

Intravesical electromotive drug administration of mitomycin-C for non-muscle invasive bladder cancer.

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Summary

This article reviews intravesical application of electromotive drug administration (EMDA) for the treatment of bladder cancer and the evidence in support of intravesical passive diffusion chemotherapy in the management of non-muscle invasive bladder cancer. Two recently published randomised trials adopting protocols that use EMDA to enhance urothelial transport of intravesical mitomycin-C showed it provided a therapeutic advantage and suggested that intravesical passive diffusion administration of chemotherapeutic drugs may be suboptimal. Further studies are required to demonstrate feasibility and advantage of intravesical EMDA of mitomycin-C in the wider uro-oncological community.

KEY WORDS: *Electromotive drug administration (EMDA); Mitomycin C, Non-muscle invasive bladder cancer; Intravesical chemotherapy*

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INTRODUCTION

The most frequently diagnosed bladder tumors are non-muscle invasive transitional cell carcinomas. The disease may be confined to the urothelium (flat carcinoma in situ [Cis]) and papillary stage Ta) or invade the lamina propria (stage T1) (1). Although transurethral resection (TUR) is the first routine diagnostic and therapeutic step in management, recurrence rates after TUR alone range from 31 to 78% with progression to muscle invasion in 0.8-45% of cases

The high probability of disease recurrence and progression has led to widespread use of intravesical therapies with cytotoxic and immunotherapeutic agents, which offer the advantages of little systemic drug uptake and optimal contact between drug, tumor, tissue at risk and viable cancer cells with tumour seeding potential that might have been shed. The goals of intravesical therapy are to eradicate existing tumor, prevent recurrences and progression, minimize morbidity and costs of further surgery and identify refractory/progressive disease before it becomes metastatic.

Most early reports of intravesical treatment for superficial bladder cancer, which has been used for the past 4–5 decades, were anecdotal and its effects were not clarified until the early to mid 1990s (2). Beneficial in terms of frequency of recurrence and time to recurrence in grade 1–2 stage Ta tumours, which are usually non-invasive, it has negligible effects on disease recurrence and progression in high-risk superficial bladder cancer—ie, grade 3,

stage T1, and Cis. BCG, however, as induction and maintenance treatment effectively delays progression (3).

Mitomycin (MMC), a common chemotherapeutic agent in intravesical treatment, was widely studied at various doses, concentrations, infusion volumes and bladder residence times, usually in non-selected groups of patients; benefits are highly variable (4). MMC pharmacokinetics in superficial bladder cancer patients during intravesical therapy (5), the concentrations required for a cytotoxic effect on histocultures of patient bladder transitional carcinoma (6), and penetration in dog and human bladders (7, 8) were all extensively investigated. Data suggest that intravesical MMC is inadequate for treatment of cancer cells that are deeply located in bladder wall tissues either because of reduced tumor sensitivity or lower drug concentrations at target sites beyond the urothelium. Wientjes et al. (9) combined data from laboratory, animal, and human studies and computer simulations to describe a compelling MMC regimen that was primarily based on optimising diffusion down concentration gradients. Au et al. (10) reported a phase III trial demonstrating the optimised regimen (40 mg MMC with pharmacokinetic manipulation to increase drug concentration by decreasing urine volume and urine alkalinisation to stabilise the drug) was better than a standard MMC regimen (20 mg MMC) in all risk groups. However, results in subgroups with Cis, stage T1, or grade 3 disease were less definitive, although a trend was noted towards longer time to recurrence.

In cases of high risk superficial bladder cancer several reasons must be assumed to underlie the failure of intravesical MMC. Obvious causes that apply to all intravesical regimens are under staging and/or incomplete disease resection. Furthermore, T1 tumors usually invade to a depth that is beyond what the required therapeutic concentrations of MMC can reach, no matter how optimal the intravesical treatment. Finally, aggressive high grade cancer cells are less chemosensitive, which may explain why carcinoma in situ responds poorly to MMC. If Cis, grade III and T1 cancers require higher concentrations than can be delivered by passive transport, accelerated MMC administration rates with greater accumulation in tissue may improve the clinical response.

KINETICS OF INTRAVESICAL ELECTROMOTIVE ADMINISTRATION OF MITOMYCIN-C

Terminology involving "electromotive drug administration" (EMDA) of solutes is yet to be finalized (11). Iontophoresis, electro-osmosis/electrophoresis, and electroporation, which are involved in electromotive transport, can be recruited to accelerate drug administration across biological membranes and into underlying tissues. Iontophoresis describes the accelerated transport of ions (into tissues) by means of an electric current passed through a solution containing the ions (i) to be administered (12) at a rate defined by Faraday's Law:

$$J_i = I(\text{tr})/z F \text{ mol/s (A)}$$

where I is the current (amperes), tr the proportion of applied current carried by i , and z the valency; F is Faraday's constant (13). Iontophoresis is usually associated with increased water transport that will entrain any non-ionized solutes which may be present. This form of "solvent drag" is often termed electroosmosis (11). Drug transport rate (dD/dt) is the the formula expressing the sum of transport induced by passive diffusion (PD) and by EMDA ($dD/dt = PD + EMDA$). When dealing with a low permeability membrane such as the urothelium, EMDA is so dominant that, for all practical purposes, it may be considered as the sole force manipulating drug transport. Thus, administration rates are not only markedly increased but are controlled simply by varying the current intensity ($dD/dt = K z I$).

As MMC is almost totally non-ionized within the full pH range that is tolerated by the bladder (4.5– 8.5 units), realistic clinical or laboratory investigations involve electroosmosis only. The requisite ions for this mode of EMDA come as a sodium chloride excipient in MMC crystals. When a positive polarity current is applied to a solution containing $\text{Na}^+/\text{Cl}^-/\text{MMC}$, sodium ions are iontophoresed into underlying tissues. This process that includes transport of water in hydration shells around Na^+ (14) as well as in the free form (13).

Electroporation implies increasing biological membrane permeability under the influence of an electric field, which increases transport rates down concentration gradients (15).

Urothelial penetration of MMC was investigated in vitro using a two-cell diffusion chamber to analyze MMC con-

centrations in human bladder tissue sections by high-performance liquid chromatography. The first study (16) was designed (a) to establish an appropriate tissue pharmacokinetic model to compare MMC quantities and concentrations in the human bladder wall after PD or EMDA and (b) to determine the effects of EMDA on tissue morphology and viability, and (c) MMC structure. In all tissue samples exposed to electric current MMC concentrations were increased and the variability in drug delivery rate was reduced; the applied electric current caused no histological damage to tissue and no chemical modification to MMC.

The objectives of the in-depth second study (17) were (a) to make a preliminary assessment of MMC concentration-depth profiles in the bladder wall at specified time intervals after PD and (b) to compare MMC concentration-depth profiles after PD and EMDA. The preliminary investigation with PD alone demonstrated a plateau was reached in all compartments after 15 min and MMC concentrations did not undergo any significant changes in up to 60 min incubation, indicating that MMC was probably rapidly metabolized within the bladder wall or absorption was blocked.

The study comparing PD and EMDA showed EMDA significantly enhanced MMC administration rates and reduced the variability in drug delivery rate into all bladder wall layers, achieving IC90 levels in the urothelium and lamina propria.

These in vitro experiments were limited by being performed on tissue deprived of blood supply. Much more convincing are in vivo data from a clinical study that compared MMC given by PD with EMDA of MMC (18). Peak plasma MMC concentrations were significantly higher with EMDA of MMC (43 vs. 8 ng/ml) and the EMDA-related increase in MMC penetration most likely improved the response rate, as was seen in this study. Estimates for the ratio of plasma concentration-time area under the curve values are of the order of 3-fold in favour of EMDA of MMC. Although electromotive administration markedly increased MMC transport, plasma levels in the current study remained well below toxic concentrations (400 ng/ml).

TECHNIQUE OF INTRAVESICAL ELECTROMOTIVE ADMINISTRATION OF MITOMYCIN-C

EMDA (Physion[®], Medolla, Italy) offers a means of controlling and enhancing tissue penetration of certain drugs when applied to a surface epithelium where they have a local therapeutic effect, in order to increase efficacy. Using intravesical EMDA, drug delivery through the bladder urothelium is accelerated by applying an electric field, that stimulates directional ionic and solute movement, across the bladder wall. A small, controlled electric current (0-30mA, 0-55V dc) is passed between two electrodes connected to the Physionizer[®] 30 Mini battery powered generator. The dispersive ground electrodes, placed on cleaned, unblemished skin of the lower abdominal wall, provide a wide contact area. The active intravesical electrode, which is integrated within a specifically designed urethral catheter, ensures uniform distribution of the electric current. Active electrode

polarity and current intensity are set on the Physionizer by the operator. Correct catheter placement in the bladder is ensured by filling its 4-5 ml balloon with saline solution and drawing it gently against the bladder neck. One application of EMDA is treatment of non-muscle invasive bladder cancer with intravesical MMC. With the patient lying supine on a couch throughout the procedure, the special electrode catheter for bladder therapies is inserted transurethrally into the bladder using a standard sterile technique. The catheter balloon is then filled and the bladder is carefully drained and washed with distilled water to clear urinary solutes that would alter electromotive activity. A solution of 40mg MMC and 100 ml water is instilled through the catheter. This somewhat larger volume than is conventionally used for passive administration ensures even drug distribution throughout the bladder wall. The catheter and ground electrodes are connected to the generator, and the active electrode set to positive polarity. The generator gradually increases the current to the established level. When the maximum current of 25 mA is tolerated, the total treatment time is 30 minutes. At completion, the generator switches off. Side effects related to the instilled drug include a tingling or burning sensation from the electric current in some patients. Bladder spasm, which occasionally occurs, is minimised by reducing the electric current which enables the procedure to be well-tolerated albeit over a longer treatment time. The relatively greater diameter and rigidity of the catheter electrode compared with the standard 12 or 14 F catheter used for intravesical therapies may cause some discomfort and bladder spasms.

EFFICACY OF INTRAVESICAL ELECTROMOTIVE ADMINISTRATION OF MITOMYCIN-C

In the laboratory EMDA of MMC increased delivery rates 4 to 7-fold compared with passive transport (16, 17), suggesting that electromotive acceleration of MMC might decrease the failure rate of current intravesical administration of chemotherapeutic drugs.

Brausi et al. (19) investigated the efficacy of intravesical EMDA of MMC in Phase II study. Thirteen patients with multifocal stages Ta-T1 and grade 1-2 transitional cell carcinoma of the bladder received 40 mg intravesical PD/MMC instillation with a dwell time of 120 minutes, once a week for 8 weeks. A second group of fifteen patients with the same characteristics were treated with 40 mg intravesical EMDA/MMC instillation, with 15 mA electric current for 20 minutes, once a week for 8 weeks. Before treatment, all bladder lesions except one (which was used as a marker) were resected in each patient. The complete macroscopic and histological disappearance of the marker lesion was reported in 5/12 patients (41.6%) in the PD/MMC group and in 6/15 patients (40%) in the EMDA/MMC group. The recurrence rate in complete responders was 60% in the PD/MMC group and 33% in the EMDA/MMC group, after 7.6 and 6 months follow-up respectively. The disease-free interval was 10.5 months for the PD/MMC group and 14.5 months for the EMDA/MMC group. Another small observational study on patients with non-muscle invasive bladder cancer reported low recurrence rates after intravesical 40 mg

EMDA/MMC instillation, with 15 mA electric current for 20 minutes, once a week for 4 weeks (20). After a median follow-up of 14.1 months 9/16 patients (56%) were recurrence-free. Findings in both studies, even though they had short follow-ups and small patient cohorts, suggested intravesical EMDA/MMC was better than PD/MMC in terms of recurrence rate and disease-free interval.

The efficacy of intravesical EMDA/MMC was assessed in a prospective randomized study, comparing PD/MMC versus EMDA/MMC and using BCG as a comparative treatment, in patients with high risk non-muscle invasive bladder cancer (18). After TUR and multiple biopsies 108 patients were randomized to 3 groups of 36. Patients received either 40 mg EMDA/MMC instillation with 20 mA electric current for 30 minutes, 40 mg PD/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 non-responders and a follow-up of 10 monthly treatments for responders. The complete response for EMDA/MMC versus PD/MMC at 3 and 6 months was 53% versus 28% ($p=0.036$) and 58% versus 31% ($p=0.012$). BCG response rates were 56% and 64%. Median time to recurrence was 35 versus 19.5 months ($p=0.013$) versus 26 months for BCG. Peak MMC plasma concentrations were 5.5 times higher after intravesical EMDA/MMC than intravesical PD/MMC, suggesting that bladder wall cells were exposed to incremental concentrations of this magnitude. Electromotive delivery increased the toxic effects in the bladder, but these were substantially less than with BCG alone. In terms of complete response and recurrence, which are, however, unreliable predictors of the long-term outcome in these high risk patients, intravesical EMDA/MMC and BCG appeared to be effective treatments for high risk non-muscle invasive bladder cancer and both seemed better than PD/MMC transport. In some refractory cases BCG-EMDA/MMC crossover and *viceversa* is beneficial. As response rates match those induced by BCG, Electromotive/MMC may be an alternative or complementary therapy.

COMBINATION TREATMENT: SEQUENTIAL INTRAVESICAL EMDA/MMC AND BCG

The rationale for combining anticancer drugs, as in most current systemic regimens, is based on the need to increase efficacy and reduce emergence of resistant malignant cells. Curiously, this approach is not frequently applied when using intravesical agents to treat non-muscle invasive bladder cancer, even though immunotherapeutic BCG and chemotherapeutic MMC seem to be a potentially effective combination. Although previous studies (21-24) showed the combination was not better than either MMC alone (21-23) or BCG alone (24) they all assigned MMC the separate roles of (a) its chemotherapeutic action and (b) a tissue scarifying effect to prepare the ground for a more efficient BCG attachment to the urotelium

Di Stasi et al. (25) recently reported the results of a prospective, randomised comparison of BCG alone ver-

Table 1.

Findings from a randomised trial of intravesical BCG alone versus sequential BCG and EMDA/MMC (2).

	BCG	Sequential BCG + MMC/EMDA	P value
Disease free interval (months)	21	69	0.001
Recurrence rate (%)	57.9	41.9	0.001
Progression rate (%)	21.9	9.3	0.004
Overall mortality (%)	32.4	21.5	0.453
Disease-specific mortality (%)	16.2	5.6	0.011

sus sequential intravesical BCG and EMDA/MMC in patients with stage pT1 bladder cancer. The authors inverted the roles of BCG and MMC with former preparing the ground for the latter, hypothesizing that administering BCG before MMC would induce inflammation and enhance the MMC tissue uptake and that EMDA/MMC instillations had the potential to eliminate malignant cells that escaped the BCG immunological surveillance. All patients in the trial were at high-risk of progression: pathological stage T1 bladder cancer following TUR, with 39% having grade 3 disease. The 212 patients were randomly assigned to either BCG infused over 120 min once a week for 6 weeks (n=105) or to BCG infused over 120 min once a week for 2 weeks, followed by a single treatment with EMDA/MMC (intravesical electric current 20 mA for 30 min), this 3 week cycle being repeated twice (n=107). Patients in both groups who were disease free 3 months after treatment were scheduled to receive monthly instillations for 10 months. With a median follow-up of 88 months, the results indicated that patients assigned sequential BCG and EMDA/MMC had a significantly longer disease-free interval and lower recurrence rate than those assigned BCG alone (Table 1).

Importantly, this study showed that patients assigned sequential BCG and EMDA/MMC also had lower progression, overall mortality and disease-specific mortality (Table 1). The researchers suggested that BCG-induced inflammation might have increased bladder mucosa permeability so that MMC reached target tissue more easily where it exerted its anticancer effect. Alternatively, improved efficacy might have been an additive, rather than synergistic, effect rather. This is the first study to report the BCG and MMC combination was better than BCG alone in the treatment of bladder cancer (24). It is also the first study to investigate EMDA/MMC delivery with BCG. However, even in the sequential BCG and EMDA/MMC group the frequency of progression in patients with pathological T1 and grade 3 disease was significant (11.8 without Tis - 16.7% with Tis) and remains a clinical challenge.

CONCLUSIONS

In patients with high risk non-muscle invasive bladder cancer the technique of intravesical EMDA/MMC is both safe and effective. As demonstrated in-vitro and in-vivo.,

applying an electric current (EMDA) significantly increases the concentration of MMC delivered into the bladder wall. One randomised study showed EMDA/MMC is better than standard MMC in reducing the recurrence rate and prolonging the disease-free interval while another demonstrated that a protocol including sequential intravesical BCG and EMDA/MMC reduced recurrence, tumour progression and mortality in patients with high risk non-muscle invasive bladder cancer. These are clinically substantial and important favourable outcomes, with an effect on mortality that has not been previously demonstrated in any randomised study. Further controlled clinical trials are required to confirm these outcomes, and examine the role of EMDA in the overall management of non-muscle invasive bladder cancer.

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