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Clinical-Bladder cancer

A systematic review of the efficacy of intravesical electromotive drug administration therapy for non-muscle invasive bladder cancer

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Abstract

Background: Non-muscle invasive bladder cancer (NMIBC) is characterized by a high rate of recurrence and progression, despite surgery and adjuvant therapies.

Objective: To analyze the published results on the effectiveness of mitomycin C (MMC) applied with an electromotive drug administration device (EMDA) in the treatment of patients with non-muscle invasive bladder tumors.

Method: A systematic review was conducted using the PubMed and Google Scholar search platforms. We selected the studies that included the recurrence and/or progression rates or complete response rate in patients diagnosed with NMIBC according to their treatment and included MMC applied with EMDA. The last search was performed in November 2021.

Results: The search yielded 64 articles; 11 articles met the selection criteria. In two of the 11 selected articles, mitomycin C was applied with an EMDA device (MMC-EMDA) as an ablative treatment, avoiding surgery in 50% of the patients. In 1 of the 11 studies, the application of MMC-EMDA was used as an induction treatment using a single preoperative instillation with promising results. In the remaining 8 studies, adjuvant MMC was applied with the EMDA device; in 3 of these 8 cases, treatment with MMC-EMDA alone was applied initially. In another3 cases the same treatment was applied after nonresponse to bacillus Calmette Guerin (BCG), and in the last 2 studies, MMC-EMDA was applied in combination with the classic therapy (BCG). All the studies selected supported the efficacy and safety of MMC-EMDA in patients with intermediate and high- risk bladder cancer. In 3 studies, adjuvant therapy with MMC-EMDA was performed in nonresponders to BCG, finding that adjuvant therapy with MMC-EMDA applied to BCG nonresponders without CIS avoided or delayed surgery.

Conclusions: The application of EMDA-enhanced MMC has been studied at different times of disease and with different administration protocols. It appears to delay bladder tumor recurrence and progression in certain populations. However, the methodological limitations of the published studies prevent definitive conclusions about its efficacy.

Keywords: Bladder cancer; Intravesical drug administration; NMIBC; EMDA; Device-assisted

1. Introduction

Non-muscle invasive bladder cancer (NMIBC) represents the initial diagnosis in 75−85% of bladder cancers [1]. Its treatment is based on transurethral resection of the bladder tumor (TURBT) followed by adjuvant intravesical treatment adjusted to the risk of recurrence and/or progression. Despite this, bladder cancer maintains high recurrence and progression rates [2].

In order to optimize the effect of endovesical chemotherapy treatments, devices have been developed to increase drug penetration into the bladder wall. One of the most

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widely used devices is the EMDA® (ElectroMotive Drug Administration), which generates an electromotive force on mitomycin C (MMC). Intravesical administration of MMC has hardly any adverse systemic effects because its molecular weight (334 kDa) makes it difficult to cross the urothelium. However, this high molecular weight is a negative factor when treating tumors located in the deepest layers when MMC diffusion is passive, as its penetration is insufficient for successful treatment [3].

The EMDA device increases MMC penetration four to seven times more than passive diffusion of the drug [4]. This occurs due to the generation of an electric current through the biological barrier, inducing a directional and accelerated movement of the intravesical ionized drug toward the neoplastic tissue. During this process, different electrokinetic phenomena take place: electroosmosis, iontophoresis, and electroporation.

This device consists of a 16 Fr 3-way bladder catheter inserted into the bladder using the usual aseptic technique. The EMDA session begins with emptying the bladder, washing it with sterile water, and removing the ions. This probe also allows the introduction of the cytostatic agent and functions as an anode. An external generator emits a controllable electrical current at low intensity (0−30 mA and 0−55 V) from the anode placed inside the bladder to a cathode made up of two ground electrode pads placed on the hypogastrium of patients. After completion of treatment, the bladder is emptied, and the patient is discharged.

The electric field generates the movement of sodium and water ions toward the bladder wall (iontophoresis), causing electro-osmotic entrainment of MMC molecules (electroosmosis). Electroporation increases the permeability of biological membranes due to the electric field generated. However, according to Kos et al. 2016 [5], the latter mechanism of action seems unlikely.

2. Objective

To analyze the effectiveness of MMC applied with the EMDA device in the treatment of patients with NMIBC based on published results up to the end of 2021.

3. Method

A systematic review was performed using the search platform PubMed by searching based on the combination of the following terms: "Bladder cancer," "non-muscle invasive bladder cancer," "Electromotive drug administration," "EMDA," "device-assisted." The search was extended until November 2021.

The combinations of terms that gave the best results were: "Bladder cancer," "EMDA," and "Electromotive drug administration." A total of 64 articles were obtained.

Simultaneously, a search was performed in Google Scholar without finding additional articles that could have been left out of the PubMed search.

We selected the articles that included among their results the recurrence and/or progression rates or complete response (CR) of NMIBC, published in the last 20 years in English and Spanish. Review articles, conference abstracts, and editorials were excluded. Nonhuman articles were also excluded.

After reading the title and abstract, 17 studies were initially selected. After complete reading, the number of studies finally included was 11. Next, the references of the selected studies were reviewed, and no new articles were found that met the selection criteria.

Two reviewers (YCY and MTMS) independently assessed the methodological quality of the selected studies. The Cochrane bias scale was used for clinical trials, and observational studies were assessed using the Newcastle-Ottawa quality assessment scale (NOS). If there were any discrepancies, they were resolved by a third, more experienced reviewer (MAM). The Centre for Evidence-Based Medicine, Oxford (OCEBM) was used to classify the level of evidence of each work

This review was written in accordance with the Preferred Reported Items for Systematic Reviews and Meta-analyses (PRISMA) statement. A PRISMA checklist is shown in Supplementary Table 1.

4. Results

A final 11 articles were selected [6−16] (Fig. 1).

Of the 11 studies, 3 correspond to clinical trials (OCEBM 1b) [8,9,12]. The evaluation of the risk of bias carried out on them is very similar to that described by Jung et al. [17] (Supplementary Table 2). In addition, we found two cohort studies [6,16] (OCEBM 2b) whose assessment of bias was performed using the NOS scale (Supplementary Table 3). The remaining six studies [7,10,11,13−15] correspond to case series, which have an OCEBM 4, and we did not perform a bias assessment on them.

The analysis was performed according to the timing and purpose of treatment application. We analyzed 2 studies in which MMC-EMDA was applied as ablative treatment, 1 study in which it was applied in the immediate preoperative period and 8 studies in which MMC-EMDA was applied as adjuvant therapy: in 3 studies, patients were treated with MMC-EMDA alone, in 3 studies MMC-EMDA was applied after failure to respond to BCG and in 2 studies MMC-EMDA was applied in combination with BCG (Tables 1, 2, 3, 4, and 5).

4.1. Mitomycin C applied with EMDA device as ablative treatment

Regarding the use of MMC-EMDA as ablative therapy, we analyzed two studies: Colombo [6] published a prospective, nonrandomized study (OCEBM 2b). He investigated the ablative effect of chemohyperthermia (MMC-CHT) and chemotherapy applied with EMDA compared to passive MMC in a cohort of 80 patients with single, small, or

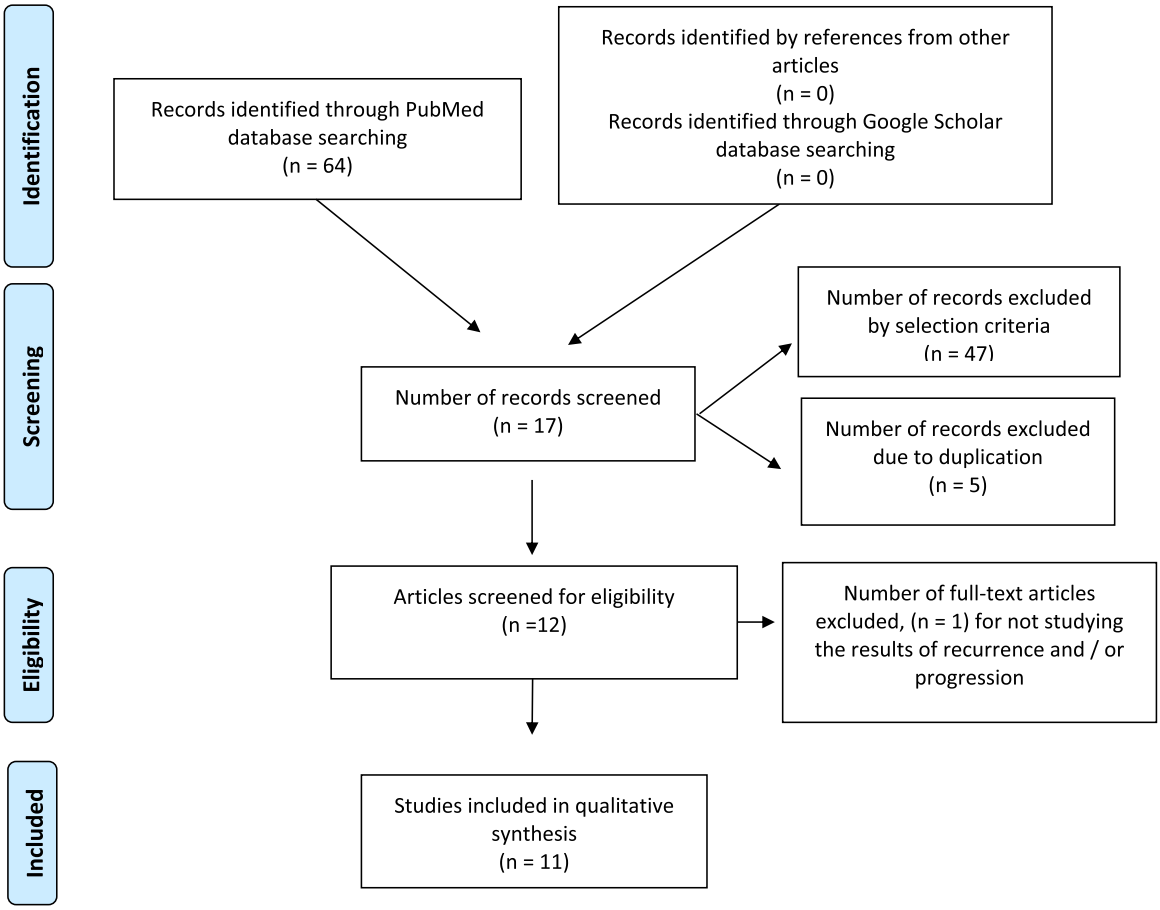

Fig. 1. Study selection flowchart.

recurrent low-risk tumors. His main objective was to evaluate the feasibility and safety of each technique. Therefore, although the results favored device-enhanced cytostatic application vs. passive application, no conclusions can be drawn about the usefulness of the EMDA. In particular, because the drug concentrations and session durations used were not similar. The AE evaluated by means of a subjective questionnaire did not show differences.

Decaestecker [7] included 26 patients with small papillary tumors, either primary or recurrent, and single or multiple. He applied a single instillation of MMC-EMDA and evaluated the response based on the disappearance or not of the lesion on cystoscopy. CR at 2−4 weeks after the start of treatment was only obtained in 28% of patients (OCEBM 4).

4.2. MMC-EMDA as immediate preoperative treatment

Di Stasi et al. [8] designed a prospective multicenter study in which 374 patients with primary NMIBC were randomized into three treatment groups: single transurethral resection, immediate postoperative instillation of passive MMC or preoperative instillation of MMC-EMDA. After a mean follow-up of 86 months, they found that patients receiving preoperative MMC-EMDA had a lower recurrence rate (MMC-EMDA 38% vs. MMC 59% vs. TURBT 64%; $P < 0.0001$) and a longer recurrence-free time compared to the other two groups (MMC-EMDA 52 months, Interquartile range (IQR) 32−184 vs. MMC 16 months, IQR 12−168 vs. TURBT alone 12 months, IQR 12 −37; $P < 0.0001$).

4.3. MMC-EMDA as adjuvant treatment in intermediate and high-risk patients

We analyzed 3 studies: one randomized study and two retrospective descriptive studies.

Di Stasi et al. [9] published a prospective randomized study including 108 patients with high-risk primary NMIBC with CIS. They compare: MMC-EMDA, passive MMC, and BCG, in a similar instillation scheme, planning a crossover between MMC-EMDA and BCG in the case of persistent disease despite a second induction cycle. His main objective was to demonstrate CR at 3 and 6 months, and recurrence and progression rates after a mean follow-up of 43 months (IQR 23). Regarding CR, the results were similar between patients treated with BCG and MMC-EMDA and superior to the passive MMC group: CR at 3 months BCG 55.5% vs. MMC 27.8% vs. MMC-EMDA 52.8% ($P = 0.036$); CR at 6 months BCG 63.9% vs. MMC

Table 1
MMC-EMDA as ablative treatment.

Author and year published	Design	Years	Country	Number of patients and groups	Population	Administration protocol	Administration scheduling	Complete response (CR)	Adverse events (AE)	OCEBM level of evidence
Colombo et al. 2001 [6]	Prospective Not randomized.	1996−1998	Italy	80 patients 36: Ablative Passive MMC 29: Ablative MMC-CHT 15: Ablative MMC-EMDA	Low-risk recurrent, single tumors, without prior treatment Small <2 cm	Passive MMC 40mg of MMC dissolved in 50 ml saline for 60 minutes MMC-CHT: 40mg of MMC dissolved in 50 ml of sterile water for 60 minutes. Synergo system (42.5˚C) MMC-EMDA: 40 mg of MMC dissolved in 150 ml of distilled water at 20 mA for 20 minutes. Physionizer 30 System	Ablative Passive MMC: 4 weekly instillations Ablative MMC-CHT: 4 weekly instillations Ablative MMC-EMDA 4 weekly instillations	Ablative Passive MMC: 27.7% at 5 weeks after the start of treatment. Ablative MMC-CHT: 66% at 5 weeks after the start of treatment. Ablative MMC-EMDA: 40% at 5 weeks after the start of treatment.	Subjective questionnaire not validated Only minor AE without significant differences between groups. Stand out: MMC-CHT: urgency and nocturia symptoms MMC-EMDA: Suprapubic pain, urethral pain.	2b
Decaestecker et al. 2018 [7]	Prospective Not randomized	2012−2015	Belgium	32 patients	Single or multiple, primary or recurrent and small tumors <2 cm Excluding CIS	MMC-EMDA: MMC 60 mg dissolved in 100 ml of distilled water with a current of 25 mA for 25 minutes	Ablative MMC-EMDA single instillation	28% at 2−4 weeks after the start of treatment.	6.25% (2/32) Severe spasms that force to suspend treatment.	4

CHT = chemo hyperthermia; CIS = carcinoma in situ; OCEBM = Oxford Centre for Evidence-Based Medicine; EMDA = electromotive drug administration; MMC = mitomycin C.

Table 2
MMC-EMDA as immediate preoperative treatment.

Author and year published	Design	Years	Country	Number of patients and groups	Population	Administration protocol	Subsequent instillations protocol	Follow-up (months)	RFR (%)	PFR (%)	Time to recurrence (months)	Adverse events (AE)	OCEBM level of evidence
Di Stasi et. al 2011 [8]	Clinical trial. Multicenter	1994 −2003	Italy	374 patients 124: TURBT 126: TURBT + passive MMC 124: MMC-EMDA + TURBT	Primary NMIBC. Exclude CIS Low risk: 6% Intermediate e Risk: 66% High risk: 28%	TURBT alone TURBT + passive MMC: 40mg MMC dissolved in 50 ml of sterile water for 60 minutes in the first 6 hours after resection MMC-EMDA + TURBT: 40 mg of MMC dissolved in 100 ml of water with EMDA (20 mA for 30 minutes) Physionizer 30 neoadjuvant	Low risk: No Intermediate Risk: 6 weekly instillations + 10 monthly maintenance with 40 mg of MMC diluted in 50 ml of water for 60 minutes High risk: 6 weekly instillations + 10 monthly maintenance with 81 mg of BCG dissolved in 50 ml of serum for 120 minutes (ImmuCyst)	86 (IQR 57−125)	TURBT: 36% TURBT + passive MMC: 41% MMC-EMDA + TURBT: 62% $P < 0.0001$	TURBT: 79% TURBT + passive MMC: 81% MMC-EMDA + TURBT: 84% $P = 0.55$	TURBT: 12 TURBT + passive MMC: 16 MMC-EMDA + TURBT: 52 $P < 0.0001$	TURBT: 4% (5/116) perforation 7% (8/116) hematuria 16% (18/116) irritative symptoms 3−7 days TURBT + MMC pasiva: 24% (28/119) do not end treatment because spasms 8% (9/119) perforation 13% (16/119) hematuria 31% (37/119) irritative symptoms 20−30 days TURBT MMC-EMDA +: 1/117 Cessation for urethral stricture 6% (7/117) perforation 8% (9/117) Mild hematuria 21% (24/117) irritative symptoms 7−12 days	1b

CIS = carcinoma in situ; EMDA = electromotive drug administration; IQR = interquartile range; MMC = mitomycin C; OCEBM = Oxford Centre for Evidence-Based Medicine; PFR = progression-free rate; RFR = recurrence-free rate; TURBT = Transurethral resection of bladder tumor.

Table 3
MMC-EMDA as adjuvant treatment.

Author and year published	Design	Years	Country	Number of patients and groups	Population	Administration protocol	Installations schedule	Follow-up (months)	RFR (%)	PFR (%)	Time to recurrence (months)	Adverse events (AE)	OCEBM level of evidence
Di Stasi et al. 2003 [9]	Clinical trial	1994−2001	Italy	108 patients 36: TURBT + passive MMC 36: TURBT + MMC-EMDA 36: TURB + BCG	Primary tumor with CIS and 91% with T1	Passive MMC: 40mg of MMC dissolved in 100 ml sterile water for 60 minutes. MMC-EMDA: 40mg of MMC dissolved in 100 ml of sterile water for 30 minutes at 20 mA Physionizer 30 BCG: 81 mg of BCG suspended in 50 ml of serum applied for 120 minutes	6 weekly and 10 monthly instillations	43 (IQR 23)	Passive MMC: 15% MMC-EMDA: 47.2% BCG: 47.2% ($P = 0.092$) CR at 3 months: Passive MMC: 28% MMC-EMDA: 53% BCG: 56% ($P = 0.036$) CR at 6 months: Passive MMC: 31% EMDA: 58% BCG: 64 % ($P = 0.012$)	Passive MMC: 77.8% MMC- MMC-EMDA: 83.3% BCG: 83.3% ($P = 0.861$)	Passive MMC: 19,5 MMC-EMDA: 35 BCG: 26 ($P = 0.013$)	Passive MMC: Cessation 5.6% (2/36) Cystitis: 25% (9/36) MMC-EMDA: Cessation 8.3% (3/36) Cystitis: 36.1% (13/36) Hematuria: 22.2% (8/36) BCG: Cessation 11.1% (4/36) Hematuria: 72.2% (26/36) Cystitis: 66.7% (24/36)	1b
Carando et al. 2019 [10]	Retrospective Multicenter Not randomized	2016−2018	Italy and Switzerland	65 patients	High and intermediate risk tumors	TURBT + MMC-EMDA: 40mg of MMC dissolved in 100 ml of sterile water for 30 minutes at 20 mA Physion Mini 30N2	Induction: 8 weekly sessions Maintenance: not defined	62 patients: 3 months 45 patients: 6 months.	83.3% of R. intermediate at 6 months 84% High Risk at 6 months			**9.2%** (6/65 patients): -4.6% (3/65) skin erythema -1.54% (1/65) Catheter intolerance -1.54% (1/65) Bladder pain and tightness -1.54% (1/65) not indicated	4

Author and year published	Design	Years	Country	Number of patients and groups	Population	Administration protocol	Installations schedule	Follow-up (months)	RFR (%)	PFR (%)	Time to recurrence (months)	Adverse events (AE)	OCEBM level of evidence
Carando et al. 2020 [11]	Retrospective Multicenter Not randomized	2016−2019	Italy and Switzerland	112 patients	Intermediate risk (25%) and high tumors (75%) -2.7% only CIS Recurring (44%) -13.9% previous MMC -8.9% nonresponders to BCG -77.2% without prior treatment	TURBT + MMC-EMDA: 40mg of MMC dissolved in 100 ml of sterile water for 30 minutes at 20 mA Physion Mini 30N2	Induction: 8 weekly sessions Maintenance: 12 monthly	6	85% at 3 months 75% at 6 months	94% at 3 months 90% at 6 months		Cessation: 1.8% (2/112) **Grade 1:** 7.1% (8/112) - skin erythema 5.3% (6/112) - Catheter intolerance 1.8% (2/112) **Grade 2:** - Bladder pain 0.9% (1/112) - Bladder tightness. 0.9% (1/112)	4

CIS = carcinoma in situ; CR = complete response; EMDA = electromotive drug administration; IQR = interquartile range; MMC = mitomycin C; OCEBM = Oxford Centre for Evidence-Based Medicine; PFR = progression-free rate; RFR = recurrence-free rate; TURBT = transurethral resection of bladder tumor.

Table 4
MMC-EMDA/BCG as adjuvant treatment.

Author and year published	Design	Years	Country	Number of patients and groups	Population	Administration protocol	Installations schedule	Follow-up (months)	RFR (%)	PFR (%)	Time to recurrence (months)	Adverse events (AE)	OCEBM level of evidence
Di Stasi et. al. 2006 [12]	Clinical trial	1994−2002	Italy	212 patients: 105: TURB + BCG 107: TURBT + BCG + MMC-EMDA	T1 tumors 27% CIS associated	BCG: 81 mg of BCG suspended in 50 ml of serum applied for 120 minutes. BCG / MMC-EMDA: Similar BCG and EMDA: 40mg of MMC dissolved in 100 ml of sterile water for 30 minutes at 20 mA	BCG: 6 weekly and 10 monthly instillations BCG / MMC-EMDA: Induction, 9 weeks separated into 3 treatment cycles BCG/BCG/MMC-EMDA Maintenance with 3 cycles of monthly instillations of MMC-EMDA/ MMC-EMDA/BCG	88 (IQR 63−110)	BCG: 41.9% BCG/ MMC-EMDA: 57.9% *P* = 0.0012	BCG: 78.1% BCG/ MMC-EMDA: 90.7% *P* = 0.004	BCG: 21 BCG/ MMC-EMDA: 69 *P* = 0·0012	BCG: Cessation 2.86% (3/105) Hematuria 58% (61/105) Dysuria 48.5% (51/105) **BCG/** MMC-EMDA Cessation 2.8% (3/107) Hematuria 59.8% (64/107) Dysuria 50.5% (51/107)	1b
Author and year published	Design	Years	Country	Number of patients and groups	Population	Administration protocol	Installations schedule	Follow-up (months)	RFR (%)	PFR (%)	Time to recurrence (months)	Adverse events (AE)	OCEBM level of evidence
Gan et al. 2016 [13]	Prospective Not randomized	2009−2013	England	107 patients	High risk, including CIS (49.5%) Primary or recurrent 26%	MMC-EMDA: 40 mg of MMC dissolved in 100 ml of 20 mA water for 30 minutes. Physionizer 30 BCG: 81 mg of BCG suspended in 50 ml of serum applied for 120 minutes.	Induction: 9 weeks. 3 weekly treatment cycles with scheme: BCG/BCG/ MMC-EMDA Maintenance: 3 instillations of BCG at 3 months after completion of induction and semiannually for 3 years	24	Per year: 86% At 2 years 62%	96.3% at 2 years		28% (30/107) need to modify the treatment. 15% (16/107) for AE: -STUI / hematuria: 8.4% (9/107) -Arthralgia: 2.8% (3/107) -Recurring ITU 1.9% (2/107) -Rash 0.9% (1/107) -BCGitis: 0.9% (1/107)	4

CIS = carcinoma in situ; CR = complete response; EMDA = electromotive drug administration; IQR = interquartile range; MMC = mitomycin C; OCEBM = Oxford Centre for Evidence-Based Medicine; PFR = progression-free rate; RFR = recurrence-free rate; TURBT = transurethral resection of bladder tumor.

Table 5
MMC-EMDA as adjuvant treatment in patients with BCG unresponsive tumor.

Author and year published	Design	Years	Country	Number of patients and groups	Population	Administration protocol	Installations schedule	Follow-up (months)	RFR (%)	PFR (%)	Adverse events (AE)	OCEBM level of evidence
Racioppi et al. 2018 [14]	Prospective Not randomized	2012−2016	Italy	26 patients	High Risk BCG unresponsive tumors 15.4% with CIS	MMC-EMDA: 40 mg of MMC dissolved in 100 ml of 20 mA water for 30 minutes	Six weekly instillations and 6 monthly instillations	36 (SD 3,4)	61.5% at 3 years	84.6% at 3 years	Cessation of treatment due to AE 11.5% (3/26 patients) Mild AE: 23.1% (6/26 patients) -Pain 11.5% (3/26 patients) -Spasms 11.5% (3/26 patients) -Dysuria 15.4% (4/26 patients) -Hematuria 3.8% (1/26 patients) -Difficulty to insert the catheter 3.8% (1/26 patients) Urgency frequency, 11.5% (3/26 patients) Nocturia 7.7% (2/26 patients	4
Juvet et al. 2020 [15]	Retrospective	2013−2017	Canada	26 patients	22 patients with criteria of BCG unresponsive (53.8% CIS)	MMC-EMDA/ BCG: BCG: 81 mg of BCG suspended in 50 ml of serum applied for 120 minutes. MMC-EMDA: 40mg of MMC dissolved in 100 ml of sterile water for 30 minutes at 20 mA	Induction: 9 weekly instillations, applying MMC-EMDA at weeks 3, 6, and 9 and BCG in the rest. Maintenance: 9 monthly instillations. BCG is applied in months 3, 6, and 9 and MMC-EMDA the rest.	29 (IQR 14,5−41)	41.9% at 1 year 27.2% at 2 years	58.3% at 1 year 48.9% at 2 years	AE grade 3: 11.5% (3/26 patients) Bacteremia AE grade 1: 50% (13/26 patients) Dysuria 19.2% (5/26 patients) -Hematuria 19.2% (5/26 patients) -Frequency 11.5% (3/26 patients)	4
Author and year published	Design	Years	Country	Number of patients and groups	Population	Administration protocol	Installations schedule	Follow-up (months)	RFR (%)	PFR (%)	Adverse events (AE)	OCEBM level of evidence
Di Gianfrancesco et al. 2020 [16]	Retrospective Cohorts		Italy	209 patients 102: Cystectomy 107 Conservative treatments: MMC-EMDA: 44 MMC- CHT: 63	209 patients 102: Cystectomy 107 conservative treatments: EMDA: 44 CHT: 63	MMC-EMDA 40 mg of MMC dissolved in 100 ml of 20 mA water for 30 minutes CHT: 20 mg of MMC dissolved in 50 ml of water at 42 +/- 2°C for 30 minutes* In case of CIS, 40 mg	Six weekly instillations and 6 monthly instillations.	59 ± 5,3	Cystectomy: 74.5% at 60 months Conservative: 43% at 60 months $P < 0.05$ MMC-EMDA: Without CIS 57.1% at 60 months With CIS 12.5% at 60 months $P < 0.001$ MMC-CHT: Without CIS 65% at 60 months With CIS 8.7% at 60 months $P < 0.001$	Cystectomy: 75.5% at 60 months Conservative: 59.8% at 60 months $P < 0.05$ MMC-EMDA: Without CIS 71.4% at 60 months With CIS 31.2% at 60 months $P < 0.001$ MMC-CHT: Without CIS 85% at 60 months With CIS 26.1% at 60 months $P < 0.001$	9% MMC-EMDA drop out due to AE Mild AE: -Spasms: 20.45% (9/44 patients) Cystitis: 20.45% (9/44 patients) Dysuria: 11.36% (5/44 patients) Hematuria: 20.45% (9/44 patients) Urinary frequency: 20.45% (9/44 patients) Incontinence: 6.8% (3/44 patients) Pain: 20.45% (9/44 patients) 9.5% CHT abandoned due to AE	2b

CIS = carcinoma in situ; EMDA = electromotive drug administration; IQR = interquartile range; MMC = mitomycin C; OCEBM = Oxford Centre for Evidence-Based Medicine; PFR = progression-free rate; RFR = recurrence-free rate; SD = standard deviation; TURBT = transurethral resection of bladder tumor.

30.5% vs. MMC-EMDA 58.3% ($P = 0.012$). Similarly for recurrence and progression rates: Recurrence BCG 52.8% vs. MMC 75% vs. MMC-EMDA 52.8% ($P = 0.092$); Progression BCG 16.7% vs. 22.2% vs. MMC-EMDA 16.7% ($P = 0.861$).

Carando et al. [10] published the results of a multicenter study with 65 patients. He evaluated the response to treatment at 3 and 6 months, and obtained similar results in terms of recurrence-free rate (RFR) at 6 months between intermediate and high-risk patients (intermediate risk 83.3%, high risk 84% $P > 0.05$). Subsequently, Carando et al. [11] published the results of a similar study with 112 patients with intermediate and high-risk NMIBC. He obtained response rates of 85% at 3 months and 75% at 6 months and progression-free rates (PFR) of 94% at 3 months and 90% at 6 months.

4.4. MMC-EMDA combined with BCG as adjuvant treatment in intermediate and high-risk patients

Di Stasi et al. [12] published a multicenter, randomized study in which he analyzed the combination of MMC-EMDA/BCG vs. BCG in patients with primary or recurrent high-risk T1 NMIBC. After 88 months of follow-up (IQR 63−110), combination therapy had a higher RFR than BCG alone (MMC-EMDA/BCG 57.9% vs. BCG 41.9%; $P = 0.0012$) with a disease-free time difference of 48 months ([IQR: 42−54] ($P = 0.0012$)).

Gan [13] performed a prospective descriptive study of a single cohort. He administered a combination of MMC-EMDA/ BCG following the scheme described by Di Stasi in 2006 [12] to refute the results obtained by that group 10 years before. He recruited 107 patients with primary or recurrent high-grade NMIBC. He obtained a disease-free rate of 87% at 1 year, and four patients progressed after 2 years of follow-up.

4.5. MMC-EMDA as adjuvant treatment in patients who do not respond to BCG

Racioppi [14] designed a prospective phase II study including 26 patients. After 3 years of follow-up, 65% of his patients preserved their bladder. However, patients with CIS had an inferior response to treatment: RFR of 37.5% vs. 72.2% without CIS at 3 years (log-rank = 4.98, $P < 0.05$).

Juvet [15] presented a retrospective study of 26 patients (53.8% with CIS) treated with the combination of MMC-EMDA/ BCG. He obtained an RFR of 41.9% at 1 year and 27.2% at 2 years with a median time to recurrence of 9 months. The RFR is 48.9% at 2 years with a median time to progression of 21.4 months.

Di Gianfrancesco [16] published a retrospective cohort study. He compared the results obtained by treating 209 patients (36% with CIS) by radical cystectomy vs. intravesical treatment assisted by diffusion-enhancing devices: EMDA or CHT. After a mean follow-up of 59 months, he observed that surgery continued to obtain superior results to the other techniques in terms of RFR (RFR 43% with conservative techniques and 74.5% with surgery at 60 months ($P < 0.05$)) and in PFR (PFR 59.8% and 75.5% at 60 months, respectively ($P < 0.05$)). Patients without CIS responded better to conservative treatments: RFR in patients with CIS treated with MMC-EMDA 12.5%, in patients without CIS treated with MMC-EMDA 57.1% ($P < 0.05$); PFR in patients with CIS and conservative treatment 25.6%, in patients without CIS and conservative treatment 79.4% ($P < 0.05$).

5. Discussion

The electromotive application of intravesical mitomycin C using the EMDA device increases the penetration of the drug into the tissues [4]. The ablative application of MMC-EMDA aims to eliminate tumors, avoiding hospital admission and surgical and anesthetic risks for the patient. This is based on previous pilot studies demonstrating how MMC-EMDA can reduce tumor size after instillations [18] or even obtain CR [19]. After analyzing the studies in which local chemotherapy with EMDA was applied ablatively [6,7] we deduce that there is currently insufficient evidence to recommend chemotherapy with EMDA for the purpose of ablation.

The European Urology Guidelines recommend the administration of a single immediate postoperative instillation of chemotherapy in patients with NMIBC [1]. However, this cannot be performed in cases where perforation is suspected or where there is hematuria after surgery. The preoperative administration of EMDA allows the application of this technique without taking into account the complications arising from surgery. Di Stasi et al. in 2011 [8] obtained promising results with the use of this technique as a single preoperative instillation, however, there are no studies in other cohorts that support these results.

BCG is currently the adjuvant treatment of choice for patients classified as high risk of progression. Despite this, there is a high rate of relapse and progression [16]. In addition, there have been problems with a shortage of BCG at times of high demand [15]. All this favors the search for alternatives through MMC [20].

The use of MMC-EMDA as adjuvant therapy achieves good short-term clinical safety and efficacy results. However, these results have been obtained in different patient profiles. Di Stasi et al. [9] selected patients with CIS, obtaining similar CR rates between BCG and MMC-EMDA. The two studies carried out by Carando [10,11] also showed good response rates. However, they include a small number of patients with CIS apart from having a retrospective design and a short follow-up period.

Another scenario in which MMC-EMDA has been studied is in combination with BCG in order to potentiate and improve the effects of BCG and decrease its side effects.

Combination therapy demonstrated its efficacy in the clinical trial conducted by Solsona et al. [21]. They administered an instillation of MMC the day before each BCG instillation. Their objective was to generate an inflammatory response that would facilitate adherence of the bacillus. They demonstrated increased disease-free time and RFR in the combination: 20.6% vs. BCG alone 33.9%, (HR: 0.57;95% CI, 0.39−0.83; $P = 0.003$) at the expense of greater toxicity.

Di Stasi and Gan [12,13] applied BCG first and then combined it with MMC-EMDA. With this administration order, it is postulated that BCG generates inflammation in the urothelium, and MMC reaches its target tissue and generates its antitumor effect more easily. In addition, MMC optimizes the urothelium for BCG to be more effective. With this treatment scheme, Di Stasi et al. [12] observed benefits in terms of disease and recurrence-free time, as well as improvements in overall survival and progression; results not obtained in the meta-analyses performed with the combination of BCG with passive MMC [22,23].

MMC-EMDA/BCG has good oncologic outcomes in intermediate- and high-risk patients even with the presence of CIS, where it appears to exhibit a favorable trend in response to combination therapy compared to treatment with BCG alone (difference in CR at 6 months of 11.9% [−0.9 to 24.7]; $P = 0.417$) [12]. However, this is achieved at the cost of reduced tolerability necessitating modifications to the treatment regimen [13].

Another scenario occurs in patients who do not respond to treatment with BCG, as even with BCG therapy, approximately 55% of patients may relapse, and 15−25% may progress. When this occurs, clinical guidelines recommend radical cystectomy, which has been shown to be oncologically superior to other conservative treatments [1]. In some cases, this recommendation cannot be carried out when patients are not candidates for surgery or wish to preserve their bladder. For these reasons, the most recent studies focus on this subgroup of patients.

In the studies analyzed we found that conservative treatment with MMC-EMDA alone or in combination is a valid option in patients with BCG therapy failure who want to preserve their bladder. However, these patients should be followed very closely because of the risk of progression. Especially patients with the presence of CIS, which plays an important role in the prognosis of these patients [12,16].

Regarding toxicity, only 2−12% of patients drop out of treatment due to an AE from the application of MMC-EMDA [10,14] Studies dealing with combination therapy report a higher frequency of AEs [13,15], but, in general, these were still lower than those produced by BCG [24]. It remains to be elucidated what happens to patients with a recurrence of the disease after chemotherapy with an EMDA device. Only Di Stasi et al. [9], in 2003, reported on a small group of patients with tumor persistence after MMC-EMDA who underwent crossover and received BCG, CR was obtained in 32% of these patients at 1-year follow-up.

This review is not without limitations as it was not possible to carry out a meta-analysis due to the heterogeneity in the design of the included studies. Due to the scarcity of published studies, we decided to include all those that met the inclusion criteria even though their level of evidence was low. We only found three clinical trials published on this device, all of them from the Di Stasi group [8,9,12], and were analyzed by means of a meta-analysis published by Jung et al. [17]

6. Conclusions

The application of MMC potentiated with the EMDA device has been studied at different times of the disease, presenting itself as a safe tool in the treatment of patients with intermediate and high-risk NMIBC, including in those in whom BCG has previously failed. However, the different administration protocols and the methodological limitations of the published studies prevent drawing definitive conclusions about its efficacy. Its ablative role has been ruled out. Good results have been obtained as a single preoperative instillation, although evidence is limited because it has been studied in a single cohort. Regarding adjuvant treatment, three studies support its safety in intermediate and high-risk patients, one of them exclusively in patients with CIS. It has also been studied in combination with BCG, improving results during prolonged follow-up at the expense of a detriment in tolerability.

Finally, in patients with tumors that do not respond to BCG, MMC-EMDA has been shown to be useful as adjuvant therapy in patients without CIS, delaying or even avoiding surgery, which remains the standard treatment in these patients.

Conflict of interest

All authors have no conflict of interest to report.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2022.09.016.

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