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European Association of Urology

Platinum Priority – Bladder Cancer
Editorial by XXX on pp. x–y of this issue

Sequential Combination of Mitomycin C Plus Bacillus Calmette-Guérin (BCG) Is More Effective but More Toxic Than BCG Alone in Patients with Non–Muscle-invasive Bladder Cancer in Intermediate- and High-risk Patients: Final Outcome of CUETO 93009, a Randomized Prospective Trial

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Article info

Article history:
Accepted September 18, 2014

Keywords:
BCG
MMC plus BCG
Intermediate- to high-risk groups
Randomized trial
Subgroup analysis

Abstract

Background: Intravesical bacillus Calmette-Guérin (BCG) is an effective therapy in non–muscle-invasive bladder cancer (NMIBC), but it has limitations in terms of recurrence and toxicity.
Objective: To determine whether the sequential combination of mitomycin C (MMC) and BCG is superior to BCG alone in increasing a disease-free interval (DFI).
Design, setting, and participants: We conducted a prospective randomized trial including 407 patients with intermediate- to high-risk NMIBC and allocated 211 to the MMC and BCG arm and 196 to the BCG-alone arm.
Outcome measurements and statistical analysis: The trial was designed to provide concurrently a power of 80% for the detection of a relative risk reduction of 35% (hazard ratio [HR]: 0.65) of disease relapse with a type I error of 0.05. Times to events were estimated using cumulative incidence functions and compared using the Cox regression model. We used the Kaplan-Meier technique to estimate survival curves.

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http://dx.doi.org/10.1016/j.eururo.2014.09.026

Results and limitations: In the intention-to-treat analysis at 5 yr, DFI was significantly improved by the sequential scheme (HR: 0.57; 95% confidence interval [CI], 0.39–0.83; $p = 0.003$), reducing the disease relapse rate from 33.9% to 20.6%. Higher toxicity was observed with the combination, even reducing the MMC dose, especially in G3 local toxicity compared with BCG with a difference of 17.4% (95% CI, 7.6–27.2; $p < 0.001$). In recurrent T1 tumors, the potential benefit of the sequential scheme was more evident than in the remaining subgroup (18.8% vs 12.8%), with a number needed to treat of five versus eight to avoid an event and with similar toxicity.
Conclusions: Although the sequential scheme is more effective than BCG alone in reducing disease relapse, due to higher toxicity it could be offered only to patients with a high likelihood of recurrence, such as those with recurrent T1 tumors.
Patient summary: We analyzed the outcomes of a randomized trial demonstrating that in intermediate- to high-risk non–muscle-invasive bladder cancer, mitomycin C and bacillus Calmette-Guérin (BCG) reduced disease relapse compared with BCG alone but was more toxic. Consequently, it could be offered only to patients with recurrent T1 tumors.
Trial registration: CUETO 93009.

1. Introduction

In patients with non–muscle-invasive bladder cancer (NMIBC), bacillus Calmette-Guérin (BCG) is the most effective intravesical therapy in decreasing recurrence and delaying progression [1–5]. However, BCG has some limitations. In intermediate- and high-risk groups, we can expect recurrence rates ranging from 23% to 49% and progression rates from 4.8% to 25.6% at 5 yr, respectively [6]. Another limitation is the reported high toxicity [1–5,7].

Using different schedules of alternating mitomycin C (MMC) and BCG, some authors observed decreased toxicity compared with BCG alone [8]. However, no trial demonstrated an improved efficacy with any of the alternating chemoimmunotherapy approaches when compared with BCG alone [9,10], except for one using an electromotive device [11].

The mechanism of action of BCG is not completely understood, but fibronectin seems to be an important step because BCG binds to urothelial and tumor cells via fibronectin attachment protein on bacillus, inducing the immune reaction [12–15]. It has been suggested that BCG efficacy could be improved, increasing fibronectin exposure by creating an inflammatory reaction in the bladder mucosa [16] and thus facilitating bacillus attachment. We attempted to develop this inflammatory reaction with the MMC instillation. Whether MMC administered in this way is able to contribute to a decreased disease recurrence rate remains to be proven. However, evidence from an in vitro study would support this hypothesis [17].

2. Materials and methods

2.1. Inclusion and exclusion criteria

Patients with papillary NMIBC, TaG2 multiple tumors, TaG3 or T1G1–3 tumors, and Tis alone or associated with papillary tumors Ta-1G1–3, following the 1973 World Health Organization (WHO) classification, were included in this trial. Patients with primary TaG1, TaG2 single tumors, T1G1 single with a size <3 cm, upper urinary tract tumors, and muscle-invasive tumors were excluded.

Patients with a life expectancy <3 yr or with other concomitant malignancies (except for epithelial nonmelanoma tumors) were excluded. Patients who had received BCG or were receiving intravesical chemotherapy during the previous 3 mo were also excluded.

The study was conducted according to the Helsinki recommendations. All patients signed fully informed consent, and the study protocol was approved by the local ethics committee.

2.2. Randomization

After transurethral resection of the bladder tumor (TURBT) and a complete pathology report, patients meeting the inclusion criteria were randomly allocated within 3 wk into the two arms by central randomization. Before communicating the arm allocation, a Club Urológico Español de Tratamiento Oncológico (CUETO) committee reviewed the patient records and excluded those unsuitable for the study (eg, lack of required explorations, incomplete medical records). Finally, each center was informed if patients were included or not, as well as the assigned arm.

In arm A, the combination arm (MMC and BCG), patients received a weekly intravesical BCG instillation for 6 wk, with a dose of MMC the previous day. This was followed by three more instillations 2 wk apart.

In arm B, BCG alone (BCG), patients received BCG alone with the same schedule.

2.3. Therapy schedule

Cystoscopy and cytology were performed in all cases before TURBT. All exophytic lesions underwent a complete resection including deep resection of the tumor base. Target and random bladder biopsies including prostatic urethra were systematically taken. Upper urinary tract evaluation by intravenous urography was also required before randomization. Repeat transurethral resection (re-TUR) was not included in the protocol.

Intravesical 81 mg BCG Connaught strain ($1.5–5 \times 10^8$ CFU) in 50 ml 0.9% saline and 30 mg MMC in 50 ml 0.9% saline were used for instillations and administered passively and retained for 1 hr. The first intravesical instillation was administered between 14 and 28 d after TURBT. Local and systemic toxicity were recorded for each instillation and/or visit to the office and classified following the criteria shown in Table 1. In a planned interim analysis, an excessive toxicity was observed in the combination arm (toxicity grade 3 >50%). Consequently, the MMC dose was reduced from 30 mg to 10 mg.

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Table 1 – Toxicity

Type	Grade 1	Grade 2	Grade 3	Grade 4
Systemic				
Hematology				
Hemoglobin, g/100	≥10	8–10	6.5–7.9	<6.5
Leukocytosis, 1000/ml	1.5–1.9	1–1.4	0.5–0.9	<0.5
Platelets, 1000/ml	≥75	50–74.9	25–49.9	<25
Renal: creatinine	<1.5 × normal	1.5–3 × normal	3.1–6 × normal	>6 × normal
Hepatic: GOT, GPT, bilirubin	1.26–2.5 × normal	2.6–5 × normal <1.5 × normal	5.1–20 × normal 1.5–3 × normal	>20 × normal >3 × normal
Fever	Mild flu-type symptoms	Moderate flu-type symptoms	Severe flu-type symptoms requiring hospitalization	Life-threatening, sepsis
Respiratory: Dyspnea, infection	Asymptomatic/chest x-ray (abnormal signs, negative culture)	With exercise only, requiring steroids	With daily activity, requiring oxygen	At rest, requiring ventilatory support
Allergic	Skin rashes	Joint pain/myalgias	Rheumatoid arthritis	
Local				
Dysuria/burning	Mild dysuria	Burning sensation controlled with treatment	Burning sensation not improved with treatment	
Frequency	2-fold increase	2-fold increased frequency >1 hour	Urgency at frequency >1 h with or without catheter	
Hematuria	Microscopic	Macroscopic no blood clots	Macroscopic with blood clots	Requiring transfusion
Epididymitis/prostatitis	Epididymitis	Prostatitis	Abscess	

GOT = glutamic-oxaloacetic transaminase; GPT = glutamic-pyruvic transaminase.

2.4. End points

The primary end points were toxicity and duration of the disease-free interval (DFI), defined as time from randomization to the development of disease relapse, which was considered when patients developed Ta, T1, Tis, or upper urinary tract tumors, prostatic urethral involvement, T2 or higher tumors, as well as nodal or metastasis, during the follow-up.

Secondary end points included duration of progression-free interval (PFI), time to T2 or higher tumor or nodal or metastatic development, cancer-specific survival (CSS), time to cancer death, overall survival (OS), or time to death by any cause.

2.5. Statistical considerations

The trial was designed to provide concurrently a power of 80% for the detection of a relative reduction of 35% (HR: 0.65) in the risk of disease relapse with a type I error of 0.05. The enrollment goal was 396 patients.

Quantitative data were described by the mean (standard deviation) or median (interquartile range) and qualitative data as counts, percentages. For quantitative data, differences between arms were tested using the Student *t* test for unrelated samples and the qualitative data by the chi-square test. Duration of DFI and PFI curves were estimated using cumulative incidence functions to take into account patients who died of other causes before the event of interest (competing risks). Duration of survival curves was estimated using the Kaplan-Meier technique. Times to events were compared using the Wald test from a Cox proportional hazards regression model. Exploratory post hoc subgroup analyses of HRs for DFI in the two study groups were performed to assess whether the treatment effect was consistent across subgroups. HRs were based on a nonstratified proportional hazards model. Cox regression models were used in additional analysis to assess the independent effect of treatment adjusted by several risk factors with interaction effect if necessary. Two-sided tests were used, and $p < 0.05$ was considered statistically significant.

In the present trial, preplanned analysis included an interim analysis, performed when patients reached half of the randomization; first evaluation, when the planned therapy schedule was ended; and a final evaluation in June 2005. Post hoc analysis also included a subgroup analysis at the end of first evaluation; a definite analysis was also decided according to the June 2005 analysis and was performed in September 2012.

3. Results

From January 1993 to November 1994, 443 patients from 21 different Spanish institutions were randomized. After randomization and before initiating therapy, 36 cases (8.1%) were excluded due to the poor quality of patient records. The remaining 407 patients were allocated with 211 in the combination arm and 196 in the BCG arm and evaluated in an intention-to-treat (ITT) analysis. Patients receiving at least one dose of intravesical therapy were considered for toxicity assessment. Twenty-one patients (5.1%) did not receive any instillation; thus in total 386 patients were evaluated for toxicity. All patients who received at least one instillation and met inclusion criteria were evaluated for treated patient analysis, 21 patients did not receive any instillations, and 4 patients did not meet the inclusion criteria in the review analysis at the first evaluation. Thus 382 patients were eligible (Fig. 1).

Table 2 shows the patients and tumor characteristics. Toxicity was evaluated following the criteria shown in Table 1 and is summarized in Table 3. Although toxicity decreased by reducing the MMC dose to 10 mg, it remained higher than with BCG alone, especially in terms of local toxicity G3 (28.4% vs 11%, respectively; difference of 17.4%; 95% CI, 7.6–27.2; $p < 0.001$).

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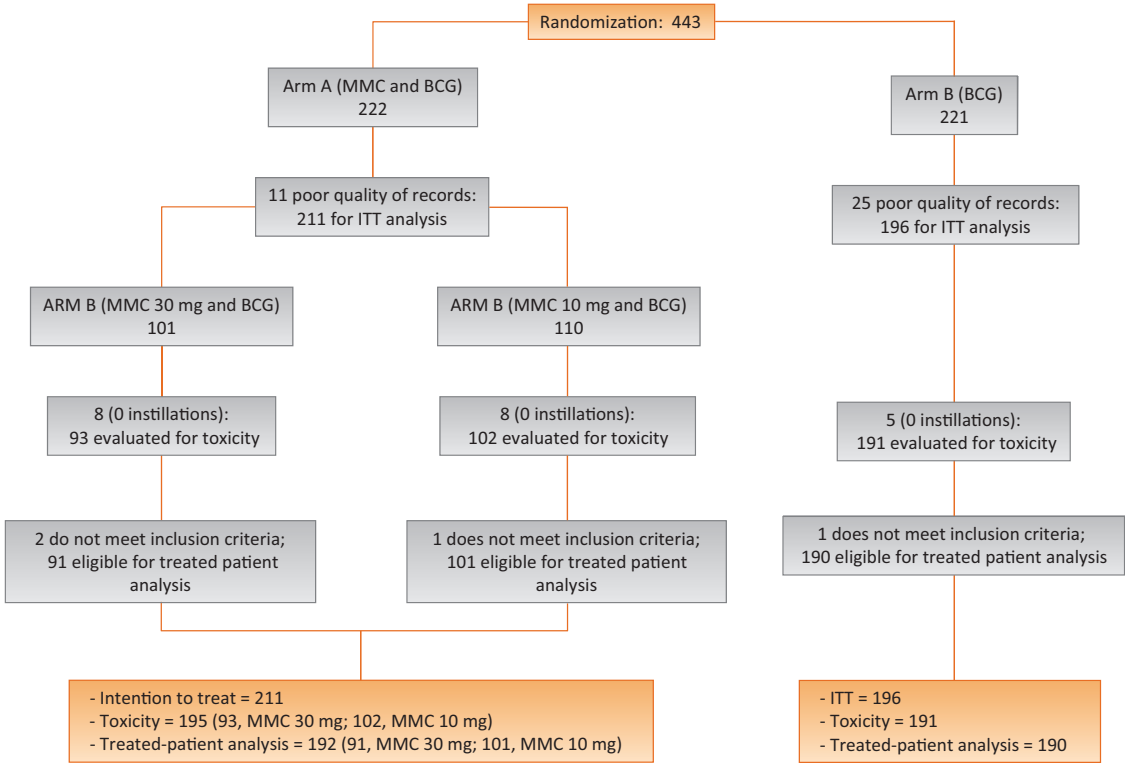

Fig. 1 – Consolidated Standards of Reporting Trials flow diagram of CUETO 93009 trial.
BCG = bacillus Calmette-Guérin; ITT = intention to treat; MMC = mitomycin C.

Table 2 – Patient characteristics

Characteristic	MMC and BCG	BCG	Total
No. of patients	211	196	407
Age, yr, median (IQR)	65 (57–71)	66 (59–72)	67 (61–72)
Categories, *n* (%)			
Aged ≤65 yr	112 (53.1)	86 (43.9)	198 (48.6)
Aged >65 yr	99 (46.9)	110 (56.1)	209 (51.4)
Male	192 (91.0)	174 (88.8)	366 (89.9)
Female	19 (9.0)	22 (11.2)	41 (10.0)
Disease status			
Primary	149 (70.6)	128 (65.3)	277 (68.1)
Recurrent	62 (29.4)	68 (34.7)	130 (31.9)
No. of tumors			
1	96 (45.5)	83 (42.3)	179 (44.0)
2–3	58 (27.6)	60 (30.6)	118 (29.0)
>3	57 (27.0)	53 (27.0)	110 (27.0)
Tumor size, cm			
≤3	139 (65.9)	135 (68.9)	324 (67.3)
>3	72 (34.1)	61 (31.1)	133 (32.7)
T category			
Ta	35 (16.6)	31 (15.8)	66 (16.2)
T1	163 (77.3)	144 (73.5)	307 (75.4)
Tis with or without Ta–1	13 (6.1)	21 (10.8)	34 (10.0)
G category			
G1	33 (15.6)	19 (9.7)	52 (12.8)
G2	135 (64.0)	116 (59.2)	251 (61.7)
G3	43 (20.4)	61 (31.1)	104 (25.6)
Risk group			
Intermediate	161 (76.3)	128 (65.3)	289 (71.0)
High	50 (23.7)	68 (34.7)	118 (29.0)

BCG = bacillus Calmette-Guérin; IQR = interquartile range; MMC = mitomycin C.

Table 4 shows the number of instillations administered in both arms. An imbalance was observed between both arms receiving nine instillations, 58.7% of patients in the sequential arm versus 82.7% in the BCG-alone arm, difference of 24% (95% CI, 15.9–32.9; $p < 0.001$) and between patients receiving different MMC doses, 50.5% (MMC 30 mg and BCG) versus 65.5% (MMC 10 mg and BCG), difference of 15% (95% CI, 1.7–28.1; $p = 0.035$), due to the toxicity profile in each arm.

With a median follow-up of 7.1 yr and a maximum of 13 yr, 112 patients (27.5%) experienced a disease relapse. Fifty patients (12.2%) experienced progression. A total of 103 patients (25.3%) died by any cause, and 25 patients (6.1%) died of bladder cancer (Table 5).

In the ITT analysis, at 5 yr DFI was significantly prolonged in the sequential arm compared with the BCG arm (HR: 0.57; 95% CI, 0.39–0.83; $p = 0.003$) (Fig. 2), with a disease relapse of 20.6% and 33.9% at 5 yr, and 24.3% and 39.3% at 10 yr, respectively.

No statistically significant difference was found at 5 yr between both arms in terms of PFI (HR: 1.05; 95% CI, 0.61–1.83; $p = 0.852$) (Fig. 3), CSS (HR: 0.64; 95% CI, 0.29–1.43; $p = 0.276$), and OS (HR: 0.71; 95% CI, 0.48–1.08; $p = 0.108$) (Fig. 4).

A subset analysis was performed stratifying by MMC dose, and comparisons were also performed using the Cox proportional model. At the 5-yr evaluation, DFI remained significantly increased with MMC doses, MMC 30 mg and BCG (adjusted hazard ratio [aHR]: 0.49; 95% CI, 0.30–0.82;

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Table 3 – Toxicity of the three difference schemes

Schedule	MMC 30 mg and BCG		MMC 10 mg and BCG		BCG	
No. of patients	93		102		191	
Toxicity	Local	Systemic	Local	Systemic	Local	Systemic
Without (%)	12 (12.9)	36 (38.7)	26 (25.5)	64 (62.7)	63 (33.0)	140 (73.3)
With (%)	81 (87.1)	57 (61.3)	76 (74.7)	38 (37.2)	128 (67.0)	51 (26.7)
Grade 1–2 (%)	29 (31.2)	44 (47.3)	47 (46.1)	31 (30.4)	107 (56.0)	42 (21.9)
Grade 3–4 (%)	52 (55.9)	13 (13.9)	29 (28.4)	7 (6.8)	21 (10.9)	9 (4.7)
Withdrawn	30 (32.2)		9 (8.8)		8 (4.2)	

BCG = bacillus Calmette-Guérin; MMC = mitomycin C.

$p = 0.006$), and MMC 10 mg and BCG (aHR: 0.62; 95% CI, 0.32–0.99; $p = 0.038$) when compared with BCG alone.

In the treated patient analysis at 5 yr, no significant deviations of the analyzed items were observed, compared with the ITT analysis: DFI (HR: 059; 95% CI, 0.39–0.85; $p = 0.005$), PFI (HR: 1.14; 95% CI, 0.64–2.05; $p = 0.637$), CSS (HR: 0.74; 95% CI, 0.32–1.69; $p = 0.484$), and OS (HR: 0.75; 95% CI, 0.49–1.13; $p = 0.177$).

Due to the difficult balance between reducing the time to disease relapse and the higher toxicity of the sequential arm, an exploratory subgroup analysis of HRs for DFI at 5 yr was performed including the variables showed in Figure 5. Interaction analysis did not show any significant difference in the size of treatment effect in the different subgroups.

4. Discussion

In patients with intermediate- to high-risk NMIBC, the combination of MMC and BCG significantly prolonged the DFI at 5 yr (HR: 0.57; 95% CI, 0.39–0.83; $p = 0.003$) compared with BCG alone. Because an imbalance in risk groups distribution was observed among arms, DFI at 5 yr was adjusted to risk groups, and the results did not change when comparing both arms (HR: 0.589; 95% CI, 0.40–0.840; $p = 0.006$).

Contrary to other published alternating chemoimmunotherapy schedules with MMC and BCG, which showed equal [10] or less efficacy [9] than BCG alone in decreasing recurrence and progression rates, our combination therapy was significantly more effective in reducing disease relapse at 5 yr (20.6% vs 33.9%). In former trials, MMC plus BCG was administered on a weekly alternating schedule [9,10]. In the present trial, MMC was administered sequentially, 1 d before the BCG instillation. Probably this different scheme justifies the disease relapse reduction observed in our trial and probably corroborates the potential synergistic effect of the MMC and BCG combination.

The sequential scheme showed significantly more local toxicity than BCG alone (80.4% vs 69.7%), an important limitation of this schedule. Even decreasing the MMC dose to 10 mg, toxicity remained higher than BCG alone, particularly in local side effects grade 3 (28.4% vs 10.9%; difference of 17.4%; 95% CI, 7.6–27.2; $p < 0.001$). Furthermore, the MMC and BCG combination did not significantly improve the PFI at 5 yr (HR: 1.05; 95% CI, 0.61–1.83; $p = 0.852$) and CSS (HR: 0.64; 95% CI, 0.29–1.43; $p = 0.276$), but clinically meaningful differences were not excluded by the CI.

In an attempt to strike a balance between efficacy and toxicity, an exploratory subgroup analysis was conducted, identifying several subgroups of patients for whom the sequential scheme could potentially be more effective than in others. However, in the interaction analysis, a significant difference was not observed in the size of the treatment effect among the subgroups.

To outline a more specific target subgroup, we considered that patients more likely to recur could be the most suitable for the most effective scheme. Analysis of the different prognostic factors suggested that patients with recurrent T1 disease carry the highest likelihood of recurrence at 5 yr, ranging from 46% to 78% according to the Sylvester predictive tables [18]. However, in these patients the difference of disease relapse at 5 yr between sequential and BCG-alone schemes was 18.8% (30.2% vs

Table 4 – Number of instillations in each group

No. of instillations	MMC 30 mg and BCG	MMC 10 mg and BCG	BCG	Total
No. of patients	101	110	196	407
None (%)	8 (7.9)	8 (7.2)	5 (2.5)	21 (5.1)
1–2 (%)	1 (0.9)	6 (5.4)	5 (2.5)	12 (2.9)
3–6 (%)	24 (23.7)	11 (10.0)	4 (2.0)	39 (9.5)
7–8 (%)	17 (16.8)	13 (11.8)	20 (10.2)	50 (12.2)
9 (%)	51 (50.5)	72 (65.4)	162 (82.6)	285 (70.0)

BCG = bacillus Calmette-Guérin; MMC = mitomycin C.

Table 5 – Intention to treat: disease outcome of both arms

	MMC and BCG	BCG	Total
No. of patients	211	196	407
Disease relapse rate, no. of patients (%)	44 (20.8)	68 (34.6)	112 (27.5)
Progression rate (%)	−26 (12.3)	−24 (12.2)	−50 (12.3)
Survival status, no. of patients (%)			
Alive	160 (75.8)	144 (73.4)	304 (74.7)
Dead by any cause	51 (24.1)	52 (26.5)	103 (25.3)
Dead by bladder cancer	10 (4.7)	15 (7.6)	25 (6.1)

BCG = bacillus Calmette-Guérin; MMC = mitomycin C.

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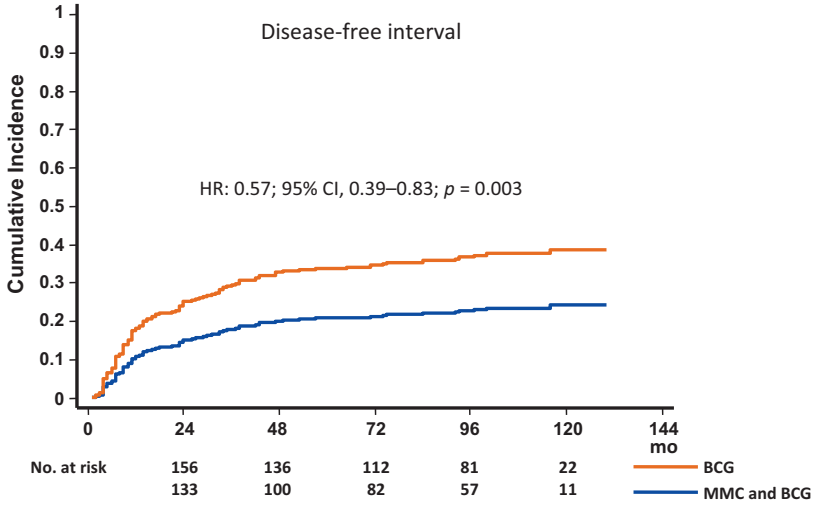

Fig. 2 – Intention-to-treat analysis: duration of disease-free interval by treatment arm.
BCG = bacillus Calmette-Guérin; CI = confidence interval; HR = hazard ratio; MMC = mitomycin C.

49.0%), whereas this difference was 12.8% (19.8% vs 32.6%) in the remaining subgroup in favor of the sequential scheme. This higher potential benefit of the sequential scheme in patients with recurrent T1 tumors means an NNT of five patients and two patients experiencing a grade 3 local side effect to avoid one disease relapse in 5 yr, whereas these figures were eight and three, respectively, in the remaining subgroup. The decrease of NNT in patients with recurrent T1 tumors maintaining a similar toxicity suggests that the sequential scheme could be recommended for these patients, although a careful follow-up should be applied due to the high toxicity. As a result, with the currently available data, although the sequential scheme significantly improves 5-yr DFI, the high toxicity limits its use in patients with intermediate- and high-risk NMIBC. Nevertheless, taking into account the balance toxicity/efficacy, the sequential scheme could be recommended for patients with recurrent T1 disease, once fully informed of the potential additional marginal benefit, as well as the high side effects rate of the scheme.

Although decreasing the MMC dose from 30 mg to 10 mg reduced toxicity, with the available data in a regression model using MMC dose as predictor (none, 10 mg, or 30 mg), the risk reduction of 5-yr DFI between MMC 10 mg plus BCG and BCG alone, although inferior, remains significantly independent (HR: 0.65; 95% CI, 0.32–0.99; $p = 0.038$ vs HR: 0.49; 95% CI, 0.30–0.82; $p = 0.006$) for MMC 30 mg plus BCG. There is an imbalance in the number of

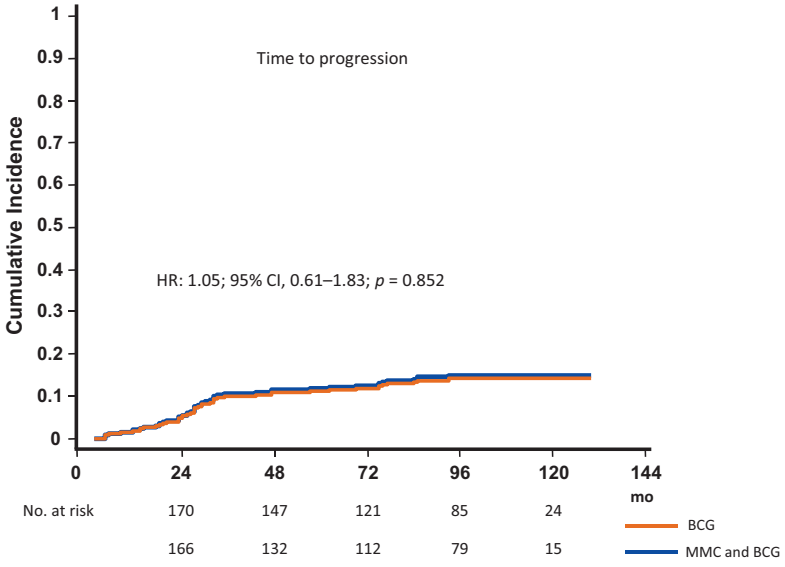

Fig. 3 – Intention-to-treat analysis: time to progression by treatment arm.
BCG = bacillus Calmette-Guérin; CI = confidence interval; HR = hazard ratio; MMC = mitomycin C.

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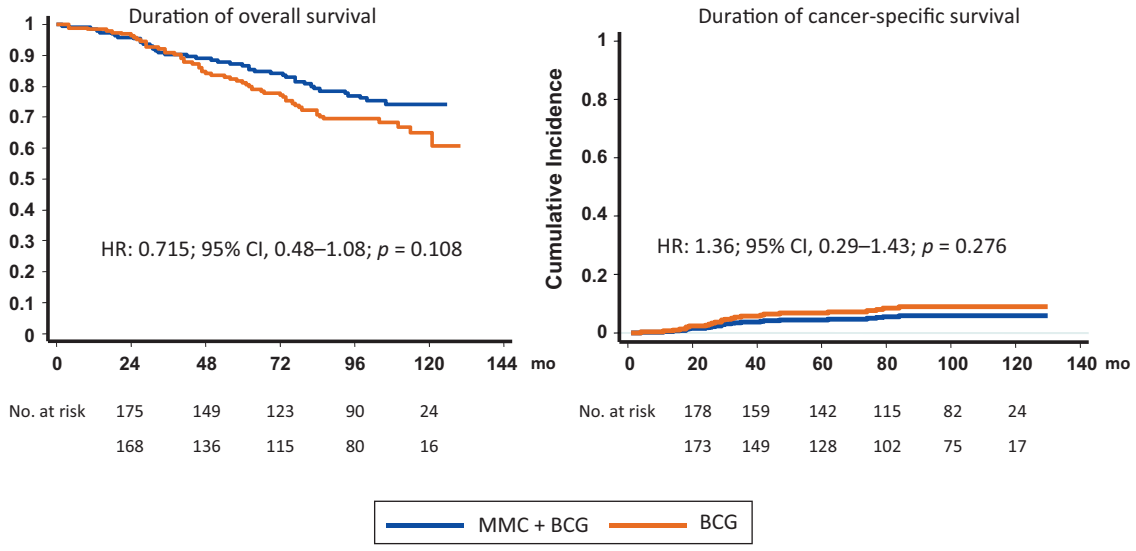

Fig. 4 – Intention-to-treat analysis: overall and cancer-specific survival by treatment arm.
BCG = bacillus Calmette-Guérin; CI = confidence interval; HR = hazard ratio; MMC = mitomycin C.

instillations administrated in each arm, with 50.5%, 65.4%, and 82.6% of patients of those receiving MMC (30 mg) and BCG, MMC (10 mg) and BCG and BCG alone, respectively, completing the treatment, due to the different percentages of patients withdrawing due to toxicity in each arm. However, 5-yr DFI remains significantly prolonged by the sequential scheme (HR: 0.56; 95% CI, 0.38–0.83; $p = 0.004$). Consequently, MMC dose reduction and the decrease in the

Variable	HR
High risk	0.628 (0.330–1.196)
Intermediate risk	0.566 (0.352–0.908)
G3	0.599 (0.285–1.259)
G2	0.600 (0.371–0.970)
G1	0.470 (0.143–1.543)
Tis	0.843 (0.303–2.348)
T1	0.519 (0.328–0.819)
Ta	0.666 (0.263–1.688)
Size >3 cm	0.537 (0.325–0.888)
Size <3 cm	0.586 (0.328–1.046)
Multiple: >3	0.650 (0.334–1.265)
Multiple: 2–3	0.547 (0.269–1.113)
Single	0.510 (0.277–0.941)
Recurrent	0.503 (0.277–0.914)
Primary	0.601 (0.367–0.984)
Aged ≤65 yr	0.431 (0.236–0.788)
Aged <65 yr	0.655 (0.399–1.083)

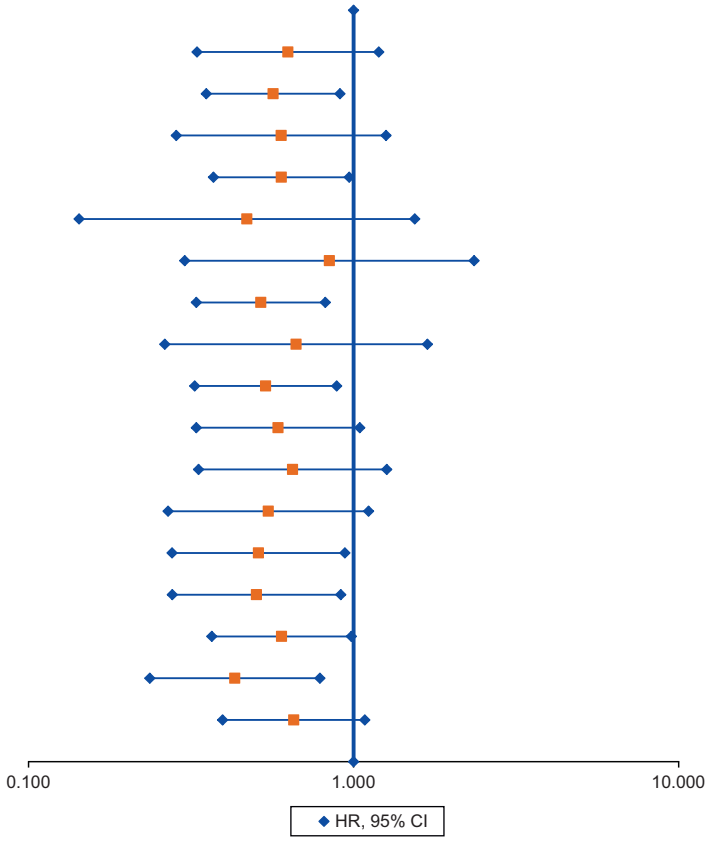

Fig. 5 – Subgroup analysis: disease-free interval in subgroups of patients defined by baseline characteristics. Hazard ratios <1 favor the mitomycin C and bacillus Calmette-Guérin (BCG) arm and >1 favor the BCG arm.
CI = confidence interval; HR = hazard ratio.

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number of instillations do not seem to influence the efficacy of the sequence scheme significantly.

We acknowledge some limitations of the study. First, no patient received a systematic re-TUR, and a long-term maintenance schedule was not applied in the present trial as currently recommended in the guidelines [19]. Both approaches could probably improve our results, although robust conclusions cannot be drawn with the available data. Nevertheless, re-TUR and long-term maintenance can be recommended for these patients if a sequential scheme is decided. Due to the period studied, tumor grade was classified according to the 1973 WHO classification, but today it is used together with the 2004 WHO classification in many European centers. The risk groups were considered empirically before the European Organization for Research and Treatment of Cancer and CUETO risk tables were published [18,20].

5. Conclusions

This is the first trial demonstrating a significant improvement in the DFI and decreased disease relapse with intravesical sequential chemoimmunotherapy compared with BCG alone without using devices. However, no significant impact was found on PFS, CSS, and OS. The sequential schedule was more toxic, especially in G3 local toxicity, even reducing the MMC dose from 30 mg to 10 mg. Taking into account the balance of toxicity and efficacy, the sequential scheme could be offered to patients with a high likelihood of recurrence, such as those with recurrent T1, keeping in mind the potential benefit and the high toxicity of this scheme.

Author contributions: Eduardo Solsona had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Solsona, Madero.
Acquisition of data: Solsona, Madero, Chantada, Fernandez, Zabala, Portillo, Astobieta, Unda, Martinez-Piñeiro, Rabadan, Ojea, Rodriguez-Molina, Beardo, Muntañola, Gomez, Montesinos, Piñeiro.
Analysis and interpretation of data: Solsona.
Drafting of the manuscript: Solsona, Madero, Fernandez.
Critical revision of the manuscript for important intellectual content: Solsona, Madero, Fernandez.
Statistical analysis: Madero.
Obtaining funding: None.
Administrative, technical, or material support: Solsona, Madero, Chantada, Fernandez, Zabala, Portillo, Astobieta, Unda, Martinez-Piñeiro, Rabadan, Ojea, Rodriguez-Molina, Beardo, Muntañola, Gomez, Montesinos, Piñeiro.
Supervision: Solsona, Piñeiro.
Other (specify): None.

Financial disclosures: Eduardo Solsona Narbon certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

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