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The effects and effectiveness of electromotive drug administration and chemohyperthermia for treating non-muscle invasive bladder cancer

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Abstract

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Introduction

Preliminary studies show that device assisted intravesical therapies appear more effective than passive diffusion intravesical therapy for the treatment of non-muscle invasive bladder cancer (NMIBC) in specific settings, and phase III studies are now being conducted. Consequently, we have undertaken a non-systematic review with the objective of describing the scientific basis and mechanisms of action of electromotive drug administration (EMDA) and chemohyperthermia (CHT).

Methods

PubMed, ClinicalTrials.gov and the Cochrane Library were searched to source evidence for this non-systematic review. Randomised controlled trials, systematic reviews and meta-analyses were evaluated. Publications regarding the scientific basis and mechanisms of action of EMDA and CHT were identified, as well as clinical studies to date.

Results

EMDA takes advantage of three phenomena: iontophoresis, electro-osmosis and electroporation. It has been found to reduce recurrence rates in NMIBC patients and has been proposed as an addition or alternative to bacillus Calmette–Guérin (BCG) therapy in the treatment of high risk NMIBC. CHT improves the efficacy of mitomycin C by three mechanisms: tumour cell cytotoxicity, altered tumour blood flow and localised immune responses. Fewer studies have been conducted with CHT than with EMDA but they have demonstrated utility for increasing disease-free survival, especially in patients who have previously failed BCG therapy.

Conclusions

It is anticipated that EMDA and CHT will play important roles in the management of NMIBC in the future. Techniques of delivery should be standardised, and there is a need for more randomised controlled trials to evaluate the benefits of the treatments alongside quality of life and cost-effectiveness.

Keywords: Bladder cancer, Urothelial cancer, Electromotive drug administration, Chemohyperthermia

In the Western world, bladder cancer is the fourth most common cancer in men and the ninth most common in women,[1] with a rising global incidence.[2,3] In the UK, the disease accounts for approximately 10,000 new cases

and 5,000 deaths per year.[1,4] Over 90% of bladder cancers are transitional cell carcinomas of urothelial origin (urothelial carcinomas), and at presentation 75–85% will be non-muscle-invasive tumours (non-muscle-invasive bladder cancer [NMIBC], stages Ta/T1/Tis), with the remainder being muscle-invasive (stages T2–4).[4–6]

Over half (50–55%) of bladder cancer patients present with Ta tumours, where recurrence is the main clinical issue, occurring in up to 80% of cases; for the 20–25% of patients presenting with T1 tumours, progression is the main clinical concern, occurring in up to 45% of cases.[4,6] Progression to (or presentation with) muscle-invasive disease (stages T2–4) represents a critical step, necessitating more radical and aggressive therapies, and carries a five-year survival rate of only 27–50%.[4,6–8]

The four mechanisms of NMIBC recurrence are described as incomplete tumour resection, tumour cell reimplantation, the growth of microscopic tumours present (but undetected) at initial transurethral resection of a bladder tumour (TURBT) and 'genuine' new tumour formation.[9,10] As highlighted by Brausi,[11] optimising all of our existing capabilities to abrogate each of these mechanisms could further improve our therapeutic impact on NMIBC, and new technologies should be seriously and critically evaluated, not only for efficacy but also for cost-effectiveness.[12]

In this regard, device-assisted intravesical chemotherapy regimens appear to show improved efficacy versus passive diffusion regimens: studies comparing electromotive drug administration (EMDA) and chemohyperthermia (CHT) with conventional treatment have yielded promising results, demonstrating potential to improve intravesical therapy for NMIBC patients.[13] In this review, we outline the scientific basis and mechanisms of action of EMDA and CHT, present a brief summary of their clinical utility and highlight important areas for future studies.

Methods

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PubMed, ClinicalTrials.gov and the Cochrane Library were searched to source evidence for this non-systematic review. Search terms used included 'EMDA', 'hyperthermia' and 'bladder cancer'. Randomised controlled trials (RCTs), systematic reviews and meta-analyses were evaluated primarily. Thirty-four papers were selected for this review.

Results

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Electromotive drug administration

EMDA uses an electric current to enhance transepithelial drug penetration.[14] EMDA is administered via a battery powered generator delivering an electric current of 0–30mA DC at 0–55V, which is passed between two electrodes:[15] an active electrode is placed into the bladder as part of a transurethral catheter, and dispersive ground electrode pads are placed on the skin of the lower abdomen.

EMDA takes advantage of three phenomena: iontophoresis, electro-osmosis and electroporation. Iontophoresis involves propelling a substance into tissues by passing an electrical current through a solution containing the active charged ingredient.[16] Electro-osmosis transports non-ionised polar molecules (eg mitomycin C [MMC]) against their columbic gradients when there is convective flow of water in association with ions.[16] Electroporation is the increase in electrical conductivity and permeability of cell plasma membranes due to the application of an electrical field.[16]

MMC is a polar and non-ionised molecule in the range of pHs that may be present in the bladder (4.5–8.5).[17] It is delivered in a solution of Na^+/Cl^-/MMC, and when a current with a positive polarity is applied to this solution, the sodium ions move via iontophoresis and MMC molecules are carried with them via electro-osmosis, increasing the rate and depth of delivery.[17]

In vitro studies demonstrate that the penetration of MMC into non-cancerous bladder wall with EMDA is significantly greater than that achieved by passive diffusion (PD) alone:[16,17] concentration measurements made in the urothelium, lamina propria and muscularis layers are significantly greater for EMDA at all levels than for PD (EMDA increases MMC delivery by 4–7 times).[17] In these studies, penetration of the drug into the muscularis propria was insufficient to inhibit a significant proportion of the proliferating cells in this layer,[18] but as cancerous tissue is more permeable to water and solute than normal urothelium, the drug concentration in bladder tumours may be sufficient to achieve inhibition of proliferating cells in the muscularis propria.[19]

In terms of efficacy, the results of published EMDA clinical trials are summarised in Table 1. The majority of these studies have evaluated EMDA MMC as first-line intravesical therapy following TURBT (adjuvant therapy) and there remains a paucity of evidence supporting the use of EMDA MMC following failure of bacillus Calmette–Guérin (BCG) therapy.[20] In terms of tolerability, the use of EMDA MMC in clinical practice to date has never resulted in haematological toxicity, severe allergic reactions, life-threatening adverse events or any treatment-related deaths.[21]

Table 1
Summary of comparative electromotive drug administration study results to date

Chemohyperthermia

The effect of hyperthermia on cancer cells has been investigated since the 1950s and the use of CHT to manage bladder cancer has recently been the subject of a systematic review.[22] The review indicated potential for CHT in becoming a part of standard therapy for high-risk NMIBC patients with recurrent tumours who are unsuitable for radical cystectomy or who have contraindications for BCG therapy. The Synergo® SB-TS 101 (Medical Enterprises, Amsterdam, Netherlands) system is currently the most common system of CHT delivery,[23] using a radiofrequency generator to deliver radiofrequency (heat) energy at 915MHz.

The Combat BRS (Combat Medical, Wheathampstead, UK) system is now also in the marketplace, using a heat exchanger instead of a radiofrequency system. There is a theoretical independent advantage of radiofrequency energy for tumour cell killing, additional to hyperthermia, but a heat exchange fluid recirculation system is likely to reduce hot and cold spots and burning of the bladder wall.[24] However, until the Combat BRS system becomes more widely used, direct comparisons cannot be made.

Hyperthermia affects the tumour cell directly, the vascular supply to the tumour and it also triggers an immune response:[25]

- Hyperthermia induces cell killing (cytotoxicity) above 40.5°C: up to 43°C there is linear growth arrest involving reduced ribonucleic acid/deoxyribonucleic acid (DNA) synthesis and cell cycle arrest; exponential growth arrest occurs above 43°C along with impaired DNA repair.[25]
- Increasing temperatures can alter blood flow, and so the vascular effects of hyperthermia are dependent on the type and size of tumour. Increasing the temperature to 43°C increases tumour blood flow by vasodilation, allowing more MMC to be delivered, while above 43°C, tumour blood flow is reduced, possibly limiting the oxygen supply to the tumour (swelling/lysis of endothelial cells, adherence of leucocytes to vessels, increased rigidity of red blood cells, increased blood viscosity).[26] Tumour vasculature is less able to dissipate heat and cancer cells are therefore more likely to be heat damaged than non-cancerous cells.[26]
- On heating, the tumour microenvironment becomes increasingly hypoxic and acidic, further increasing the sensitivity of cells to both heat and cytotoxic therapeutics,[26] and angiogenesis is inhibited by the upregulation of plasminogen activator inhibitor-1 in endothelial cells.[27]
- Hyperthermia mimics the increased body temperature seen in fever,[28] stimulating an immune response constituting multiple changes to enhance immune surveillance:[29] induction of heat shock proteins can prime CD8+ cytotoxic T-cells and lead to autovaccination against the tumour[25] as well as increased natural killer cell infiltration, increased migration and adhesion of lymphocytes, increased T-cell and antibody numbers, increased concentrations of cytokines and acute phase proteins, and a lowering of the activation threshold required for many immune system effector molecules.[25,28]

In vitro studies have shown that hyperthermia also has a synergistic effect on MMC administration.[30] This is potentially caused by increased MMC uptake by heated tumour cells, increased drug activation and tumour cells being less able to counteract MMC's cytotoxic effects.[25]

The 2011 systematic review by Lammers *et al* of 22 studies indicated a 59% reduction in NMIBC recurrence rate when CHT is compared with MMC alone, and an improved bladder preservation rate (87.6%) could be a significant benefit of this treatment regimen.[22] However, definitive conclusions could not be drawn owing to the limited number of RCTs and heterogeneity in the study designs.

Subsequently, Moskovitz *et al* published their ten-year experience with CHT in both the adjuvant (CHT delivered after primary therapy, TURBT) and neoadjuvant settings (CHT delivered before primary therapy), demonstrating 72% recurrence-free survival for the adjuvant protocol with a progression rate of 4.7%.[31] They achieved an initial complete response of 79% for their neoadjuvant protocol, with 84% of these patients remaining free from recurrence. The use of CHT MMC in the setting of patients experiencing recurrence following induction or maintenance BCG is being assessed in the UK's HYMN RCT (CHT MMC vs a second course of BCG or standard therapy), which, at the time of writing, is in the patient follow-up phase.

The currently available CHT trial data on side effects and adverse events are limited.[22] However, preliminary results reveal that bladder spasms and pain are the most common side effects, reported in around 20% of patients during active treatment, along with mild and transient lower urinary tract symptoms following the procedure.[22] Two studies report a contracted bladder and severe urinary incontinence but the cause of these adverse events was not certain. Side effects are slightly more frequent than in PD MMC patients but, as suggested by Lammers *et al*, a structured questionnaire for adverse events is recommended in future research for effective evaluation.[22]

Discussion

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The effective treatment of NMIBC encompasses a range of different procedures and interventions, and improvements to all of these areas should be considered as we strive to enhance both outcomes and quality of life for NMIBC patients.[12] Optimising our existing intravesical chemotherapy regimens is just one aspect albeit an important one. In this review, we see that both EMDA and CHT appear safe and effective in reducing recurrence of NMIBC although more data are needed. Whereas the mechanism of EMDA is quite simple (increasing the rate and depth of MMC delivery to the urothelium), the effects of hyperthermia are varied and have not yet been elucidated thoroughly.

EMDA has been studied more extensively in RCTs than CHT, and there is evidence to support its utility for the treatment of high-risk NIMBC as an alternative to or in addition to BCG and, possibly, perioperatively. Larger, adequately powered RCTs should be carried out to further evaluate the addition of EMDA to current BCG therapy. Studies are also needed to evaluate whether the timing of EMDA administration alters efficacy, either prior to TURBT (perioperative or neoadjuvant) or following TURBT (adjuvant). Radical cystectomy should be the default position following failure of intravesical BCG[20] although bladder-sparing options may be desirable for the very elderly or patients unfit for cystectomy. While beyond the scope of this review, to date, bladder-sparing options following BCG failure only achieve recurrence-free survival of around 50% at up to two years[20] and evaluation of EMDA is required in this setting.

With regard to CHT, there are only a small number of completed RCTs and so more evidence is required before definitive conclusions can be drawn and before practice could change.[22] We eagerly await the results of the HYMN trial. In addition, CHT protocols must be standardised, including variables such as duration and temperature as well as the equipment/delivery system used.

There remain a number of questions to be answered for both EMDA and CHT, and a coordinated series of carefully conducted clinical trials are needed to address these. Both modalities are, however, interesting and seemingly effective, and they are likely to form an important part of our NMIBC armamentarium in the future. Trials to directly compare the clinical effectiveness and cost-effectiveness of EMDA and CHT, as well as effects on quality of life, may also be necessary before implementation into routine clinical practice. Nevertheless, it is important to note that there have been no new therapeutic agents developed for bladder cancer in over a decade and we should continue our search for such agents in parallel to developing new strategies for the administration of existing agents.[32,33]

Conclusions

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The potential advantages of EMDA and CHT are important in the management of NMIBC. However, the techniques and timing of delivery must be standardised, and there is a need for more RCTs to evaluate not only the benefits of the treatments in terms of disease-specific outcomes but also quality of life and cost-effectiveness. It is anticipated that these therapies will play a significant role in the management of NMIBC in the future but we should not forget the urgent and ongoing unmet need for new therapeutic agents to treat patients with bladder cancer.

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