Expert Opinion

Electromotive drug administration with mitomycin C for intravesical treatment of non-muscle invasive transitional cell carcinoma

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This article reviews the use and application of electromotive drug administration for the intravesical treatment of bladder cancer. Strong evidence supports the use of passive intravesical chemotherapy in the management of non-muscle invasive bladder cancer. More recently, two published randomised trials have shown therapeutic advantage with protocols that use electromotive drug administration to enhance urothelial penetration of intravesical mitomycin C. The results suggest that the passive intravesical administration of chemotherapeutic drugs may be suboptimal. Further studies are required to demonstrate the feasibility and advantage of electromotive intravesical mitomycin C in the wider uro-oncological community.

Keywords: chemotherapy, electromotive drug administration, intravesical, mitomycin C, non-invasive bladder cancer, transitional cell carcinoma

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1. Introduction

Electromotive Drug Administration® (EMDA) (Physion®) offers a means of controlling and enhancing the tissue penetration of certain drugs when applied to a surface epithelium, where they have a local therapeutic effect, in order to increase their efficacy. One application is the treatment of non-muscle invasive bladder cancer with intravesical chemotherapy. In this setting, the opportunity for therapeutic advantage relates to enhanced drug permeation of the urothelium and sub-urothelial connective tissue, retaining tolerability and avoiding systemic toxicity.

Using intravesical EMDA, drug delivery through the bladder urothelium is accelerated by the application of an electric field across the bladder wall, which stimulates directional ionic and solute movement. A small, controllable electric current (0 – 30 mA, 0 – 55 V dc) is passed between two electrodes connected to the Physionizer® 30 Mini battery powered generator. The dispersive ground electrodes are placed on cleaned and unblemished skin of the lower abdominal wall, providing a wide area of contact. The active intravesical electrode is integrated within a specifically designed urethral catheter that ensures uniform distribution of the electric current. The catheters and electrodes are disposable, single-use items (**Figure 1**).

The polarity of the active electrode and the current intensity are set on the Physionizer by the operator, following the instruction for the particular EMDA protocol to be used. The correct position of the catheter in the bladder is assured by filling its 3 ml balloon with air, then drawing it gently against the bladder neck. Various designs of electrode catheter are available, suitable for a variety of electromotive applications, and allow for treatment of the bladder wall alone,

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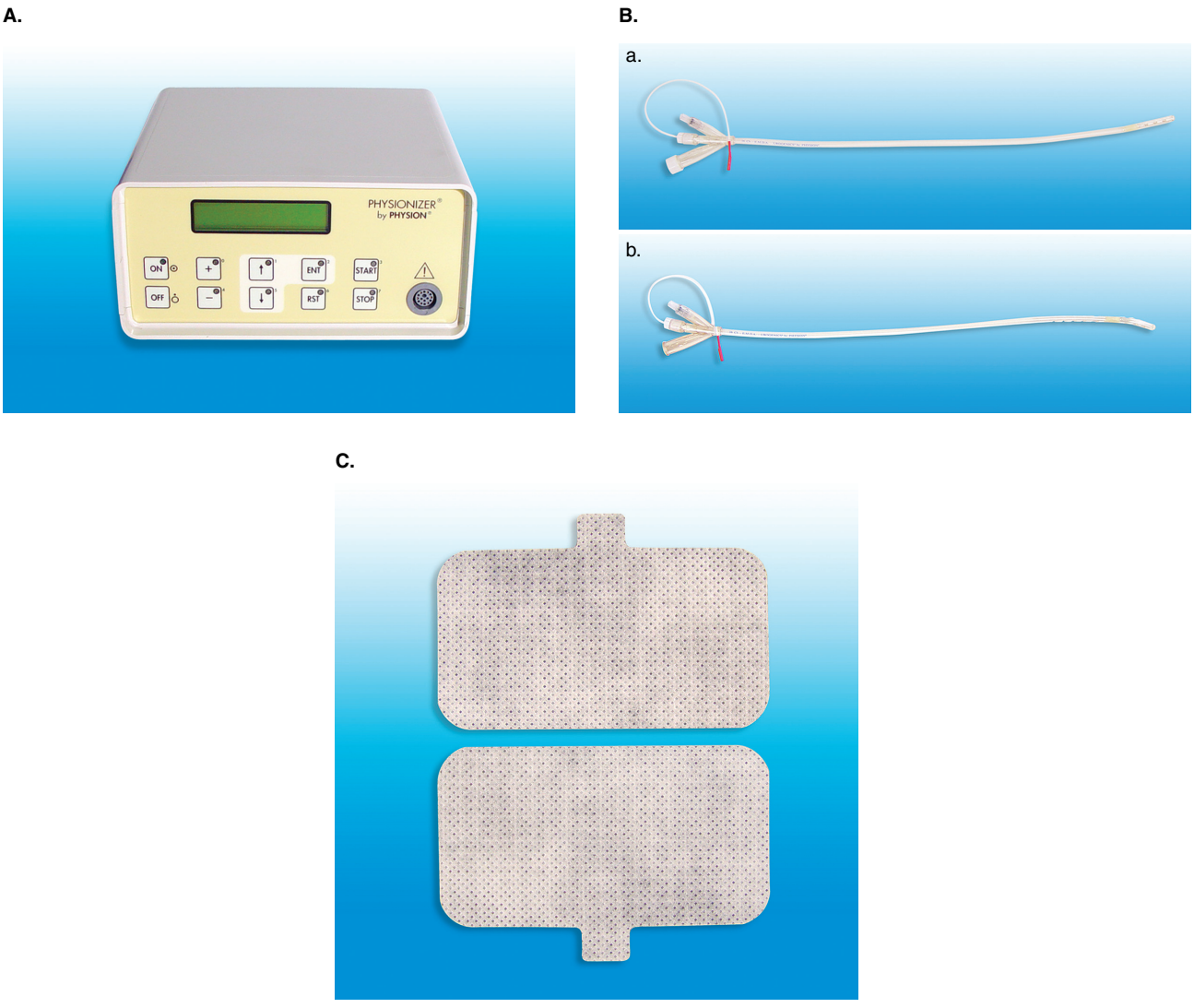

Figure 1. Equipment for intravesical Electromotive Drug Administration®. A. Physionizer® 30 Mini battery powered generator (Physion®); **B.** Urethral catheters incorporating the active electrode for electromotive delivery of drug to a) bladder only b) bladder and prostate; **C.** Adhesive skin pads that are applied to the lower anterior abdominal wall as the ground electrode connected to the generator.

the prostatic urethra alone, or both the bladder wall and prostatic urethra, according to the position of the holes in the catheter relative to the balloon. Catheters are only available in size 18F.

For electromotive intravesical chemotherapy, the patient lies supine on a couch throughout the procedure. The specifically designed electrode catheter for bladder therapies is inserted transurethrally into the bladder using a standard sterile technique and intraurethral local anaesthetic, lubricant gel. The same catheter is suitable for patients of either gender. The catheter balloon is then filled, the bladder carefully drained and then washed with distilled water to clear urinary solutes that would alter electromotive activity. A drug solution of mitomycin C 40 mg, lidocaine 4% 10 ml and 140 ml bi-distilled water is then instilled through the catheter. 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 desired level. When a maximum current of 25 mA is tolerated, the total treatment time is ~ 25 min. At completion, the generator switches off.

Side effects relate to the instilled drug, and some patients may experience a tingling or burning sensation from the electric current, and occasionally bladder spasm. If bladder spasm is induced, this can be minimised by reducing the electric current. This enables the procedure to be well-tolerated, albeit with a longer treatment time. The relatively greater diameter and rigidity of the catheter electrode

compared with a standard 12 or 14 F catheter used for intravesical therapies may cause some discomfort and occasional difficulty with insertion.

EMDA appears to offer significant therapeutic advantage for the intravesical administration of mitomycin C in patients with non-muscle invasive bladder transitional cell carcinoma [1,2]. It can also be used with other intravesical agents [3,4]. These include lidocaine and epinephrine solution providing local anaesthesia of the prostate and bladder wall sufficient for some invasive urological procedures. This technique may be combined as necessary with bladder wall infiltration of local anaesthesic and/or systemic sedo-analgesia [5-7]. A similar and suitably adjusted approach with the appropriate drug cocktail solution can be used for relief of painful bladder syndromes and prostatitis [8-11]. It has also been used in the treatment of the unstable bladder [12] and hypocontractile bladder [13]. Intravesical EMDA may enhance the penetration of certain antibiotics into the bladder wall and prostate, and, therefore, it has been used for the treatment of certain urinary tract infections, particularly recurrent cystitis, prostatic infection and catheter-related infection. Percutaneous EMDA with dexamethasone and verapamil (using the Physionizer Mini generator) has been used for treatment of Peyronie's disease of the penis [14-16]. These applications are not widely established in clinical practice, with limited data from controlled trials [15,16].

2. The principles of intravesical chemotherapy

Intravesical chemotherapy is widely used for the treatment of non-muscle invasive transitional cell carcinoma, with proven therapeutic efficacy [17-21]. The advantages of intravesical delivery include minimal systemic absorption and, therefore, very low risk of the systemic toxicity that occurs with systemic administration. Drug is administered as a solution through a urethral catheter, and is generally retained within the bladder for 1 h to assure adequate urothelial exposure. The advantage arises from the very high local concentration applied to the urothelial tumour, including viable cells that may have been shed with potential for tumour seeding.

The general determinants of passive drug penetration through urothelium include:

i) pharmaceutical: relative molecular weight, molecular polarity, concentration, osmolality and temperature.
ii) bladder: urothelial structure and extent of pathology (inflammation, neoplasia), bladder distension and recent surgical or other intravesical interventions.
iii) patient: urine output during drug instillation, urinary pH and time from intravesical interventions.

Other factors that may contribute to variable efficacy of intravesical treatment include:

i) The treatment regimen (number and interval of doses) and its timing with respect to tumour resection.
ii) Tumour depth and drug penetration into tumour and adjacent lamina propria.
iii) Tumour sensitivity to the chemotherapeutic agent.

A number of chemotherapeutic agents are given into the bladder. Mitomycin C has shown efficacy, and only occasionally is toxicity seen. This has lead to its popularity. Bladder wall toxicity – chemical cystitis – is uncommon, suggesting that more intensive treatment is possible and this may be why studies with EMDA have concentrated on mitomycin C.

3. Action of intravesical mitomycin C

Mitomycin C has a molecular weight of 334 kDa. It cross-links nuclear DNA, and the synthesis of DNA is inhibited. Although the G1 phase of the cell cycle is generally considered the most sensitive, inhibition of DNA synthesis is not specific to this phase. The dose of mitomycin C for passive intravesical chemotherapy is usually 40 mg in 40 ml water or saline, although doses of 20 – 60 mg may be used.

Thrombocytopenia and leucopenia, which may occur with systemic administration of mitomycin C, are very rare following intravesical delivery, owing to the small fraction absorbed. The absorption that does take place is confirmed by the occasional occurrence of allergic skin reactions. Local bladder reactions occur and these are related to chemical cystitis or urinary infection. This is not surprising considering the very high drug concentrations achievable in the bladder lumen. Similarly, extravesical leak (particularly following surgical bladder perforation) may cause severe perivesical reaction that may lead to bladder contracture, perivesical fibrosis and ureteric obstruction [22-26].

A single instillation of mitomycin C following resection of a newly diagnosed bladder tumour has been shown to have a beneficial effect on the long-term recurrence rates and overall disease control. Recurrence rates may be reduced by ~ 40% at 2 years, and 15 – 20% at 5 years, but there appears to be no significant effect on disease progression [18-21]. The timing of adjuvant instillation following tumour resection may be important [27]. Generally, the drug should be administered within 24 h, but it may be more efficacious when given immediately or within 6 h.

For frequent and multiple recurrences of bladder tumours, a common practice is to give a course of six to eight intravesical doses at weekly intervals.

Great concern relates to the progression from non-invasive to muscle-invasive disease, which is frequently lethal. This is commonly seen following the failure of intravesical therapies. Although tumour progression rates have been shown to be reduced by intravesical bacillus Calmette-Guérin (BCG) [28,29], no such effect has been demonstrated with intravesical chemotherapy alone. Clinical practice guidelines emphasise the importance of recognising established risk

factors for recurrence and progression, as well as selecting appropriate treatment [30-32].

It can be presumed that suboptimal treatment regimens and inadequate drug delivery contribute to treatment failure.

4. Pharmacokinetics of intravesical mitomycin C

The penetration of intravesical mitomycin C into bladder tissue by passive diffusion has been studied in patients who received intravesical chemotherapy at the time of radical cystectomy [33]. An intravesical dose of mitomycin C (20 mg/40 ml) was instilled and maintained in the bladder for 60 – 120 min, at which time the solution was drained. Concentrations in the bladder wall were found to decline semi-logarithmically with tissue depth from the urothelium to the deep muscle, and reached a plateau at ~ 2000 µm in depth. The median mitomycin C concentrations were 5.6 µg/g in the urothelium and lamina propria interface, 2.7 µg/g in the lamina propria and 0.9 µg/g in the muscularis. The concentration ratio between the urine and urothelium/lamina propria interface was ~ 35. This study also found that the concentration in tumours was higher than in normal tissues. As the blood supply was interrupted before individual tissues were isolated, these figures may not truly represent the *in vivo* situation.

The pharmacokinetics of intravesical mitomycin C in patients with non-muscle invasive bladder cancer has been assessed by Dalton *et al.* [34]. In this study, treatment consisted of transurethral resection of the tumour followed by six weekly intravesical treatments with mitomycin C (20 mg in 40 ml of water). The dosing solution was maintained in the bladder for 2 h. The study reported that maximal plasma mitomycin C concentrations averaged 43 ng/ml in Treatment 1. For a comparison, the mitomycin C plasma concentration required for myelosuppression is ~ 400 ng/ml. Maximal plasma concentrations in Treatments 2, 4 and 6 were at least fourfold lower than those in Treatment 1, consistent with greater absorption of mitomycin C with treatment given shortly after surgery, presumably reflecting epithelial damage.

The same study evaluated the dilution of mitomycin C during treatment [34]. Urinary mitomycin C concentrations were found to decline from 519.4 ± 34.8 µg/ml (mean ± S.D.) in the dosing solution to 64.6 ± 39.4 µg/ml after 2-h instillation. Superficial bladder tissue is, therefore, exposed to drug concentrations 300- to 34,000-fold higher than plasma-perfused systemic tissues. Urothelial exposure to mitomycin C showed large intra- and intersubject variability, and this was shown to correlate inversely with the residual urine volume at the time of drug administration, urinary production, as well as the rate of drug removal by degradation and absorption during therapy.

Computer simulations have been developed that model how changes in treatment parameters affect therapeutic outcome in the following rank order: dose > residual volume > urine production > dosing volume > urine pH > dwell time [35]. Therefore, it should be expected that treatment response could be enhanced by increased dose, complete bladder emptying, reduced fluid intake, use of the minimal dosing volume, and alkalinization of the urine to a neutral pH. Gao *et al.* have shown that drug penetration into bladder tissue is linearly related to drug concentration [36]. This approach is, however, ultimately limited by the toxicity and solubility of an increased concentration of drug.

Au *et al.* (2001) carried out a prospective, randomised, Phase III trial to assess whether enhancing the drug's concentration in urine would improve its efficacy [37]. In the study, patients with histologically proven transitional cell carcinoma and at high risk for recurrence were enrolled. Patients in the optimised-treatment arm (n = 119) received a 40-mg dose of mitomycin C, with pharmacokinetic manipulations to increase drug concentration by decreasing urine volume and urine alkalinization to stabilise the drug. Patients in the standard-treatment arm (n = 111) received a 20-mg dose without pharmacokinetic manipulations or urine alkalinization. Both treatments were given weekly for 6 weeks. Patients in the optimised arm showed a longer median time to recurrence (29.1 months) and a greater recurrence-free fraction (41.0%) at 5 years than patients in the standard arm (11.8 months and 24.6%). Pharmacologically optimised intravesical mitomycin C treatment is, therefore, likely to enhance the efficacy of treatment.

5. The kinetics of electromotive drug administration

EMDA enhances the penetration and absorption of drug compared with passive diffusion, through the effects of iontophoresis and electro-osmosis.

Iontophoresis describes the accelerated transport of ions into tissues by means of an electric current passed through a solution containing ions (i). The rate of administration (Ji [mol/s]), is defined by Faraday's law:

$$Ji = I(tr)/zF$$

I is the current (amperes), tr the proportion of applied current (I) carried by ions, z the valency and F the Faraday constant.

Successful iontophoresis is associated with the increased transport of water that also entrains any non-ionised solutes present, a phenomena termed electro-osmosis. In a low permeability membrane such as urothelium, drug administration can be controlled by varying the current intensity.

With EMDA, urothelial penetration of the non-ionised mitomycin C molecule is enhanced by electro-osmosis, allowing treatment times to be reduced from 1 h to 20 – 25 min. Mitomycin C 40 mg in 140 ml water and lidocaine 4% in 10 ml are instilled via the

Table 1. Mitomycin C concentration–time profiles (μg/g of wet tissue) in bladder wall layers after passive diffusion.

Exposure time (mins)	Urothelium	Lamina propria	Muscle
5	15.3	2.2	0.45
15	59.9	18.9	1.95
30	58.2	19.2	1.8

Data from [38].

Table 2. Mitomycin C concentration–time profiles (μg/g of wet tissue) in bladder wall layers after passive diffusion and EMDA (20 mA) for 30 mins.

	Urothelium	Lamina propria	Muscle
Passive diffusion	46.6	16.1	1.9
EMDA	170.0*	65.6‡	15.9§

Data from [38].
*$p < 0.0001$.
‡$p < 0.0001$.
§$p < 0.0005$.
EMDA: Electromotive drug administration.

catheter electrode – a somewhat larger volume than conventionally used for passive administration to assure even drug distribution across the urothelial surface. The generator applies positive polarity to the catheter, and the controllable current is typically increased incrementally to 25 mA.

The urothelial penetration of mitomycin C has been investigated *in vitro* using a two-cell diffusion chamber with human bladder, allowing assessment of the concentration–depth profiles [38]. In this study, bladder wall sections were analysed by high-performance liquid chromatography for mitomycin C concentration. After passive diffusion, the concentration of mitomycin C was highest in the urothelium and lowest in the muscle of the bladder wall, and the concentrations at all tissue levels increased from an exposure time of 5 min to 15 – 30 min (**Table 1**).

The effect of passing current (20 mA) between the chambers on mitomycin C tissue penetration was assessed by comparison with passive penetration after 30 min of exposure, with a significant increase in the mitomycin C content in all wall layers (**Table 2**). Based on the trypan-blue exclusion test and histological examination, these increases in mitomycin C concentration occurred without any detrimental change in the bladder wall viability.

It is uncertain the extent to which these data reflect tissue concentrations under physiological conditions, as loss of blood supply during and after the cystectomy is likely to have allowed greater tissue penetration. As capillary removal of drug is available deep to the urothelial basement membrane, it is doubtful whether effective treatment of the lamina propria – let alone muscle – can be achieved by intravesical drug.

Certainly, when drug penetration across the peritoneum of experimental animals has been studied, the presence of a capillary bed produces rapid removal of drug from tissues [39].

Much more convincing are the *in vivo* data from a clinical study that compared mitomycin C given by passive diffusion with electromotive mitomycin C [1]. Peak plasma mitomycin C concentrations were shown to be significantly higher with electromotive mitomycin C (43 versus 8 ng/ml). The increase in mitomycin C penetration with EMDA is likely to have resulted in the improved response rate seen in this study. Estimates for the ratio of the plasma concentration–time area under the curve values are of the order of threefold in favour of electromotive mitomycin C.

6. The efficacy of electromotive mitomycin C

Brausi *et al.* investigated the efficacy of electromotive mitomycin C in patients with multi-focal superficial bladder tumour [40]. In their Phase II study, 13 patients with multifocal Stages Ta-T1 and G1-G2 transitional cell carcinoma of the bladder (primary or recurrent, Group A) received mitomycin C 40 mg once a week for 8 weeks. In the second group, 15 patients with the same characteristics were treated with electromotive mitomycin C (Group B) at a current of 15 mA for 20 min once a week for 8 weeks. All lesions in the bladder except one (used as a marker) were resected in each patient prior to treatment. In the passive diffusion mitomycin C group, 5 out of 12 patients (41.6%) demonstrated complete macroscopic and histological disappearance of the marker lesion (complete response). In the electromotive mitomycin C group, 6 out of 15 patients (40%) had a similar complete response. The recurrence rate in responders was 60% in group A, versus 33% in group B after 7.6 and 6.0 months, respectively. The disease-free interval was reported to be 10.5 months in the mitomycin C group, and 14.5 months in the electromotive mitomycin C group. Another small observational study also reported low recurrence rates after EMDA [3]. Of the 16 patients with superficial bladder cancer, 9 were free of recurrence for a mean of 14.1 months. Both studies had a short follow-up period and a relatively small number of patients. The findings suggest that, in responders, electromotive mitomycin C may be superior to mitomycin C alone with respect to recurrence rate and disease-free interval.

The first large-scale prospective randomised study using electromotive mitomycin C in patients with high-risk non-muscle invasive bladder cancer assessed the efficacy of intravesical EMDA versus passive mitomycin C, and used BCG as a comparative treatment [1]. Following transurethral resection and multiple biopsies, 108 patients were

Table 3. Comparison of complete response rate and time to recurrence for passive mitomycin C, electromotive mitomycin C, and BCG in patients with high-risk non-muscle invasive bladder cancer.

Follow-up	Passive MMC	EMDA MMC	BCG	p Value comparing MMC vs EMDA MMC
Complete response at 3 months (%)	28.0	53	56	0.036
Complete response at 6 months (%)	31.0	58	64	0.012
Time to recurrence (months)	19.5	35	26	0.013

Data from [1].
BCG: Bacillus Calmette-Guérin; EDMA: Electromotive drug administration; MMC: Mitomycin C.

Table 4. Findings from a randomised trial of sequential intravesical electromotive mitomycin C and BCG versus BCG alone.

	Electromotive MMC and BCG	BCG alone	Difference	p Value
Disease-free interval (months)	69.0	21.0	48.0	0.001
Recurrence rate (%)s	41.9	57.9	16.0	0.001
Progression rate (%)	9.3	21.9	12.6	0.004
Overall mortality (%)	21.5	32.4	10.9	0.45
Disease-specific mortality (%)	5.6	16.2	10.6	0.01

Data from [2].
BCG: Bacillus Calmette-Guérin; EDMA: Electromotive drug administration; MMC: Mitomycin C.

randomised to 3 equal groups of 36. Patients received either 40 mg electromotive mitomycin C instillation with a 20 mA electric current for 30 min, or 40 mg passive mitomycin C with a dwell time of 60 min or 81 mg BCG with a dwell time of 120 min. Patients initially had 6 weekly treatments, followed by a further 6 weekly treatments for non-responders or 10 monthly treatments for responders. Electromotive mitomycin C had a statistically significant effect, improving complete response rate and time to recurrence (**Table 3**).

7. Combination treatment: sequential intravesical electromotive mitomycin C and BCG

Di Stasi *et al.* (2006) recently reported the results of a prospective, randomised comparison of BCG alone with that of sequential BCG and electromotive mitomycin C in patients with stage pT1 bladder cancer [2]. All patients were classified as at high-risk of progression for inclusion in the trial, based on pathological stage T1 bladder cancer following transurethral resection, with 39% having grade 3 disease. The 212 patients enrolled 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 electromotive mitomycin C (intravesical electric current 20 mA for 30 min), this 3-week cycle being repeated twice (n = 107). Complete responders underwent maintenance treatment. With a median follow-up of 88 months, the results indicated that patients assigned sequential BCG and electromotive mitomycin C had a statistically significant longer disease-free interval and lower recurrence than did those assigned BCG alone (**Table 4**). Importantly, this study showed that patients assigned sequential BCG and electromotive mitomycin C also had lower progression, lower overall mortality and lower disease-specific mortality (**Table 4**). The researchers have suggested that BCG-induced inflammation might increase the permeability of the bladder mucosa such that mitomycin C can reach the target tissue more easily and exert its anticancer effect. The alternative view is that the improvement in efficacy is an additive effect rather than synergy.

This is the first study to report the combination of mitomycin C and BCG for the treatment of bladder cancer to be better than either mitomycin C alone [41-43] or BCG alone [44]. It is also the first study to investigate electromotive mitomycin C delivery with BCG. The median time to first recurrence of tumour was nearly doubled with EMDA compared with that of passive diffusion, and was similar to BCG alone. However, even in the electromotive mitomycin C with BCG group, the frequency of progression in patients with pathological T1 grade 3 disease was significant (11.8 without Tis, -16.7% with Tis) and remains a clinical challenge.

8. Other techniques

Preliminary studies suggest enhanced efficacy of mitomycin C with hyperthermia [45,46]. Colombo *et al.* compared hyperthermia and EMDA in patients with non-muscle invasive bladder cancer [47]. In the study, 80 patients with single, recurrent, low-stage, low-grade superficial bladder tumours entered a prospective non-randomised study. Thirty-six of them were treated by means of mitomycin C instillation as a standard procedure. In 29 patients, mitomycin C solution was administered in combination with local microwave-induced hyperthermia, and in 15 patients the mitomycin C solution was administered according to the electromotive drug procedure. The results suggest that although local toxicity induced by thermo-chemotherapy was more severe than the EMDA or standard intravesical chemotherapy, it was associated with a higher complete response rate on marker lesion.

9. Conclusion

The technique of electromotive mitomycin C has been shown to be both safe and effective. Studies have demonstrated that applying a current (EMDA) can significantly increase the concentration of mitomycin C delivered into the bladder wall both *in vitro* and *in vivo*. One randomised study has shown that electromotive mitomycin C is superior to standard mitomycin C with respect to reducing the recurrence rate and increasing the disease-free interval. A further study has demonstrated that a protocol including sequential electromotive mitomycin C and BCG reduced recurrence as well as tumour progression and mortality. 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, therefore, required to confirm these benefits and examine the role of EMDA and other techniques in the overall management of superficial bladder cancer.

10. Expert opinion

Intravesical therapy with mitomycin C is widely used in the management of non-muscle invasive transitional cell carcinoma. High-level evidence supports this practice, with demonstrable advantage over transurethral resection alone shown in randomised trials, by reduction in overall tumour recurrence and increase in disease-free interval.

Many patients will have recurrence regardless of intravesical therapy, and among these are those at greatest risk of tumour progression. Various considerations addressed in this article suggest that passive intravesical mitomycin C therapy, although often efficacious, is frequently suboptimal in that it is well below an individual patient's threshold for tolerability. Where intravesical treatment is inadequate in patients with high-risk disease, therapeutic efficacy will be compromised with increased risk of recurrence, progression and the need for additional treatment.

A prospective randomised study evaluating electromotive mitomycin C has shown that this is a more effective treatment than passive mitomycin C. The measurement of plasma drug concentrations has shown increased absorption from the bladder into the blood stream. The implications must be that the deep layers of the bladder epithelium and superficial lamina propria are exposed to higher concentrations. The advantages are potentially very significant for long-term outcome in high-risk patients, and this has to be considered against the immediate marginal additional discomfort, time and cost of each administration compared with passive delivery.

At present, intravesical BCG is the standard treatment for high risk non-muscle invasive bladder cancer, with a meta-analysis showing benefit in terms of progression as well as recurrence. A randomized study is now published showing that a regimen combining electromotive mitomycin C and BCG therapy is associated with lower recurrence, progression and mortality rates than BCG alone.

The observation that the combination of electromotive mitomycin C with BCG may be more efficacious than either alone warrants further investigation. Although mitomycin C is active only for the duration of its instillation, BCG probably remains necessary for a durable response and assuring optimal mitomycin C penetration with EMDA. The possibility that BCG may enhance the efficacy of mitomycin C activity against high-grade transitional cell carcinoma and carcinoma *in situ* represents an important new therapeutic perspective in the high-risk group. Future developments may enable electromotive mitomycin C to be considered in standardised treatment protocols, and the potential advantages of electromotive mitomycin C should certainly not be ignored.

Electromotive mitomycin C is not presently a standard treatment, nor yet widely adopted in clinical practice. Recognising that maximal therapeutic impact is likely to occur in high-risk patients, and that low-risk patients may not require an intravesical course of treatment, it is likely that electromotive mitomycin C will be offered specifically in intermediate and high-risk disease. Further studies are needed to demonstrate whether the reported advantages can be achieved in a multi-institutional setting. Studies will need to evaluate the feasibility of this more intensive intravesical intervention in the uro-oncological community. Although the initial cost of the generator and additional costs of consumables appear modest, particularly in relation to that of failed intravesical therapy, this will inevitably be subject to scrutiny along with the additional procedure time and supporting resources.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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