

# Efficacy and safety of a new device for intravesical thermochemotherapy in non-grade 3 BCG recurrent NMIBC: a phase I–II study

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## Abstract

**Purpose** We report for the first time the activity and safety of Unithermia<sup>®</sup> (Elmedical Ltd, Hod-Hasharon, Israel), a novel device for administration of MMC-C with hyperthermia (HT), that employs conductive heating, in a series of non-grade 3 non-muscle-invasive bladder cancer (NMIBC) that failed Bacillus Calmette–Guerin (BCG).

**Methods** Patients with non-grade 3 NMIBC recurring after at least a full induction course of BCG were eligible for this phase I–II prospective single-arm study. Six weekly instillations with Unithermia<sup>®</sup> were scheduled following complete TUR. Primary end points were treatment safety and response rate (RR), and the latter defined as the absence of any unfavourable outcome at 12 months. Any grade 3 and/or muscle-invasive (T > 1) recurrence was considered disease progression. Kaplan–Meier estimation of the time to recurrence and progression, cancer-specific survival and overall survival was taken as secondary end points.

**Results** Thirty-four eligible patients entered the study between January 2009 and April 2011. RR was documented

in 20/34 (59 %). Among the 14/34 (41 %) non-responders, four developed G3 disease, one developed carcinoma in situ, and one progressed to muscle-invasive bladder cancer, with an overall 18 % progression rate at 1 year. At a median follow-up of 41 months, recurrence and progression rates were 35.3 and 23.5 %, respectively. Toxicity did not go beyond grade 2 except in five cases.

**Conclusions** Initial experience with MMC-HT with Unithermia<sup>®</sup> showed an interesting activity and safety profile in non-grade 3 NMIBC recurring after BCG, suggesting a role as second-line therapy in this selected subgroup of NMIBC.

**Keywords** Bladder cancer · Intravesical chemotherapy · BCG failure · Thermochemotherapy · Device assisted

## Introduction

Bacillus Calmette–Guerin (BCG) is currently considered the most effective first-line intravesical therapy in non-muscle-invasive bladder cancer (NMIBC) and the standard conservative treatment option in the high-risk category [1]. Up to 40–50 % of patients will eventually recur after BCG [2]. This clinical condition represents a therapeutic challenge. The current evidence strongly recommends radical cystectomy for NMIBC failing BCG in view of their aggressive behaviour [1, 3, 4]. On the other end, radical surgery may represent an over treatment, especially for those patients with non-high-grade BCG failure [1]. Furthermore, some patients may be considered unfit for radical surgery because of significant comorbidities and/or age. A number of intravesical therapeutic options, including gemcitabine, BCG plus interferon alpha (IFN- $\alpha$ ) and valrubicin have been assessed in

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NMIBC BCG failures yielding modest disease-free survival rates [5–7].

Administration of intravesical chemotherapy has been combined with hyperthermia (HT) in order to improve treatment efficacy by increasing drug permeability in the bladder and the cytotoxic effect (directly induced by heat) [8]. Thermochemotherapy with mitomycin C (MMC-C) has proved to be more effective than MMC-C alone in NMIBC in both ablative and prophylactic setting [9, 10]. Promising response rates were also documented in subgroups of BCG-refractory NMIBC [11]. In all published studies, the intravesical thermochemotherapy was performed by means of Synergo<sup>®</sup> (Medical Enterprises, Amsterdam, the Netherlands), a specifically designed system that delivers HT to the bladder lumen using an intravesical microwave applicator [12]. The routine clinical use of Synergo<sup>®</sup> system, however, is limited by the high costs of disposables (catheters) and the high skillfulness required to assure a correct positioning of the catheter [13]. Direct microwave irradiation could determine a non-uniform temperature distribution, resulting in the formation of “Hot” or “Cold” spots into the bladder with the risk of burns or lower efficacy of the treatment [14].

The aim of our study was to explore safety, pharmacological stability, pharmacokinetics and efficacy of Unithermia<sup>®</sup> (Elmedical Ltd, Hod-Hasharon, Israel), a new HT device for intravesical chemotherapy that uses conductive heating, in a series of non-high-grade NMIBC recurring after BCG.

## Patients and methods

### Objectives and end points

The trial was designed as a phase I–II single arm and received approval from Ethics Committee on 01/09/2008 (Protocol No. 0065331). Primary study objectives were treatment safety and the prophylactic activity of MMC-C administered with the HT device Unithermia<sup>®</sup> in preventing tumour recurrence in Ta–T1, G1–G2 NMIBC BCG failures.

Primary study end point was the detection and grading of adverse events according to the Common Terminology Criteria for Adverse Events (CTCAEv6) [15].

Co-primary end point was the assessment of treatment “response rate” (RR), defined as the absence of an unfavourable outcome at 12 months from the start of treatment. We defined “unfavourable outcome” anything of the following:

- Recurrence of a Ta–T1, G1–G2 NMIBC
- Progressive disease, i.e. any occurrence of G3 disease, CIS or muscle-invasive (MI) disease ( $T > 1$ )

The Kaplan–Meier estimation of the time to first unfavourable outcome as well as cancer-specific survival (CSS) and overall survival (OS) at the available follow-up was considered as secondary end points.

### Inclusion and exclusion criteria

Patients with a pathologically confirmed recurrent Ta–T1, G1–G2 (according to WHO 1973 grading system) transitional NMIBC after at least a full induction course of BCG were eligible for the study. In the current study, BCG recurrence was defined as any disease evidence between 6 and 24 months from BCG start. A WHO performance status (PS) of 0–2 and an age range between 18 and 80 years old were also required.

Any history of MI bladder cancer ( $T > 1$ ), CIS, G3 NMIBC, high-grade transitional cell carcinoma (TCC) at urine cytology or upper urinary tract or prostatic urethra TCC was an exclusion criteria. Patients with a white blood cell count below 3.000/mm<sup>3</sup>, a platelet count below 100.000/mm<sup>3</sup>, hepatic and kidney function values twice exceeding the laboratory reference limit, uncontrolled urinary tract infections and inability to hold the urine for more than 1 h were also ineligible.

### Baseline patient investigations and TUR

Upper urinary tract investigation (IVP or contrast CT) had to be conducted within 3 months of study entry. Full blood count, kidney and liver function, urine culture and urine cytology were assessed preoperatively. TUR of all visible lesions and biopsy of all suspected areas had to be performed.

### Device description

The Unithermia<sup>®</sup> device is an office-based system consisting of a compact console that allows instillation of a heated solution of chemotherapy (MMC-C) in the bladder through an 18-F three-way balloon catheter. The console delivers conductive heat to a MMC solution, which is then continuously pumped in a closed circulating unit up to the bladder through a 20-Ch three-way balloon catheter. The system is designed to maintain uniform HT to the bladder (medium temperature of  $42.5 \pm 1$  °C with a maximum peak of 44.5 °C) through high inflow and outflow of the solution whose temperature is continuously checked by a needle-tip thermometer placed in the catheter.

## Treatment schedule

Six weekly intravesical instillation of mitomycin C (MMC) 40 mg in 50 cc of 0.9 % saline solution (concentration 0.8 mg/ml) were delivered through Unithermia® device in sessions of 45 min each starting 2 weeks from TUR. In the first 11 patients, the solution was replaced after 22 min in order to assess drug stability (see next paragraph). All sessions were conducted on an outpatient basis, using a transurethral anaesthetic gel before catheter placement.

## Assessment of drug stability and pharmacokinetic

The MMC-C stability was evaluated for the first 11 patients in 64 consecutive instillation cycles. In these patients, MMC-C solution was recovered from the bladder after 22 min and replaced with a fresh one up to the end of the session (23 additional minutes). Volume and pH of the solution recovered at 22 and 45 min were determined and aliquots immediately stored at  $-80^{\circ}\text{C}$  until analysis. Pharmacokinetics of the solution was evaluated in the first seven patients during the third cycle through serial blood samples immediately before the instillation and then at 11-, 22- and 45-min intervals. Plasma was immediately separated by centrifugation and stored at  $-80^{\circ}\text{C}$  until analysis. Details on the methodology for assessing MMC-C stability and pharmacokinetics have been already published elsewhere [15].

## Safety and quality of life (QoL) assessment

Adverse events according to the WHO Common Toxicity Criteria for Adverse Events classification version 6.0 (CTCAEv6) and version 2.0 adapted to intravesical treatment were recorded after each instillation. Patients were also asked to complete two validated QoL questionnaires (EORTC QIQ-C30 and BLS-24) at baseline and at the end-of-treatment course.

## Follow-up

Follow-up consisted of urine cytology and cystoscopy at 3, 6, 12 months for the first year and then every 6 months for the second and the third year and yearly thereafter. Recurrence with or without progression at any time prompted exclusion of the patient from the study, and his management left to the judgement of the investigator.

## Statistical analysis

Treatment RR was reported descriptively. Time to events (recurrence, progression and survival rates) were determined using the statistical analysis SPSS® version 18.0 and

Kaplan–Meier curves. Results of QoL questionnaires were reported using two-tailed significance tests with a significance level of  $p < 0.05$ .

## Results

### Baseline demographic and tumour characteristics

Between January 2009 and April 2011, 38 eligible patients were screened and 34 entered the study in four Italian centres. Baseline characteristics are summarized in Table 1. The median number of recurrences between first diagnosis and enrolment was 2 (range 1–7). Sixteen patients (47 %) received intravesical therapy before BCG (MMC alone  $n = 4$ , gemcitabine  $n = 9$ , epirubicin  $n = 3$ , farmorubicin  $n = 1$ ).

### Safety and patients QoL

The treatment was overall well tolerated and safe. No life-threatening adverse event occurred. Four patients failed to complete the course of weekly instillation due to grade 3 toxicity (bladder spasms  $n = 2$ , systemic cutaneous rash  $n = 2$ ) and discontinued it at the fourth ( $N = 2$ ) and fifth ( $N = 2$ ) cycle, respectively. These patients were retained in the outcome analysis. The most common adverse event was bladder spasm (8/34) (G1 in 4, G2 in 1 and G3 in three patients, respectively) and frequency (5/34). Side effects and their grading according to CTCAE v2 are reported in Table 2.

The EORTC QLQ-C30 and QLQ-BLS24 questionnaires were completed by 34 (100 %) patients at baseline (T0) and 32 (94.1 %) at the end of the treatment (T1). Main domain scores changes are shown in Fig. 2. Global Health Status/QoL and Functional Scales of the EORTC QLQ-C30 showed a non-significant trend for improvement at T1 compared to T0. Urinary symptoms assessed with the BLS-24 showed an opposite (non-significant) trend towards worsening in the same time intervals (T0 vs. T1).

### Stability and pharmacokinetics of MMC-C administered with Unithermia

Median rate of MMC recovery in the first (0–22 min) and second (23–45) part of the instillation was 66.2 % (range 38.6–92.3) and 99.6 % (range 68.6–136), respectively. These results indicate that the MMC absorption occurs mainly during the 0- to 22-min instillation period, and that the degradation of MMC maintained at  $45^{\circ}\text{C}$  in the bladder was minimal, as indicated by the high recovery after the 22- to 45-min period.  $C_{\text{max}}$  MMC plasmatic levels were considerably lower than the reported threshold concentration for

**Table 1** Baseline patients' characteristics and oncological outcomes

<i>Baseline patients' characteristics</i>	
Age (years), median [range]	70 [51–85]
Sex, <i>N</i> (%)	
Males	28 (82.4)
Females	6 (17.6)
Pathology, <i>N</i> (%)	
Staging	
Ta	26 (76.5)
T1	8 (23.5)
Grading	
G1	16 (47)
G2	18 (53)
Focality	
Single	23 (67.7)
Multiple	11 (32.3)
Previous intravesical therapies, <i>N</i> (%)	
BCG	34 (100)
Chemotherapy	13 (38.2)
Mitomycin C	5 (14.7)
Gemcitabine	6 (17.6)
Epirubicin	3 (8.8)
Farmorubicin	1 (2.9)
Previous number of recurrence, median [range]	3 [1–4]
<i>Oncological outcomes</i>	
Median follow-up, <i>N</i> of months (range)	41 (18–78)
Recurrence rate, <i>N</i> (%)	12 (35.3)
Ta	10 (83.3)
T1	2 (16.7)
G1	6 (50)
G2	6 (50)
Median time to first recurrence, <i>N</i> of months (range)	10.5 (3–42)
Early (within 12 months) recurrence based on previous pathology), <i>N</i> (%)	9 (75)
Ta	4 (44.4)
T1	5 (56.6)
Progression rate, <i>N</i> (%)	8 (23.5)
G3	6 (75)
T > 1	2 (25)
Previous pathology of progressing cases, <i>N</i> (%)	
Ta	4 (50)
T1	4 (50)
G1	3 (37.5)
G2	5 (62.5)
Median time to progression, <i>N</i> of months (range)	10.5 (3–51)
Cystectomy rate, <i>N</i> (%)	5 (14.7)
Tumour pathology at cystectomy, <i>N</i> (%)	
CIS	1 (20)
Ta	1 (20)
T1	1 (20)

**Table 1** continued

T2	–
T3	2 (40)
N0	4 (80)
N1	1 (20)
Median time to cystectomy, <i>N</i> of months (range)	20 (8–60)
Disease-free rate, depending on previous pathology, <i>N</i> (%)	14 (41.2)
Ta	13 (50)
T1	2 (25)
G1	8 (50)
G2	11 (61.1)
Monofocal	14 (58.3)
Multifocal	5 (50)
5 years CSS, %	97.1
5 years OS, %	97.1

toxicity (400 ng/ml). Detailed information on drug stability and pharmacokinetics of these study patients have been published elsewhere [16].

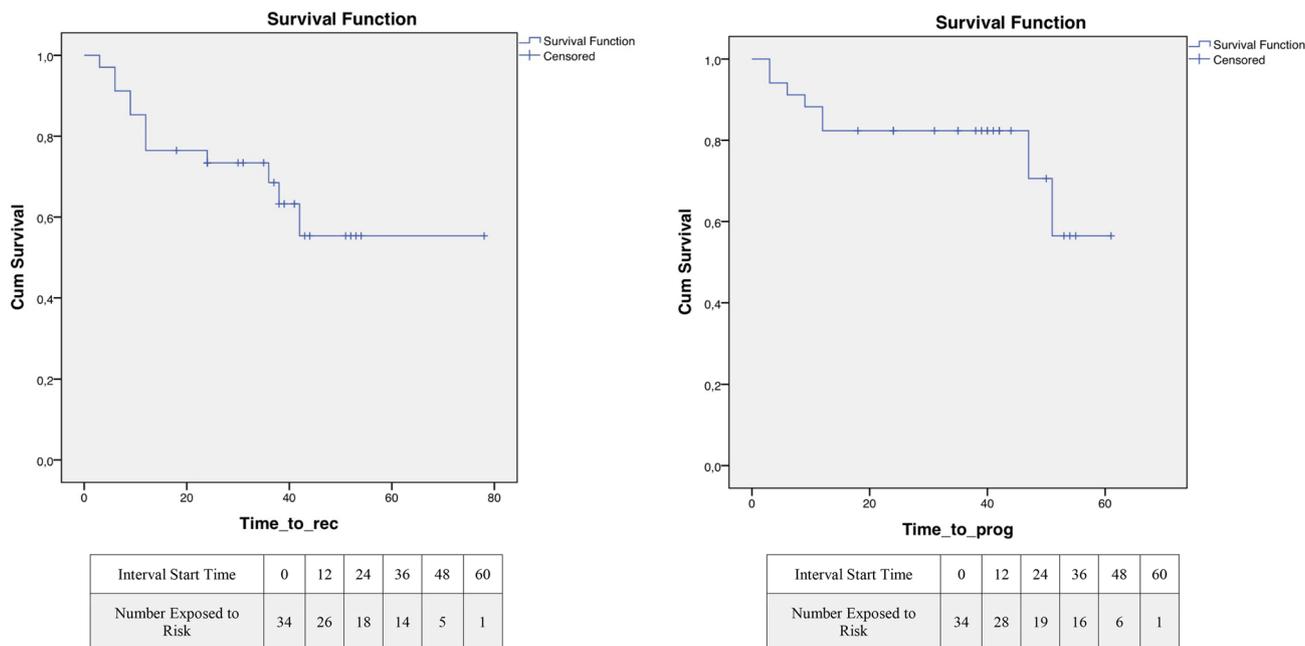
### Efficacy

Treatment RR was documented in 20/34 patients (59 %). Among the 14/34 (42 %) non-responders, three developed G3 disease, two developed CIS, and one progressed to MI bladder cancer, with an overall 18 % progression rate at 1 year.

At a median follow-up of 41 months, 15/34 patients (44.1 %) remained disease free. Beyond 1 year, four additional patients showed non-G3 recurrence, one had G3 recurrence, and one developed muscle-invasive disease. Median time to recurrence and progression were 10.5 and 29.5 months, respectively. Kaplan–Meier curves for recurrence and progression are reported in Fig. 1. Cystectomy was performed in five patients with two out of five found to have pathological muscle-invasive disease. At the median follow-up, recurrence and progression rates were 35.3 and 23.5 %, respectively. Oncological outcomes are summarized in Table 1.

### Discussion

Different intravesical therapeutic options have been tested in NMIBC BCG failures, either as single chemotherapeutic agents such as gemcitabine or as combinations of immunotherapies such as BCG + interferon [5, 17, 18]. Results have shown short-term disease-free rates not exceeding 50 %, making this disease category a therapeutic challenge [6, 19].



**Fig. 1** Kaplan–Meier curves for time to recurrence (*left*), time to progression (*right*) and patients at risk at each point time

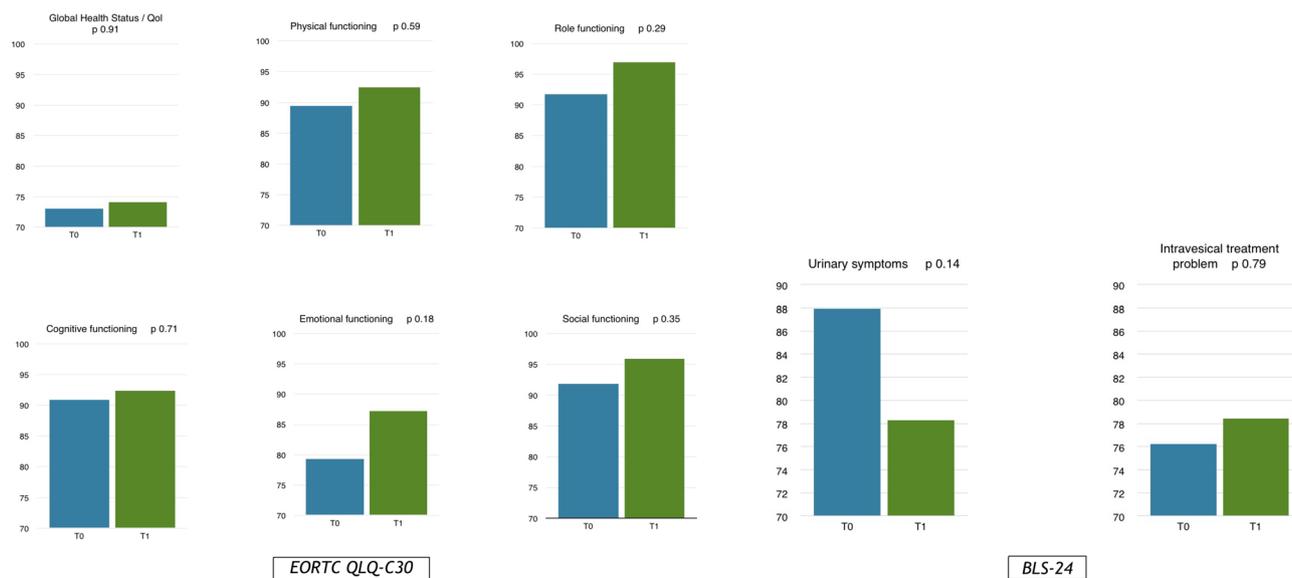
In later years, encouraging results in the treatment of NMIBC that have failed previous intravesical therapy have emerged from the combined use of chemotherapy and heat [12]. All available studies have been conducted using MMC-C that has become the reference chemotherapeutic agent for intravesical HT. Several explanations have been claimed for improved efficacy by combining MMC-C with HT. Firstly, HT suppresses the synthesis of nucleic acids and could damage the double-strand DNA [20]. Furthermore, hyperthermia increases cell membrane permeability, thus enhancing MMC-C penetration in the urothelium, and finally, HT has been shown to directly enhance MMC-C cytotoxicity [8, 21]. Until now, the Synergo<sup>®</sup> system (Medical Enterprises, Amsterdam, the Netherlands), which provides HT through direct irradiation of bladder wall by a 915-MHz microwave applicator, has represented the reference standard of intravesical MMC-C HT. Extensive research conducted over the last 20 years has shown synergic effects of “in vivo” MMC-C and HT on NMIBC superficial bladder corroborated by improved efficacy of MMC-C plus HT compared with MMC-C alone both in a neoadjuvant and in an adjuvant setting [8–10]. In the context of BCG recurrent NMIBC, Synergo<sup>®</sup> achieved initial response rates as high as 92 % in a small retrospective series of CIS and 85 % cancer-free rates at 1 year in 111 papillary NMIBC [11, 22].

One of the major drawbacks of Synergo<sup>®</sup> HT is represented by the high costs of the device and disposable catheters, thus limiting widespread adoption of the

**Table 2** Main local and systemic adverse events, graded according to CTCAEv2

Adverse event	Grade 1 (N, %)	Grade 2 (N, %)	Grade 3 (N, %)	Total (N, %)
Bladder spasms	4 (11.8)	1 (2.9)	3 (8.8)	8 (23.5)
Frequency	2 (5.9)	3 (8.8)	–	5 (14.7)
Incontinence	–	1 (2.9)	–	1 (2.9)
Infection	–	3 (8.8)	–	3 (8.8)
Allergic reaction	–	–	2 (5.9)	–

technology in the current constraint condition of health-care systems. Unithermia<sup>®</sup> is a device designed to provide HT of the bladder wall by direct irrigation with a heated solution. Unlike the microwave Synergo<sup>®</sup> system, Unithermia MMC-C HT occurs via conductive heating. Costs of the device and disposable catheters are significantly lower compared with Synergo<sup>®</sup>. Costs of Unithermia device amount to 42.000€ compared to 90.000€ of Synergo console. Disposable catheters of Unithermia amount to 200€ each, compared to about 600€ of three-way catheters used in the treatment with Synergo. This translates into a saving only for disposables of 2.400€ each six instillation induction course. Fifty-nine per cent of the patients in our series were disease free at 1 year. These results are interesting when compared with an early response rate below 50 % observed in a similar



**Fig. 2** Baseline (T0) and end of treatment (T1) and main domain scores of the EORTC QLQ-C30 and QLQ-BLS24 questionnaires

population of non-grade 3 BCG recurrent NMIBC with second-line gemcitabine (unpublished data) but inferior to those achieved with Synergo<sup>®</sup> in BCG failures [11, 22]. The different “heating” methodology may account for the discrepancy in MMC-C HT activity across the two systems. While a similar proportion of MMC-C is absorbed when administered under HT conditions either with Unithermia or with Synergo, the degree of heating obtained at the bladder wall level may vary between the two methodologies [15, 20]. During Synergo, a temperature of 42–43 °C is achieved at the bladder wall through a microwave thermal effect as confirmed by thermocouples placed in contact with the bladder mucosa [23]. With Unithermia, the bladder is irrigated by a solution constantly kept at 42–43 °C as confirmed by a thermometer placed at the tip of the catheter while the temperature reached at the bladder surface remains unknown. Failure to achieve optimal HT condition at the bladder wall with Unithermia may account for the relatively high early recurrence rate in the T1 disease subgroup as a result of suboptimal drug penetration. Indeed, 55.6 % of patients who underwent recurrence within 12 months belong to T1 subgroup. Further studies assessing the depth of MMC-C penetration under different HT conditions would clarify this hypothesis. Forty-five per cent remained disease free at a median follow-up of 41 months, a rate similar to that reported with Synergo in BCG-refractory series [11, 22]. Progression rate in our series (23 %) should be interpreted in the light of the broad definition of progression adopted that included also non-muscle-invasive grade 3 diseases. Notably, progression to muscle-invasive disease occurred only in two cases. All these data taken together

suggest that Unithermia may represent a reasonable second-line treatment option in non-high-grade/G3 BCG recurrent NMIBC.

We previously reported that a negligible proportion of MMC-C is absorbed under HT conditions with Unithermia [16]. The safety of MMC-C Unithermia was confirmed in the current study by the low prevalence of systemic side effects, with the exception of systemic allergic reaction reported in two cases. Toxicity was mainly confined at the lower urinary tract and usually not exceeding grade 2 except in three patients that experienced grade 3 bladder spasms. The four patients that discontinued treatment did so after at least four cycles. The toxicity profile of Unithermia mostly overlapped that of Synergo. None of the patients experienced haematuria, and an adverse event reported instead in the 6 % of the patients treated with Synergo device. Notably, we did not observe the thermal bladder injury typically reported in up to 10 % of patients at the first check cystoscopy after Synergo [12].

## Conclusions

In a selected series of non-grade 3 BCG recurrent NMIBC, MMC-HT with Unithermia achieved 58.8 % 1-year treatment response. At a median follow-up of 41 months, 41 % remained disease free. Progression to muscle-invasive disease was low. The treatment resulted overall tolerable with no significant impact on quality of life, making this novel type of intravesical HT an attractive second-line treatment for NMIBCs.

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical standard** The study has been approved by Ethics Committee on 01/09/2008 (Protocol No. 0065331). The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All the enrolled patients gave their informed consent before the inclusion in the study.

## References

- Babjuk M, Burger M, Zigeuner R et al (2013) EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. *Eur Urol* 64(4):639–653
- Martin FM, Kamat AM (2009) Definition and management of patients with bladder cancer who fail BCG therapy. *Expert Rev Anticancer Ther* 9:815–820
- Hall MC, Chang SS, Dalbagni G et al (2007) Guideline for the management of nonmuscle invasive bladder cancer (stages Ta, T1 and Tis): 2007 update. *J Urol* 178(6):2314–2330
- Lerner SP, Tangen CM, Sucharew H et al (2009) Failure to achieve a complete response to induction BCG therapy is associated with increased risk of disease worsening and death in patients with high risk non muscle invasive bladder cancer. *Urol Oncol* 27:155–159
- Gallagher BL, Joudi FN, Maymi JL et al (2008) Impact of previous bacilli Calmette-Guérin failure pattern on subsequent response to bacilli Calmette-Guérin plus interferon intravesical therapy. *Urology* 71:297–301
- Yates DR, Brausi MA, Catto JW et al (2012) Treatment options available for bacillus Calmette-Guérin failure in non-muscle-invasive bladder cancer. *Eur Urol* 62:1088–1096
- Sternberg IA, Dalbagni G, Chen LY et al (2013) Intravesical gemcitabine for high risk, nonmuscle invasive bladder cancer after bacillus Calmette-Guérin treatment failure. *J Urol* 190(5):1686–1691
- Van der Heijden AG, Verhaegh G, Jansen CF et al (2005) Effect of hyperthermia on the cytotoxicity of 4 chemotherapeutic agents currently used for the treatment of transitional cell carcinoma of the bladder: an in vitro study. *J Urol* 173:1375–1380
- Colombo R, Da Pozzo LF, Lev A et al (1996) Neoadjuvant combined microwave induced local hyperthermia and topical chemotherapy versus chemotherapy alone for superficial bladder cancer. *J Urol* 155:1227–1232
- Colombo R, Salonia A, Leib Z et al (2011) Long-term outcomes of a randomized controlled trial comparing thermochemotherapy with mitomycin-C alone as adjuvant treatment for non-muscle-invasive bladder cancer (NMIBC). *BJU Int* 107(6):912–918
- Nativ O, Witjes JA, Hendricksen K et al (2009) Combined thermo-chemotherapy for recurrent bladder cancer after bacillus Calmette-Guérin. *J Urol* 182:1313–1317
- Lammers RJ, Witjes JA, Inman BA et al (2011) 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* 60:81–93
- Slater SE, Patel P, Viney R et al (2014) The effects and effectiveness of electromotive drug administration and chemohyperthermia for treating non-muscle invasive bladder cancer. *Ann R Coll Surg Engl* 96(6):415–419
- Colombo R, Salonia A, Da Pozzo LF et al (2003) Combination of intravesical chemotherapy and hyperthermia for the treatment of superficial bladder cancer: preliminary clinical experience. *Crit Rev Oncol Hematol* 47(2):127–139
- Trotti A, Colevas AD, Setser A et al (2003) CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol* 13(3):176–181
- Milla P, Fiorito C, Soria F et al (2014) Intravesical thermo-chemotherapy based on conductive heat: a first pharmacokinetic study with mitomycin C in superficial transitional cell carcinoma patients. *Cancer Chemother Pharmacol* 73(3):503–509
- Kamat AM, Witjes JA, Brausi M et al (2014) Defining and treating the spectrum of intermediate risk nonmuscle invasive bladder cancer. *J Urol* 192(2):305–315
- Jones G, Cleves A, Wilt TJ et al (2012) Intravesical gemcitabine for non-muscle invasive bladder cancer (Review). *Cochrane Database Syst Rev* 1:CD00929
- Prasad SM, Eyre S, Loughlin KR (2013) Salvage combination intravesical immunotherapy with Bacillus Calmette-Guérin and interferon- $\alpha$ 2B: impact on recurrence, progression, and survival. *Hosp Pract* (1995) 41(4):31–39
- Dahm-Daphi J, Brammer I, Dikomey E (1997) Heat effects on the repair of DNA double strand breaks in CHO cells. *Int J Radiat Biol* 72:171–179
- Paroni R et al (2001) Effect of local hyperthermia of the bladder on mitomycin C pharmacokinetics during intravesical chemotherapy for the treatment of superficial transitional cell carcinoma. *Br J Clin Pharmacol* 52:273–278
- Witjes JA, Hendricksen K, Gofrit O et al (2009) Intravesical hyperthermia and mitomycin-C for carcinoma in situ of the urinary bladder: experience of the European Synergo® working party. *World J Urol* 27:319–324
- Colombo R, Lev A, Da Pozzo LF et al (1995) A new approach using local combined microwave hyperthermia and chemotherapy in superficial transitional bladder carcinoma treatment. *J Urol* 153:959–963