ELSEVIER

Urologic Oncology: Seminars and Original Investigations 41 (2023) 109.e1−109.e8

UROLOGIC ONCOLOGY

Clinical-Prostate cancer

Conductive hyperthermic chemotherapy versus electromotive drug administration of mitomycin C as intravesical adjuvant treatment of patients with intermediate or high-risk non-muscle invasive bladder cancer

María Teresa Melgarejo Segura, M.D.*, Ana Morales Martínez, M.D., Yaiza Yáñez Castillo, M.D., Miguel Ángel Arrabal Polo, M.D., Ph.D., Pablo Gómez Lechuga, M.D., Manuel Pareja Vílchez, M.D., Miguel Arrabal Martín, M.D., Ph.D.

Department of Urology, University Hospital San Cecilio, Granada, Spain

Received 6 June 2022; received in revised form 25 September 2022; accepted 16 October 2022

Abstract

Background: Devices that increase the penetration of intravesical chemotherapeutic agents have been developed as alternatives to the use of bacillus Calmette−Guérin, in short supply at a time of increasing global incidence of non-muscle invasive bladder cancer (NMIBC).

We performed a prospective observational study to compare 2 of these devices in the treatment of patients with high- and intermediate-risk NMIBC. The primary endpoint was the recurrence-free rate. Secondary endpoints were the rate of progression and adverse events.

Methods: After undergoing transurethral bladder resection, 98 patients were selected to receive 1 of 2 treatments: hyperthermic intravesical chemotherapy (HIVEC) treatment with 40 mg of mitomycin C (MMC) using Combat BRS System V2.0 at 43 ± 0.5˚C and 200 ml/min for 60 minutes (56 patients) or electromotive drug administration (EMDA) with 40 mg of MMC at 20 mA for 30 minutes (42 patients). The treatment schemes were similar: 6 weekly instillations as induction and 6-monthly instillations as maintenance. The recurrence rates were evaluated at 6 and 12 months and the progression rates at 12 months.

Results: The recurrence-free rate at 12 months was 91,1% in the HIVEC group and 88.1% in the EMDA group ($P \geq 0.05$). After the 12-month follow-up, only 1 progression occurred in each treatment group. In terms of adverse events, no significant differences were found between the treatments.

Conclusions: HIVEC and EMDA techniques are comparable in terms of recurrence, progression and adverse events at 12 months in the treatment of patients with high- and intermediate-risk NMIBC.

Keywords: Electromotive drug administration; Hyperthermic Intravesical Chemotherapy; Intravesical Treatment; Mitomycin C; Non-muscle invasive bladder cancer

1. Introduction

Non-muscle invasive bladder cancer (NMIBC) is characterized by a high recurrence capacity and the risk of progression to muscle-invasive disease. At the time of diagnosis, approximately 75% of patients present with superficial disease [1].

Initial treatment consists of complete transurethral resection of visible tumors (TURBT), followed, in most cases, by adjuvant intravesical therapy adjusted for the risk of progression. However, despite these risk-adjusted adjuvant treatments, bladder cancer maintains rates of recurrence and progression that are considered high: 31%−78% of patients present recurrence and 1%−45% will progress to a

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

*Corresponding author. Tel.: 669229045.

E-mail address: mtm.segura@gmail.com (M.T. Melgarejo Segura).

https://doi.org/10.1016/j.urolonc.2022.10.019

1078-1439/

muscle-invasive tumor in 5 years [2]. This fact necessitates close monitoring of these patients and the economic consequences that this monitoring entails.

Immunotherapy with bacillus Calmette−Guérin (BCG) remains the indicated treatment for high- and intermediate-risk NMIBC. In the latter group, intravesical chemotherapy treatment may also be offered [1]. However, BCG shortages have occurred at times of increased demand due to the increased global incidence of NMIBC [3]. This, in addition to the fact that a considerably high percentage of recurrence and progression occurs despite treatment [4], encourages the search for alternatives to classic treatment. Among the alternatives developed are therapies focused on improving the efficacy of intravesical delivery systems through active drug transportation through the bladder wall.

On the 1 hand, there is hyperthermic intravesical chemotherapy (HIVEC), in which mitomycin C (MMC) is administered at a temperature of approximately 43˚C. This enhances the effect of the drug, but also adds to the direct effect of heat on cells, causing apoptosis, increased cell permeability, and release of heat shock proteins [5].

On the other hand, electromotive drug administration (EMDA) creates an electric field inducing the phenomena of iontophoresis and electro-osmosis [6]. This increases the penetrance of mitomycin by 4 to 7 times of the passive diffusion of mitomycin [7].

These methods have been studied in the treatment of patients of different profiles. However, there are no works that directly compare both. The objective of the present study is to prospectively compare the effects of treatment with HIVEC and EMDA on the prevention of progression and recurrence of tumors at 12 months in patients diagnosed with intermediate- and high-risk NMIBC, except carcinoma in situ (CIS). This study also explores the treatments' difference in toxicity.

2. Materials and methods

2.1. Patient selection

Included patients were diagnosed histologically with intermediate and high risk NMIBC, except CIS, from 2018 at a single Spanish center. Both patients with primary and recurrent NMIBC were included. Patients with recurrent NMIBC were eligible if they had previously received BCG or MMC without EMDA or HIVEC.

The study obtained the approval of the local ethics committee before the investigation was started. We conducted the investigation in accordance with the principles set forth in the Declaration of Helsinki, and all patients signed an informed consent document accepting the treatment.

The exclusion criteria were having previous or concomitant CIS, an MMC allergy, non-urothelial carcinomas of the bladder or upper urinary tract urothelial carcinoma at the time of presentation, inadequate bone-marrow reserve (white blood cell count $< 3000 \times 10^6$ cells per l; platelet count $< 100 \times 10^9$ per l), liver or kidney function values above twice the laboratory normal value, untreated urinary-tract infection, bladder capacity less than 150 ml , treatment during the last 3 months with chemotherapy, or previous radiotherapy to the pelvis or being pregnant.

2.2. Study design

The initial assessment of the patient included performing a voiding urinary cytology; in addition, we performed a radiological study of the upper urinary tract and a TURBT. Random biopsies of the bladder mucosa were taken if the previous cytology was positive, if the patient had a history of high-grade tumors, or if a non-papillary tumor was observed. We performed a second TURBT at an interval of 2−4 weeks if the tumor resection was incomplete, if there was no muscle present in the sample, or if the histological result was a high-grade T1 tumor.

We recorded the clinical and demographic variables of the patients, including age, gender, recurrences and previous treatments, number and size of the tumors, T stage, and grade.

The choice of treatment group resulted from a consensus between the patient and the doctor, who explained the evidence and emphasized the possible adverse events; therefore, this is a non-randomized study. Both techniques were offered and were available at the same time. We also offered the standard treatment of care according to European Association of Urology guidelines [1].

Toxicity scores were assessed using the Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE v.5) [8]. In case of symptomatic grade 1 or 2 toxicity, empirical treatment was administered and instillation was postponed until clinical remission. If an allergy or grade 3 toxicity developed, treatment was discontinued.

2.3. Protocols

The administration protocol was similar in both groups. An induction of 6 weekly instillations was established, followed by a maintenance course of 6-monthly instillations. In both groups, 40 mg of MMC diluted in 50 ml of distilled water was applied. EMDA (Physionizer 30, manufactured by Physion, Medolla, Italy) was applied at 20 mA for 30 minutes. Chemo-hyperthermia was administered using Combat BRS System, version 2.0 (Combat Medical Ltd., Wheathampstead, UK), at 43 ± 0.5˚C and 200 ml /min for 1 hour.

2.4. Patient follow-up

Response to treatment was evaluated every 3 months by cystoscopy, voiding urinary cytology, and biopsy of all visible tumors and healthy bladder mucosa in cases of positive cytology. An upper urinary tract radiological study using

ultrasound or computed tomography urography was also performed every 6 months.

We defined response to treatment as follows:

Complete response: the absence of clinically/histologically (macroscopic) tumors on bladder biopsy plus a negative voiding urinary cytology for high-grade urothelial carcinoma.

Time to recurrence: time from the first instillation to the next surgery in which a similar or lower-grade tumor was histologically confirmed.

Time to progression: time from the first instillation to the next surgery in which a muscle-invasive bladder cancer or CIS was histologically confirmed.

We censored patients without progression or recurrence at the last follow-up test. Patients lost to follow-up were censored on the last known day of survival.

Prior to each instillation, we asked patients about complaints in the preceding weeks to assess any side effect of previous instillations and tolerance during the procedure.

2.5. Statistical methods

We carried out data recording prospectively by using a maintained database. Subsequently, data were retrospectively reviewed.

We performed our statistical analysis by intention to treat. Our primary endpoint was the recurrence-free rate at 6 and 12 months of treatment. Our secondary endpoints were adverse events (AE; assessed by the CTCAE v. 5) and progression at 12 months of follow-up.

Descriptive statistics are shown by percentage when the variable is categorical and by median and range when the variable is continuous. We used Pearson's chi-square or Fisher's exact test to compare categorical variables.

To calculate the response in free rate of recurrence at 6 and 12 months and progression at 12 months, we constructed Kaplan−Meier curves and made comparisons by applying a log-rank test. The reported P values were 2-sided and statistical significance was set at < 0.05. We carried out statistical analyses with IBM SPSS Statistics V21.0.

3. Results

3.1. Patient characteristics

Of the potential participants, 102 patients met the inclusion criteria and agreed to participate in the study. However, 4 patients were excluded: 2 had stage T2 bladder cancer on restaging TURBT, 1 patient refused to participate, and another was lost to follow-up before starting any treatment. After offering both treatment alternatives, we

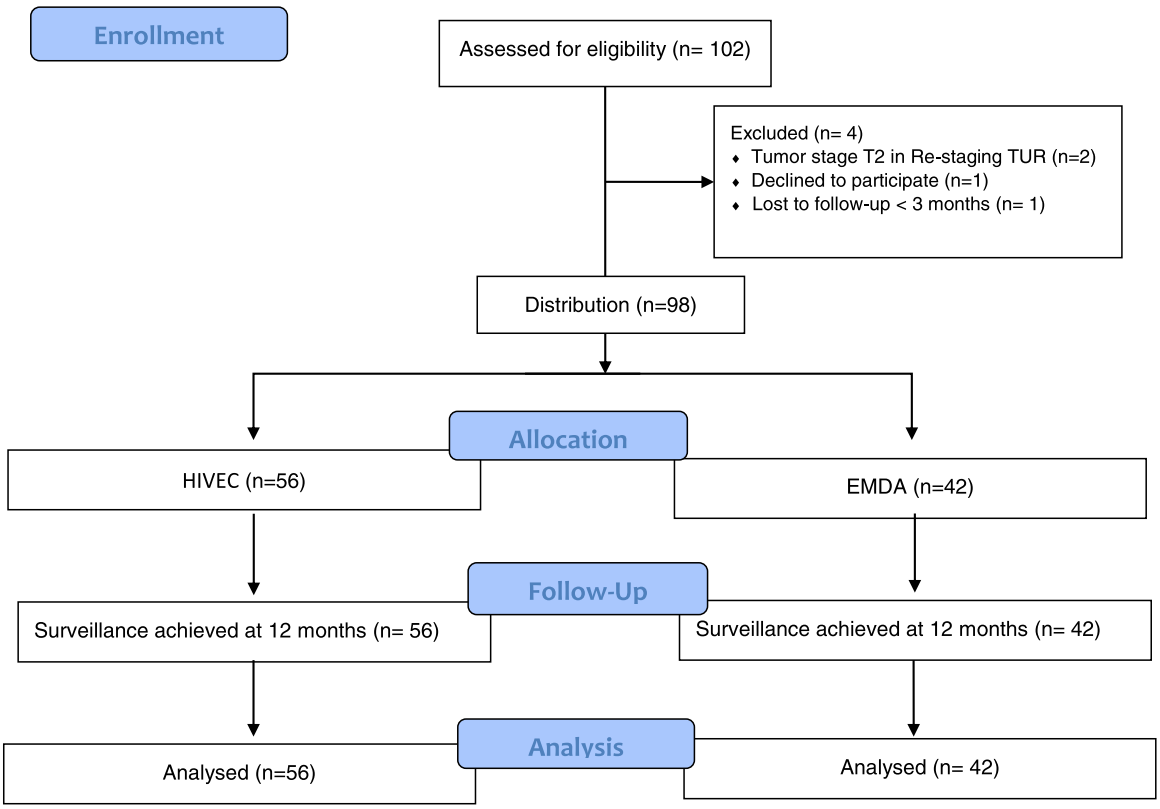

Fig. 1. Patient disposition diagram.

divided the patients into 2 groups: 42 patients received EMDA and 56 received HIVEC (Fig. 1).

3.2. Descriptive analysis

Table 1 presents the descriptive analysis of the demographic and clinical characteristics of the patients at baseline. The relevant characteristics were comparable in both groups.

3.3. Outcomes after follow-up

The primary endpoint was recurrence-free rate at 6 and 12 months of treatment.

At 6 months of follow-up, 1 patient who had received HIVEC (1.8%) and 2 patients who had received EMDA (4.8%) had tumor recurrence ($P = 0.4$).

At 12 months of follow-up, 5 patients in the HIVEC group and 5 in the EMDA group recurred, providing recurrence-free rates of 91,1% and 88,1%, respectively ($P = 0.62$). With a mean time to recurrence of 11,7 months for HIVEC and 11,6 months for EMDA ($P>0.05$). Fig. 2 shows Kaplan Meier curve.

The secondary endpoint was progression at 12 months of follow-up. After completing the 12-month follow-up, each group of patients had only 1 progression. In the HIVEC group, the progression occurred at 12 months; in the EMDA group, it occurred at 5 months. In both cases, CIS was diagnosed

Table 1
Patient and tumor characteristics at baseline.

Variable	HIVEC	EMDA	*P*
Age, median (IQR)	72,11 (48−90)	70,26 (42−90)	0,142
Sex, *n* (%)			0,806
Male	44 (78,6%)	34 (81%)	
Previous recurrence, *n* (%)			0,980
None	34 (60,7%)	25 (59,5%)	
Yes, ≥a y ago	15 (26,8%)	12 (28,6%)	
Yes, <a y ago	7 (12,5%)	5 (11,9%)	
Previous treatment, *n* (%)			0,676
None	45 (80,4%)	31 (73,8%)	
MMC-passive	6 (10,7%)	7 (16,7%)	
BCG	5 (8,9%)	4 (9,5%)	
Tumor size, *n* (%)			0,489
< 3 cm	43 (76,8%)	29 (69%)	
≥ 3 cm	13 (23,2%)	13 (31%)	
Tumor stage, *n* (%)			0,672
Ta	33 (58,9%)	26 (61,9%)	
T1	23 (41,1%)	16 (38,1%)	
Tumor grade WHO 2004, *n* (%)			0,681
Low gade	26(46,4%)	17(40,5%)	
High grade	30(53,6%)	25(59,5%)	
Number of tumors, *n* (%)			0,641
1	25 (44,6%)	20(47,6%)	
2-7	28(50%)	18(42,9%)	
≥8	3 (5,4%)	4 (9,5%)	
EAU[a] Risk Group			0,835
Intermediate	35(62,5%)	25(59,5%)	
High	21(37,5%)	17(40,5%)	

[a] EAU = European Association of Urology.

3.4. Toxicity

Table 2 shows the AEs obtained, with a mean of 9 ± 2 instillations for the HIVEC group and 8 ± 3 for the EMDA

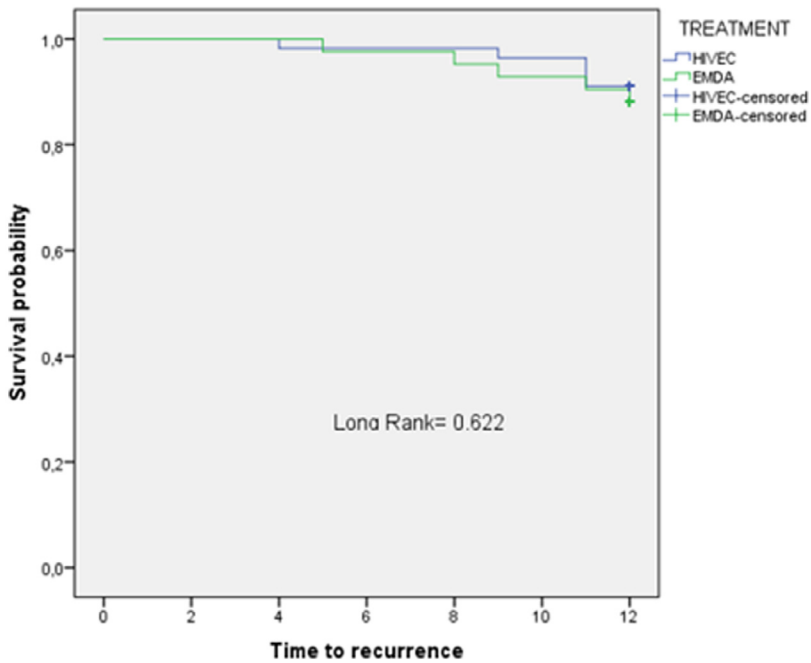

Fig. 2. Kaplan-Meier curve and long rank test on time to recurrence at 12 months follow-up.

Table 2
Adverse events reported stratified by grade and treatment.

CTCAE V.5 Grade	HIVEC *n* (%)	EMDA *n* (%)	*P*
No adverse events	38 (67,9%)	21 (50%)	0,301
Grade 1	13 (23,2%)	14 (33,3%)	
Dysuria	0	2	
Bladder spams	13	5	
Skin burns	0	5	
Rash	1	0	
Nocturia	0	1	
Hematuria	0	1	
Grade 2	3 (5,4%)	5 (11,9%)	
Dysuria	0	1	
Skin burns	0	1	
Hematuria	1	0	
Bladder spams	1	2	
Urinary tract infection	1	1	
Grade 3	1 (1,8%)	2 (4,8%)	
General malaise	1	1	
Urinary tract infection	0	1	
Grade 4	1 (1,8%)	0 (0%)	
MMC allergy	1	0	
Grade 5	0 (0%)	0 (0%)	

group. No significant differences were found between the treatments in relation to AEs assessed with the CTCAE v.5.

In total, 8 patients (8.16%) abandoned treatment due to AEs. In the HIVEC group, there were 2 dropouts. One patient presented with general malaise (grade 3) and another patient had an allergic reaction to MMC (grade 4). In the EMDA group, there were 6 dropouts. One patient suffered from a urinary tract infection (grade 3) and another patient had general malaise (grade 3). Four patients decided to drop out due to moderate AEs (grade 2) despite empirical treatment: 2 patients with bladder spasms, 1 patient with dysuria, and 1 patient with skin burns.

Furthermore, we found that both groups presented lesions in cystoscopy, which led the patient to surgery to take a biopsy without obtaining neoplasia in the sample.

In 10 of the 56 patients in the HIVEC group, chronic cystitis (4/10), followed by calcification (2/10) and eosinophilic infiltration (2/10), stood out among the histological results. Six of the 42 patients in the EMDA group had different subtypes of cystitis (3/6) and/or hyperkeratosis as metaplasia secondary to treatment (1/6).

4. Discussion

The limited availability of BCG in recent years, added to NMIBC's high recurrence rate despite adjuvant treatments, has led to the development of devices that focus on optimizing the penetration of intravesical drugs. The different devices that have been developed achieve delivery optimization in different ways.

Combat is a conductive hyperthermic chemotherapy (HIVEC) device in which the drug is externally heated and then delivered to the bladder. This method's efficacy is based on increasing the permeability of the membranes and the solubility of the molecule. Its method of action also has a direct cytotoxic effect and increases the effect of MMC [9].

The EMDA device is composed of a generator that emits a controllable and low intensity electrical current from an anode placed inside the bladder toward a cathode located in the hypogastrium of the patient. The electrical current through the bladder walls induces the movement of the drug into the tissue by electro-osmosis and iontophoresis [6].

Although the HIVEC and EMDA mechanisms are based on different concepts, they both increase the penetration of the drug. There are different studies that validate their efficacy in the treatment of patients with NMIBC, but none has directly compared the 2 devices yet.

Another improved delivery system for mitomycin that has been developed is the external radiofrequency chemo-hyperthermia device Synergo. This device is made up of a 915 MHz antenna that heats a chemotherapeutic agent, circulating from an external device, in the bladder [9]. Internal devices have also been developed to increase the residence time of intravesical drugs. In 1 such device, the chemotherapy drug is contained within a thick pretzel-shaped structure that is implanted in the bladder for a long time, releasing the drug by osmosis [10]. Another internal device is the reverse thermal gel formulation of mitomycin, which is liquid at low temperatures and solidifies into a gel at body temperature. This allows the gel to adhere to the epithelium of the bladder, slowly releasing the drug. Subsequently, this dissolves completely and is eliminated through the evacuation of urine [11].

The aim of this study was to determine if there were differences between HIVEC and EMDA in terms of recurrence, progression and tolerance in the treatment of patients with high- and intermediate-risk NMIBC without CIS.

To our knowledge, no studies had compared these treatments before. We found that, after a 12-month follow-up, there were no differences between these 2 devices, and both were safe and well tolerated.

Our results are in line with previously published works (Tables 3 and 4) in which these devices have been used.

Carando et al. [12,13] working group published the results of 2 multicenter retrospective studies in which patients with intermediate- and high-risk NMIBC were treated with adjuvant EMDA. The larger study recruited 112 patients with a low proportion of CIS tumors (2.7%). At 6 months, the results of this investigation are a recurrence-free rate and progression-free rate of 75% and 90%, respectively.

Combat as an adjuvant treatment was first studied by Sousa et al. [14], who published their results after treating 16 patients (9 high-risk and 7 intermediate-risk). With a median follow-up of 24 months, the researchers obtained a disease-free rate of 87.5% at 2 years. Years later, Grimberg et al. [15] published their results after treating 14 patients of intermediate risk (4/14) and high risk (10/14) with higher doses of MMC (120 mg) boosted with Combat. Although the follow-up time was short, 11 months, they obtained a recurrence-free rate of 85%, similar to that of the previous study.

Table 3
Summary table of the most relevant literature published on EMDA.

Author, y and journal.	Design	Y	Number of patients and groups	Population	Administration protocol	Follow-up (mo)	RFR (%)	PFR (%)
Di Stasi et al. 2003 J Urol. [16]	Clinical trial	1994−2001	108 patients 36: MMC 36: MMC-EMDA 36: BCG	Primary tumor with CIS ± T1	MMC: 40mg MMC MMC-EMDA: 40mg MMC BCG: 81 mg BCG	43 (IQR 23)	Passive MMC: 15% MMC-EMDA: 47,2% BCG: 47,2% ($P = 0.092$)	Passive MMC: 77,8% MMC- MMC-EMDA: 83,3% BCG: 83,3% ($P = 0.861$)
Carando et al. 2019 Urol Int. [12]	Retrospective	2016−2018	65 patients	High and intermediate risk tumors	MMC-EMDA: 40mg MMC	6 mo.	83.3% of R. intermediate 84% High Risk	
Carando et al. 2020 Arab J Urol [13]	Retrospective	2016−2019	112 patients	High and intermediate risk tumors	MMC-EMDA: 40mg MMC	6 mo	85% at 3 mo 75% at 6 mo	94% at 3 mo 90% at 6 mo
Racioppi et al. 2018 BMC Cancer [22]	Prospective	2012−2016	26 patients	High Risk BCG Unresponsive tumors	MMC-EMDA: 40 mg MMC	36 (SD 3,4)	61,5% at 3 y	84,6% at 3 y
Di Gianfrancesco et al. 2021 Clin Genitourin Cancer. [17]	Retrospective	-	209 patients 102: Cystectomy 107 Conservative treatments: MMC-EMDA: 44 MMC- CHT: 63	High Risk BCG Unresponsive tumors	MMC-EMDA 40 mg MMC	59 ± 5,3	Cystectomy: 74,5% at 60 mo Conservative: 43% at 60 mo ($P < 0.05$) MMC-EMDA: Without CIS 57,1% at 60 mo With CIS 12,5% at 60 mo ($P < 0.001$) MMC-CHT: Without CIS 65% at 60 mo With CIS 8,7% at 60 mo ($P < 0.001$)	Cystectomy: 75,5% at 60 mo Conservative: 59,8% at 60 mo ($P < 0.05$) MMC-EMDA: Without CIS 71,4% at 60 mo With CIS 31,2% at 60 mo ($P < 0.001$) MMC-CHT: Without CIS 85% at 60 mo With CIS 26,1% at 60 mo ($P < 0.001$)

Table 4
Summary table of the most relevant literature published on COMBAT.

Author, y and journal.	Design	Y	Number of patients and groups	Population	Administration protocol	Follow-up (mo)	RFR (%)	PFR (%)
Sousa et al 2016. International Journal of Hyperthermia. [14]	Observational	2010−2015	16	Intermediate and high risk	Combat: 40 mg MMC	24 mo (9−32 mo).	87,5% at 1 y	-
De Jong et al 2018 Bladder Cancer. [19]	Retrospective	2014−2017	52	BCG Unresponsive tumors	Combat: 80mg MMC	14.0 mo (IQR 7.6 −24.6)	47% at 1 y	
Pijpers et al 2021 Urol Oncol. [20]	Retrospective	2014−2020	56	BCG Unresponsive tumors	Combat: 40 mg MMC	32.2 mo (IQR 13.7−44.8)	53% at 1 y 35% at 2 y	
Chiancone et al 2020 Cent European J Urol [21]	Retrospective	2017−2020	103 72 MMC 26 Epirubicin (EPI)	High-risk NMIBC and BCG failure or intolerance	Combat: 40 mg MMC or 50 mg EPI	MMC: 10.5 mo; SD:13.42 ±10.55 EPI: 14; mo; SD: 15.35 ±10.58	89,23% of patients who underwent HIVEC at 14 mo	
Guerrero-Ramos et al. 2022 World J Urol. [27]	Clinical trial	2016−2021	50: 25 BCG 25 HIVEC	High-risk NMIBC	Combat: 40 mg MMC	33.7 mo (IQR 18.6−37.1)	BCG: 71.8% at 24 mo HIVEC: 86,5% at 24 mo ($P = 0.184$)	BCG: 71.8% at 24 mo HIVEC: 95,8% at 24 mo ($P = 0.043$)

Other studies have sought to identify the patient profile that would benefit the most from these therapies, such as that of Di Stasi et al. [16], who studied EMDA through a clinical trial that included 108 high-risk primary NMIBC patients with CIS. The patients were randomly assigned to receive passive MMC, EMDA, or BCG and were assessed for complete response rates. The authors found similar results between patients treated with BCG and EMDA at 3 and 6 months, both superior to passive MMC (complete response at 6 months: MMC, 31%; EMDA, 58%; BCG, 64%). However, other studies show how the presence of CIS affects treatment outcomes. This is demonstrated by the work of Di Gianfrancesco et al. [17] who applied EMDA or hyperthermia as second line after BCG failure and obtained better response rates in non-CIS-NMIBC patients compared to those with CIS either treated with EMDA (High-Grade Disease-Free Survival [HG-DFS] CIS:12.5% and without CIS: 57.1%; [$P < 0.05$]); or with hyperthermia (HG-DFS: 8.7% vs. 65% [$P < 0.05$]). Difference also found in other recent investigations [18]. For this reason, we decided to delimit our research to a defined group of patients with non-CIS-NMIBC.

Continuing with the idea of identifying the best time to apply these therapies, the most recent studies have focused on patients who do not respond to BCG and have even conducted clinical trials against standard treatment [18]. We found 2 published studies, belonging to the same group, that evaluated the Combat chemo-hyperthermia device [19,20]. In that group's most recent publication, they updated the data from their cohort of 56 BCG-unresponsive patients treated with HIVEC. The data revealed a disease-free rate of 53% at 12 months and 35% at 24 months, Another study, belonging to an Italian group [21], reported the effect obtained after conducting a prospective, non-randomized study using the adjuvant Combat with mitomycin or epirubicin in patients with BCG failure. This study obtained a mean of disease-free survival in the MMC group of 22.61 months, without finding differences between the 2 drugs ($P = 0.627$).

The studies performed on EMDA in these patients showed favorable results: a recurrence-free rate of 61.5%, with a progression-free rate of 84.6% after a 3-year follow-up(22). Promising results have been obtained with both conservative treatments, although surgery continues to obtain results superior to those of other techniques [17].

Although our study included patients who were refractory or recurrent to BCG, we found that only 9 patients had previously received BCG, all at least 2 years before starting the present study. Therefore, our study cannot draw conclusions regarding this subgroup of patients.

With regard to toxicity, we found results similar to those previously published [13,16,21]. It may appear that there is a greater trend of AEs in the EMDA group, however, it should be noted that the burns produced in the patients who received EMDA were due to failures in the patches that were located in the hypogastrium. After this fact was identified, the patches were immediately withdrawn.

We also highlight the changes that therapies produce in the urothelium. These changes have been studied by Pierconti's group [23,24]), but from examining cytologies and not from cystoscopic findings. In their work, Sousa et al. [14] refer to the presence of bladder calcification in patients who have received ablative therapies from EMDA. Colombo et al. [25] also describe sclerosis and calcification among his patients treated with the Synergo system.

Unfortunately, this was a non-randomized controlled trial; therefore, it has an inherent potential for bias. Furthermore, it was a single-center study with a limited sample size and no comparison was made with standard treatment. Finally, we are aware that our results are limited to evaluating only early response to treatment, due to our study's short follow-up period, so we believe that our findings should be validated by prospective, multicenter, randomized trials with longer follow-up.

To date, no studies have compared both treatments with the main objective of assessing their efficacy using a similar treatment regimen. We obtained promising results in that both treatments, applied to intermediate- and high-risk patients, obtained similar recurrence-free rates at 12 months of follow-up. This supports the decision to administer 1 therapy or another based on cost, availability, and preference of the clinician and the patient. However, the best moment to apply these techniques remains to be elucidated, always with the aim of avoiding or delaying such disabling surgery as cystectomy [26]. In order to identify and understand the changes that these devices produce in the urothelium, an inventory of the possible lesions expected in cystoscopies of these patients could be made in the future.

5. Conclusions

Finally, we confirm that EMDA and HIVEC techniques, with a similar treatment schedule, are comparable in terms of recurrence, progression, and AEs at 12-month follow-up in the treatment of high- and intermediate-risk patients with NMIBC.

Authors' contributions

Miguel Arrabal Martín and Manolo Pareja Vílchez were responsible for de design of the study. María T. Melgarejo Segura, Yaiza Yáñez Castillo, Miguel A Arrabal Polo collected and acquired the data. Ana Morales Martínez and María T. Melgarejo Segura wrote the manuscript. Pablo Gómez Lechuga and Miguel Arrabal Martín corrected the article and wrote the final version.

All authors have participated to drafting the manuscript, author A revised it critically.

All authors read and approved the final version of the manuscript.

All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

Acknowledgments

This work was supported by the Hospital Clínico San Cecilio de Granada. Acknowledgment to the Doctorate Program in Clinical Medicine and Public Health of the University of Granada, in which a thesis is being carried out regarding these devices.

References

[1] Professionals SO. EAU Guidelines: Non-muscle-invasive Bladder Cancer. Uroweb, https://uroweb.org/guideline/non-muscle-invasive-bladder-cancer/; [accessed 08.11.21].

[2] Sylvester RJ, Brausi MA, Kirkels WJ, Hoeltl W, Calais Da Silva F, Powell PH, et al. Long-term efficacy results of EORTC genito-urinary group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, bacillus Calmette-Guérin, and bacillus Calmette-Guérin plus isoniazid in patients with intermediate- and high-risk stage Ta T1 urothelial carcinoma of the bladder. Eur Urol 2010;57:766–73.

[3] Ourfali S, Ohannessian R, Fassi-Fehri H, Pages A, Badet L, Colombel M. Recurrence Rate and Cost Consequence of the Shortage of Bacillus Calmette-Guérin Connaught Strain for Bladder Cancer Patients. Eur Urol Focus 2021;7:111–6.

[4] Fernandez-Gomez J, Madero R, Solsona E, Unda M, Martinez-Piñeiro L, Gonzalez M, et al. Predicting nonmuscle invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guerin: the CUETO scoring model. J Urol 2009;182:2195–203.

[5] Lammers RJM, Witjes JA, Inman BA, Leibovitch I, Laufer M, Nativ O, et al. The role of a combined regimen with intravesical chemotherapy and hyperthermia in the management of non-muscle-invasive Bladder Cancer: a systematic review. Eur Urol 2011;60:81–93.

[6] Kos B, Vásquez JL, Miklavčič D, Hermann GGG, Gehl J. Investigation of the mechanisms of action behind Electromotive Drug Administration (EMDA). PeerJ 2016 24;4:e2309.

[7] Stasi SMD, Giannantoni A, Massoud R, Dolci S, Navarra P, Vespasiani G, et al. Electromotive versus Passive Diffusion of Mitomycin C into human bladder wall: concentration-depth profiles studies. Cancer Res 1999;59:4912–8.

[8] Common Terminology Criteria for Adverse Events (CTCAE). 2017;155. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

[9] Colombo R, Da Pozzo LF, Salonia A, Rigatti P, Leib Z, Baniel J, et al. Multicentric study comparing intravesical chemotherapy alone and with local microwave hyperthermia for prophylaxis of recurrence of superficial transitional cell carcinoma. J Clin Oncol 2003;21:4270–6.

[10] Cima MJ, Lee H, Daniel K, Tanenbaum LM, Mantzavinou A, Spencer KC, et al. Single compartment drug delivery. J Control Release 2014;0:157–71.

[11] Kleinmann N, Matin SF, Pierorazio PM, Gore JL, Shabsigh A, Hu B, et al. Primary chemoablation of low-grade upper tract urothelial carcinoma using UGN-101, a mitomycin-containing reverse thermal gel (OLYMPUS): an open-label, single-arm, phase 3 trial. Lancet Oncol 2020;21:776–85.

[12] Carando R, Zazzara M, Cotrufo S, Ludovico GM. Intravesical treatment with electro-mediated administration of mytomicin c as prophylaxis for intermediate and high-risk nonmuscle-invasive Bladder Cancer: a retrospective multicenter study. Urol Int 2019;103:285–90.

[13] Carando R, Pradere B, Afferi L, Marra G, Aziz A, Roghmann F, et al. The role of device-assisted therapies in the management of non-muscle invasive bladder cancer: a systematic review. Progrès en Urologie 2020;30:322–31.

[14] Sousa A, Piñeiro I, Rodríguez S, Aparici V, Monserrat V, Neira P, et al. Recirculant hyperthermic IntraVEsical chemotherapy (HIVEC) in intermediate−high-risk non-muscle-invasive bladder cancer. Int J Hyperthermia 2016;32:374–80.

[15] Grimberg DC, Dudinec J, Shah A, Inman BA. Clinical trial of high dose hyperthermic intravesical mitomycin C for intermediate and high-risk non-muscle invasive bladder cancer during BCG shortage. Urol Oncol 2021;39:498.e13–20.

[16] Di Stasi SM, Giannantoni A, Stephen RL, Capelli G, Navarra P, Massoud R, et al. Intravesical electromotive mitomycin C versus passive transport mitomycin C for high risk superficial bladder cancer: a prospective randomized study. J Urol 2003;170:777–82.

[17] Di Gianfrancesco L, Ragonese M, Palermo G, Sacco E, Bassi P, Racioppi M. Second-line conservative device-assisted intravesical treatment in selected patients with recurrent high-risk non-muscle-invasive Bladder Cancer. Clin Genitourin Cancer 2021;19:e100–19.

[18] Tan WS, Panchal A, Buckley L, Devall AJ, Loubière LS, Pope AM, et al. Radiofrequency-induced Thermo-chemotherapy effect versus a Second Course of Bacillus Calmette-Guérin or Institutional standard in patients with recurrence of non-muscle-invasive Bladder Cancer Following Induction or Maintenance Bacillus Calmette-Guérin Therapy (HYMN): a Phase III, Open-label, Randomised Controlled Trial. Eur Urol 2019;75:63–71.

[19] de Jong JJ, Hendricksen K, Rosier M, Mostafid H, Boormans JL. Hyperthermic Intravesical Chemotherapy for BCG Unresponsive non-muscle invasive Bladder Cancer Patients. Bladder Cancer 2018;4:395–401.

[20] Pijpers OM, Hendricksen K, Mostafid H, de Jong FC, Rosier M, Mayor N, et al. Long-term efficacy of hyperthermic intravesical chemotherapy for BCG-unresponsive non-muscle invasive bladder cancer. Urol Oncol 2021;40:62.e13–20.

[21] Chiancone F, Fabiano M, Fedelini M, Meccariello C, Carrino M, Fedelini P. Outcomes and complications of Hyperthermic IntraVesical Chemotherapy using mitomycin C or epirubicin for patients with non-muscle invasive bladder cancer after bacillus Calmette-Guérin treatment failure. Cent European J Urol 2020;73:287–94.

[22] Racioppi M, Di Gianfrancesco L, Ragonese M, Palermo G, Sacco E, Bassi PF. ElectroMotive drug administration (EMDA) of Mitomycin C as first-line salvage therapy in high risk 'BCG failure' non muscle invasive bladder cancer: 3 years follow-up outcomes. BMC Cancer 2018;18:1224.

[23] Pierconti F, Straccia P, Emilio S, Bassi PF, De Pascalis I, Marques RC, et al. Cytological and histological changes in the urothelium produced by electromotive drug administration (EMDA) and by the combination of intravescical hyperthermia and chemotherapy (thermochemotherapy). Pathol Res Pract 2017;213:1078–81.

[24] Pierconti F, Rossi ED, Straccia P, Fadda G, Larocca LM, Bassi PF, et al. The risk of malignancy of atypical urothelial cells of undetermined significance in patients treated with chemohyperthermia or electromotive drug administration. Cancer Cytopathol 2018;126:200–6.

[25] Colombo R, Brausi M, Da Pozzo L, Salonia A, Montorsi F, Scattoni V, et al. Thermo-chemotherapy and electromotive drug administration of mitomycin C in superficial bladder cancer eradication. a pilot study on marker lesion. Eur Urol 2001;39:95–100.

[26] Aziz A, May M, Burger M, Palisaar RJ, Trinh QD, Fritsche HM, et al. Prediction of 90-day mortality after radical cystectomy for bladder cancer in a prospective European multicenter cohort. Eur Urol 2014;66:156–63.

[27] Guerrero-Ramos F, González-Padilla DA, González-Díaz A, de la Rosa-Kehrmann F, Rodríguez-Antolín A, Inman BA, et al. Recirculating hyperthermic intravesical chemotherapy with mitomycin C (HIVEC) versus BCG in high-risk non-muscle-invasive bladder cancer: results of the HIVEC-HR randomized clinical trial. World J Urol. 2022 Jan 17.