourfold to sevenfold increase over PD [18, 19], suggesting it might be more efficacious clinically. The few available clinical data appear confirmatory.

In a phase II study Brausi et al. [21], treated 13 patients with multifocal Ta-T1/grade 1–2 bladder tumors with 8 weekly MMC 40 mg instillations (instillation time 120 min) and 15 patients with 8 weekly sessions of intravesical EMDA of MMC 40 mg (20 min with an electric current of 15 mA). Before treatment, all bladder tumours except for one marker lesion were resected. The marker lesion disappeared in 5/12 patients (41.6%) after PD and in 6/15 patients (40%) after EMDA. Recurrence rates in complete responders were 60% after PD and 33% after EMDA.

Another small observational study reported low recurrence rates of high-risk NMIBC after intravesical EMDA of MMC 40 mg (20 min, 15 mA) given once a week for 4 weeks [22]. After a median follow-up of 14.1 months 9/16 patients (56%) were recurrence free. Despite short follow-up times and small patient cohorts, findings in both these studies suggested EMDA/MMC was associated with better clinical outcomes than standard MMC instillation protocols.

In a prospective randomized study, response rates for PD/MMC, EMDA/MMC and BCG were compared in 108 patients with multifocal Tis [20]. After randomization, all patients received a 6 week treatment course: 1 h instillation of 40 mg MMC in Group 1, 30 min EMDA of 40 mg MMC with a current of 20 mA in Group 2, or 2 h instillation of 81 mg BCG in Group 3. Non-responders received another 6 week course of therapy, while responders received 10 monthly maintenance treatments. Results are summarised in Table 1. At 3 and 6 months, the EMDA/MMC response rates were significantly better than PD/MMC. After a median follow-up of 82 months [23], EMDA/MMC was equivalent to BCG in terms of complete response and recurrence, and both were superior to passive MMC instillation. However, progression to muscle invasive disease, time to progression and overall as well as disease-specific mortality were not significantly different. Peak MMC plasma concentrations were 5.5 times higher after EMDA than PD. Electromotive delivery increased toxic side effects in the bladder, which were substantially less than with BCG.

Sockett et al. [24] administered a 6 week course of weekly EMDA-MMC to a small group of 13 BCG-refractory patients with high-risk non muscle invasive recurring bladder cancer (pT1G3 and Tis) who were followed up over a 15-month-period. 4/13 patients (31%) remained recurrence-free while the others recurred without progression, so the bladder was preserved in all patients. The authors concluded that EMDA-MMC may be beneficial in some patients with high-risk NMIBC who are refractory to BCG.

Enhancing intravesical MMC efficacy for NMIBC by EMDA

The need to increase efficacy and reduce emergence of resistant malignant cells underlie the rationale for combining anticancer drugs. A MMC-related tissue scarifying

Table 1 Outcomes after intravesical PD/MMC, EMDA/MMC and BCG in patients with carcinoma in situ of the bladder [20, 23]

	PD/MMC ($n = 36$)	EMDA/MMC ($n = 36$)	BCG ($n = 36$)	P value
Complete response (%)				
3 months	10 (27.8)	19 (52.8)	20 (55.5)	0.036
6 months	11 (30.5)	21 (58.3)	23 (63.9)	0.012
Crossover	–	3/13 (23.1)	14/40 (35.0)	0.511
Median follow-up (months)	84	94	79	0.94
Recurrence				
No. of patients (%)	30 (83.3)	24 (66.7)	24 (66.7)	0.221
Median time to recurrence (months)	15.1	44.8	33.3	<0.0001
Disease progression				
No. of patients (%)	16 (44.4)	11 (30.6)	10 (27.8)	0.302
Median time to progression (months)	27.5	68.8	70.0	0.064
Mortality (%)				
Overall	19 (52.8)	17 (47.2)	19 (52.8)	0.913
Bladder cancer	11 (30.5)	8 (22.2)	8 (22.2)	0.753

effect was hypothesised to prepare the ground for more efficient BCG attachment to the urothelium, however, early studies [25–28] claimed the combination was no better than MMC [25–27] or BCG alone [28].

Di Stasi et al. [29] conducted a prospective, randomised study comparing BCG alone versus sequential intravesical BCG and EMDA/MMC in patients with stage pT1 bladder cancer, 39% of whom had grade 3 disease. The roles of BCG and MMC were inverted, as administering BCG before MMC was hypothesised to induce inflammation and enhance MMC tissue uptake. 212 patients were randomly assigned to either 6 weekly BCG 81 mg instillations for 2 h ($n = 105$) or to 2 weekly BCG 81 mg instillations followed by a single EMDA/MMC (40 mg, 20 mA/30 min), this 3 week cycle being repeated for three cycles ($n = 107$). Patients in both groups who were disease-free 3 months after treatment received monthly maintenance instillations for 10 months, either BCG or MMC/EMDA monthly for 2 months followed by BCG once as one cycle for a total of three cycles. After a median follow-up of 88 months, patients assigned to sequential BCG and EMDA/MMC had a significantly longer disease-free interval and lower recurrence rate than those assigned to BCG alone (Table 2). They also had a lower rate of progression, overall mortality and disease-specific mortality. The researchers suggested that BCG-induced inflammation might increase urothelial permeability for consecutive MMC, thus increasing tissue concentration and the anticancer effect. Despite these encouraging outcomes, however, the significant progression rate in patients with pathological stage T1 and grade 3 disease even after sequential BCG and EMDA/MMC (12% without Tis and 17% with Tis) still remains a clinical challenge.

Table 2 Outcomes after intravesical BCG and sequential BCG and EMDA/MMC in high-risk NMIBC [29]

	BCG alone ($n = 105$)	Sequential BCG/MMC ($n = 107$)	P value
Recurrence			
Patients (%)	61 (58)	45 (42)	0.001
Median disease-free interval, months (95% CI)	21 (15–54)	69 (55–86)	0.022
Progression to muscle invasive disease			
Patients (%)	23 (22)	10 (9)	0.005
Median time to progression, months (95% CI)	16 (10–21)	37 (18–58)	0.003
Mortality			
Death from any cause (%)	34 (32)	23 (21)	0.045
Death from bladder cancer (%)	17 (16)	6 (6)	0.010

A new concept of preoperative recurrence prophylaxis by one single intravesical EMDA/MMC instillation immediately before TUR was recently presented by Di Stasi et al. [30]. In a prospective study, 167 patients with pTa G1–G2 bladder tumours were randomized to three groups: TUR alone ($n = 57$), TUR followed by one single 1 h MMC 40 mg instillation ($n = 56$) or intravesical EMDA/MMC 40 mg (30 min, 20 mA) before TUR ($n = 54$). Median follow-up was 84.7 months. The recurrence rate was reduced and the disease-free interval lengthened in patients who received preoperative EMDA/MMC (Table 3). Although this study queries the value of postoperative MMC instillations and may be a milestone for future therapeutic concepts, confirmation by other investigators is needed.

Table 3 Outcomes after TUR alone, TUR plus one single immediate postoperative intravesical PD/MMC instillation (PD/MMC post-TUR) and one single immediate preoperative intravesical EMDA/MMC instillation (EMDA/MMC pre-TUR) in pTa bladder tumours [30]

	TUR/alone ($n = 57$)	PD/MMC post-TUR ($n = 56$)	EMDA/MMC pre-TUR ($n = 54$)	P value
Recurrence rate, no. of patients (%)				
Overall	38 (67)	30 (54)	20 (37)	0.007
Grade 1	6/20 (30)	4/24 (17)	1/18 (6)	0.157
Grade 2	32/37 (86)	26/36 (72)	19/36 (53)	0.007
Single	12/24 (50)	9/24 (37)	5/23 (22)	0.132
Multiple	26/33 (79)	21/32 (66)	15/31 (48)	0.039
Median time to first recurrence, months	12.8	14.7	36.8	0.009

Conclusion

In the management of non-muscle invasive transitional cell carcinoma high-level evidence supports the widespread practice of intravesical therapy with MMC. Randomized trials showed a significant reduction in short-term recurrence compared with TUR alone, but little effect on long-term progression [3, 4]. Thus, overall efficacy seems to be suboptimal and there is a considerable request for improvement, which may be achieved by changing the means of administration.

Intravesical EMDA/MMC is safe and effective [20, 29, 30]. In vitro [18, 19] and in vivo [20] studies demonstrated MMC concentrations in the bladder wall were significantly increased by applying an electric current (EMDA). Higher MMC concentrations may have a clinical impact since EMDA was associated with lower recurrence rates than PD. Further data suggested EMDA/MMC was at least equivalent to BCG in high-risk bladder tumours. New strategies such as BCG combined with EMDA/MMC as well as preoperative EMDA/MMC provided promising preliminary results in terms of higher remission rates and longer remission times. If confirmed in controlled multicentre clinical trials, these improved outcomes, particularly compared with failed intravesical therapy, would easily justify the relatively high cost of EMDA therapy. Costs will inevitably have to be scrutinised even though the initial expense of the generator and running costs of disposables appear modest.

In our view, when managing NMIBC the role of EMDA needs to be assessed in-depth and the potential advantages of EMDA/MMC should certainly not be ignored. It is to be hoped that future developments will enable EMDA/MMC to be inserted into standardised treatment protocols.

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