Original Study

Sequential Treatment With Bacillus Calmette-Güerin (BCG) and Mitomycin C Administered With Electromotive Drug Administration (EMDA) in Patients With High-Risk Nonmuscle Invasive Bladder Cancer After BCG Failure

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Abstract

We evaluated the use of BCG and Mitomicin C instillations administered with Electromotive Drug Administration (EMDA) in patients with nonmuscle invasive bladder cancer in whom Bacillus Calmette-Guerin (BCG) therapy had failed, in order to provide bladder preservation for these patients. We evaluated the oncological outcomes and tolerability in a long follow up This treatment seems to be safe and to provide good responses in well selected patients, without a high progression rate.

Background: Nowadays, there is no standard non-surgical treatment for patients with nonmuscle invasive bladder cancer (NMIBC) in whom Bacillus Calmette-Güerin (BCG) therapy has failed.**Objectives:** To assess the clinical and oncological outcomes of sequential treatment with Bacillus Calmette-Guerin (BCG) and Mitomycin C (MMC) administered with Electromotive Drug Administration (EMDA) in patients with high-risk NMIBC who fail BCG immunotherapy. **Material and Methods:** We retrospectively studied patients with NMIBC who failed BCG and received alternating BCG and Mitomycin C with EMDA between 2010 and 2020. Treatment schedule consisted in an induction therapy with 6 instillations (BCG, BCG, MMC + EMDA, BCG, BCG, MMC + EMDA) and a 1-year maintenance. Complete response (CR) was defined as the absence of high-grade (HG) recurrences during follow-up, and progression was defined as the occurrence of muscle invasive or metastatic disease. CR rate was estimated at 3, 6, 12, and 24 months. Progression rate and toxicity were also assessed. **Results:** Twenty-two patients were included with a median age of 73 years. Fifty percent of tumors were single, 90% were smaller than 1.5cm, 40% were GII (HG) and 40% were Ta. CR rate was 95.5%, 81% and 70% at 3 and 6 months, 12 months and 24 months, respectively. With a median follow-up of 28.8 months, 6 patients (27%) presented HG recurrence and only 1 patient (4.5%) progressed and ended in cystectomy. This patient died due to metastatic disease. Treatment was well tolerated and 22% of the patients presented adverse effects, being dysuria the most frequent one. **Conclusion:** Sequential treatment with BCG and Mitomycin C with EMDA achieved good responses and low toxicity in selected patients who did not respond to BCG. Only 1 patient ended in cystectomy and died due to metastatic disease, therefore, cystectomy was avoided in most cases.

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Introduction

Intravesical instillations of Bacillus Calmette-Guerin (BCG) are the standard adjuvant treatment for patients with high-risk nonmuscle invasive bladder cancer (NMIBC). They have been shown to decrease recurrence by 30%-40%[1] and also decrease progression.[2]

Despite an adequate BCG treatment, up to 40% of the tumors will recur within 5 years[3] and about 21%-73% will progress to muscle invasive disease.[1]

Failure to BCG treatment is associated with an elevated risk of progression, for this reason, radical cystectomy is considered the treatment of choice. Radical cystectomy achieves a disease-free survival of up to 90% in this group of patients but at the expense of a mortality of 0.7%-5.6% and a high postoperative morbidity.[4] In this context many patients are not suitable for this surgery, while others wish to preserve their bladders. Therefore, finding a definitive nonsurgical treatment for patients with BCG failure is a matter of great importance.

Numerous alternatives are currently being developed to allow bladder preservation in patients who fail BCG treatment. One of these alternatives is the sequential intravesical administration of BCG and Mitomycin C administered using the Electromotive Drug Administration (EMDA) system (BCG/Mitomycin C+EMDA).[5-9]

This system applies an electrical current that ionizes Mitomycin C, increasing its absorption and allowing up to 4 to 7 times higher tissue concentrations, showing greater effectiveness compared to passive Mitomycin C administration.[8] Di Stasi et al[9] demonstrated in 2006 that this treatment achieved a decrease in recurrence and progression rates compared to BCG treatment in patients with high-risk NMIBC. Recently, the alternate use of BCG/Mitomycin C + EMDA in patients with BCG failure has also been reported.[5] This therapy could be available in many hospitals and, therefore, could be an advantage to other alternatives in study.

In this context, the objective of our study was to assess the real-world clinical and oncological outcomes of the use of BCG/Mitomycin C with EMDA in patients with high-risk NMIBC who did not respond to BCG treatment.

Material and Methods

Patient Eligibility

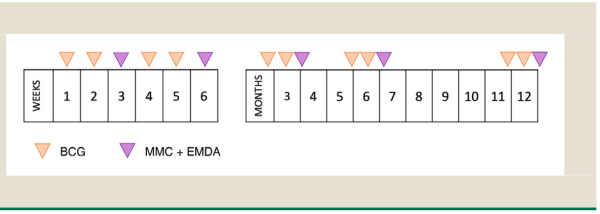
After Ethics Committee approval, we retrospectively reviewed our database of patients with high-risk NMIBC in our center who failed treatment with BCG and subsequently received sequential treatment with BCG/Mitomycin C + EMDA. The inclusion period was between 2010 and 2020.

All patients had received an adequate BCG treatment which was defined as at least 5 of 6 initial induction doses and at least 2 of 3 of a first maintenance or 2 of 6 of a second induction.[10,11]

Tumor grade was stratified according to the WHO classification 1973 and 2004/2016, and tumor staging according to the American Joint Committee on Cancer/Union for International Cancer Control TNM system.[10]

Tumors were classified according to the criteria of BCG failure established by the EAU. They were classified into *refractories* being: high-grade (HG) tumors during BCG treatment, T1 HG after 3 months since treatment initiation, CIS at 6 months and Ta AG at 3 and 6 months after treatment initiation; *early relapsing:* AG tumor within 6 months of receiving full treatment or CIS within 1 year; *unresponsives: refractory* tumors *or early relapsings; late relapsing:* high-grade relapse beyond 1 year of full treatment.[10,11]

Figure 1 Schedule of sequential treatment with BCG/Mitomycin C + EMDA. Abbreviations: EMDA = Electromotive Drug Administration; BCG = Bacillus Clamette-Guerin)



Treatment Schedule

Sequential treatment with BCG/Mitomycin C + EMDA followed the schedule described in Figure 1, with an induction and a 1-year maintenance according to the treating physician's decision. Instillations were always performed by the same team and following the same technique.

Patients emptied their bladder on arrival and then 40mg of MMC diluted in 100mL of sterile water were introduced into the bladder with specialized catheters capable of conducting current (CE-DAS ® UROGENICS ®). The intensity of the current was 25mA and the instillation lasted 30 minutes. Afterwards, patients were asked to hold the instillation for one hour.

Follow-Up

Follow-up after BCG/Mitomycin C + EMDA was done with cystoscopy and cytology every 3 months for the first 2 years and every 6 months until 5 years. Study of the upper urinary tract was performed by biannual CT scanning.

Endpoint Definitions and Outcomes

Demographic and clinicopathological data of the patients and tumors in the study were collected. Reasons for not performing cystectomy were also recorded. Complete response (CR) was defined as the absence of high-grade recurrence during follow-up, and progression as the occurrence of muscle invasive disease. CR was assessed at 3 months, 6 months, 12 months, and 2 years after treatment for the entire series and for the unresponsive patients. Patients with recurrence or progression despite BCG/Mitomycin C + EMDA treatment were analyzed.

Statistical Analysis

Qualitative variables were described with frequency rates and percentages. Quantitative variables were described using median and interquartile range. The Kaplan-Meier method was used to analyze recurrence-free survival.

Table 1.1 Demographic and Clinicopathological Characteristics of the Patients and Tumors Prior to BCG failure

Characteristics	n (%)
Sex	
Male	15 (68.2)
Female	7 (31.8)
Median age at first diagnosis	74 (68-77)
Tumor stage prior to BCG failure	
GII **(HG)**	7 (31.8)
GIII **(HG)**	15 (68.1)
Ta	9 (40.9)
T1	11 (50.0)
TIS	2 (9.0)
Tx	0 (0)
Associated CIS	8 (36.3)
Unifocal CIS	6 (75.0)
Multifocal CIS	2 (25.0)
Adequate BCG treatment	22 (100.0)
BCG failure	
Refractory	15 (68.2)
Early relapsing	3 (13.6)

Abbreviations: HG = high grade; BCG = Bacillus Clamette-Guerin; CIS = carcinoma in situ.

Results

General Features

Twenty-two patients were included in the study. Demographic and clinicopathological characteristics of the patients and the initial tumors before BCG failure and before treatment with BCG/Mitomycin C + EMDA are presented in Table 1.1 and Table 1.2, respectively.

Fifty percent of the tumors treated with sequential treatment were single, 90% were smaller than 1.5cm, 40% were GII (HG) and 40% were Ta. The indications for BCG/Mitomycin C + EMDA treatment were: refusal of radical cystectomy in 14 patients (63.6%), unfit for the procedure in 5 (22.7%) and 3 (13.6%) for other causes.

Table 2 details the sequential treatment regimens received by the patients.

Oncological Outcomes

With a median follow-up of 28.8 months (95% CI, 17.39 - 41.12) 10 patients had recurrences, 6 (27%) of which were high grade (5 TIS and 1 TaHG). These 6 recurrences were treated with re-induction of BCG/Mitomycin C + EMDA in 2 cases, BCG re-induction in 2 cases, cystectomy in 1 case (multifocal pTIS) and 1 patient had no further follow-up. Only one patient (4.5%) had progression during follow-up and eventually died due to metastatic disease.

The CR rate of the 22 patients was 95.5% at 3 and 6 months, 81% at 12 months and 70% at 2 years. The CR rate of the 18 BCG unresponsive patients was 100% at 3 and 6 months, 82.4% at 12 months and 68.8% at 24 months. The Kaplan-Meier curve for recurrence-free survival is presented in Figure 2. The median recurrence-free survival for the 22 patients was 37.78 months (3.14 years) with a 95% CI, 15.17 to 60.38.

Table 1.2 Clinicopathological Characteristics of the Tumors Prior to Sequential Treatment With EMDA

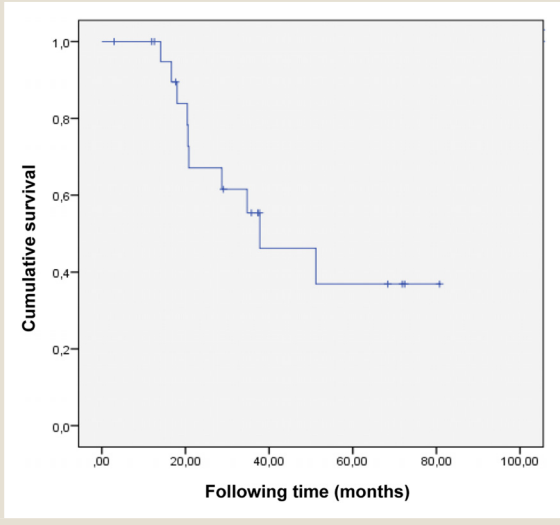
Characteristics	*n* (%)
N° tumors	
1	11 (50)
2	4 (18.2)
3	3 (13.6)
Multiple	4 (18.2)
Size of the tumor	
<1.5cm	20 (90.9)
1.5 to 3cm	1 (4.5)
>3cm	1 (4.5)
Tumor stage pre-EMDA	
GII **(HG)**	9 (40.9)
GIII **(HG)**	13 (59.1)
Ta	9 (40.9)
T1	9 (40.9)
TIS	3 (13.6)
Tx	1 (4.5)
Associated CIS	11 (50)
Unifocal CIS	9 (81.8)
Multifocal CIS	2 (18.2)

Abbreviations: EMDA = Electromotive Drug Administration; HG = high grade; CIS: carcinoma in situ.

Table 2 Treatment Regimens Received by the Patients Included in the Study

EMDA Treatment	n (%)
Only induction	11 (50)
Induction + 1st maintenance	3 (13.6)
Induction + 2nd maintenance	4 (18.2)
Induction + 3rd maintenance	4 (18.2)

Figure 2 Kaplan-Meier curve for recurrence-free survival



Toxicity and Tolerability

Treatment with BCG/Mitomycin C + EMDA was well tolerated. Twenty-two percent of the patients presented some adverse effects, being dysuria the most frequent (4 patients). Only 1 case of post-instillation fever (temperature over 38°C) was reported. There were no cases of treatment abandonment due to toxicity.

Discussion

In the present study we observed that sequential treatment with BCG and Mitomycin C with EMDA in patients with HG-NMIBC recurrence after adequate BCG treatment, achieved a CR of 95.5% at 3 and 6 months, 81% at 12 months and 70% at 2 years, with a progression rate of 4.5%. In BCG unresponsive patients the results were essentially the same.

Bladder preservation after BCG failure is becoming a controversial topic. The emergence of numerous studies referring to this subject has forced to the homogenization of definitions of BCG failure, as the EAU has done, in which *unresponsive* patients are the patients at highest risk of progression.[10] Similarly, it has been defined that, for a new treatment to be considered clinically meaningful, the initial response for CIS or the recurrence-free rate of papillary tumors must be at least 50% at 6 months, 30% at 12 months and 25% at 18 months.[11]

Numerous studies are underway but currently, the FDA has only accepted 2 treatments for BCG failure: Valrrubicin, with very modest results (21% CR at 6 months)[12] and Pembrolizumab with a complete remission rate of 41% and 19% at 3 and 12 months respectively, in patients with CIS.[13]

Nevertheless, there are other treatments available for patients who do not respond to BCG, such as Nadofaragene firadenovec with a CR rate at 3 and 12 months of 53% and 24% respectively[14] or Oportuzumab monatox with CR at 3 and 12 months of 40% and 17%.[15]

Regarding intravesical treatment, the combined use of Gemcitabine/Docetaxel showed CR rates at 12 and 24 months of 65% and 52% and a progression rate of 4%,[16] whereas hyperthermic intravesical chemotherapy with mitomycin C (HIVEC) showed CR rates of 53% and 35% at 12 and 24 months, respectively.[17]

Sequential treatment with BCG/Mitomycin C + EMDA has already been used as initial treatment of high-risk noninvasive tumors and also in patients with BCG failure. Juvet et al[5] treated, by sequential administration of BCG and Mitomycin C + EMDA, 26 patients with nonmuscle invasive bladder tumors in whom BCG treatment had failed. CR at 6, 12, and 18 months were 61.5%, 44% and 30.4% respectively, with 42% of progression.

Raccioppi et al[6] administered Mitomycin + EMDA treatment to 26 patients with NMIBC who failed after BCG treatment. CR at 36 months was 61% with 15.4% progression. At the end of the follow-up, they stratified patients according to TNM in 4 groups: Ta G3, T1G3, CIS and TaT1G3 + CIS, observing CR rates respectively of 75%, 71.4%, 50%, and 25%.

As it can be seen, our rates of CR (81% at 12 months and 70% at 2 years) and progression (4.5%) were more favorable than those obtained by Juvet et al,[5] Raccioppi et al,[6] and also than the obtained by most of the drugs listed in this study to treat BCG failure patients.

Table 3 Histopatological Stage and Number of Patients Included in the Mentioned Studies

Histopatological Stage	Riacopi et al	Juvet et al	Sanz et al
Ta	4 (15.4%)	3 (11.6%)	9 (40.9%)
T1	14 (53.8%)	9 (34.6%)	9 (40.9%)
CIS	4 (15.4%)	14 (53.8%)	3 (13.6%)
Ta/T1 + CIS	4 (15.4%)	0	0
Tx	0	0	1 (4.5%)
RC at 6 months	NA[a]	61.5%	95.5%
RC at 12 months	NA[a]	44%	81%
Progresion rate	15.4	42	4.5

[a] Not available. Authors assessed CR at the end of the follow up and according to TNM stratification.

To explain these differences, it is key to take into account what Raccioppi et al[6] observed in their study: the CR rate will vary depending on the stage of the tumors to be treated.

In Table 3 we have summarized stage and grade of the tumors included in these 2 studies and our own, as well as the outcomes obtained during the follow up. In our serie, 40.9% of the tumors were Ta and the majority of them were high-grade GII, which would make them less aggressive, 50% were single and 90% smaller than 1.5cm.

We believe that the patients included in our study selected a group of patients with more favorable pre-treatment tumor stages and, therefore, better post-treatment results.

In our center, for years we have advised cystectomy as a first-line treatment for patients who have failed BCG, and we strongly recommend it for those who also have histologies with a very high risk of progression. This could explain why our serie includes patients with more favorable histologies before starting BCG/Mitomycin C + EMDA.

Therefore, the results of any drug used for BCG failure will be influenced by the effectiveness of the treatment, but also by the characteristics of the tumors prior to treatment. One option would be to stratify the results of BCG failure drugs treatment by dividing patients into groups: Ta, T1, CIS and Ta/T1 +CIS.

Regarding toxicity and tolerability, treatment with BCG/Mitomycin C + EMDA was well tolerated. Twenty two percent of the patients presented some adverse effects, whereas Juvet et al reported dysuria in 19%, hematuria in 19.2%, pollakiuria in 15% and bacteremia in 11.5%.

Our study is not devoid of limitation. It was retrospective with a limited number of patients and not all of them received the same treatment regimen of BCG/Mitomycin C + EMDA. In addition, we had difficulties in collecting information on the adverse effects of the treatment.

Conclusions

Sequential treatment with BCG/ Mitomycin C + EMDA is a good option in selected patients with high-risk tumors who have failed BCG and do not want a cystectomy. Treatment with BCG / Mitomycin C + EMDA is well tolerated.

Clinical Practice Points

- **What is already known about this subject?**
  The standard treatment for patients with nonmuscle invasive bladder cancer who fail after BCG treatment is radical cystectomy.
- **What are the new findings?**
  We evaluated the use of BCG and Mitomycin C instillations administered with Electromotive Drug Administration (EMDA) and they showed to provide good responses and low toxicity in selected patients who did not respond to BCG.
- **How might it impact on clinical practice in the foreseeable future?**
  BCG and MMC instillations administered with EMDA can be a good option for bladder preservation in well selected patients with NMIBC who have failed to a prior BCG treatment, avoiding the complications of a major surgery like radical cystectomy.

Authors' Contributions

Isabel Sanz and Jorge Huguet had full access to all the data in the study. Conception: Jorge Huguet; Performance of work: Isabel Sanz, Alejandra Bravo and Jorge Robalino; Interpretation of the data: Isabel Sanz, Jorge Huguet; Supervision and writing reviewing: Jorge Huguet, Óscar Rodriguez Faba, Ángelo Territo, José María Gaya, Joan Palou and Alberto Breda.

Ethical Considerations

The study was reviewed and approved by our institutional ethical committee previously to its development.

Disclosure

The authors declare no conflict of interest. Joan Palou Redorta is an Editorial Board Member of this journal, but was not involved in the peer-review process nor had access to any information regarding its peer-review.

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