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To cite this article: Wael Kandeel, Ashraf Abdelal, Basheer N. Elmohamady, Ahmed Sebaey, Waleed Elshaaer, Ehab Elbarky & Osama Abdelwahab (2015) A comparative study between full-dose and half-dose intravesical immune bacille Calmette–Guérin injection in the management of superficial bladder cancer, Arab Journal of Urology, 13:4, 233-237, DOI: [10.1016/j.aju.2015.07.002](https://doi.org/10.1016/j.aju.2015.07.002)

To link to this article: <https://doi.org/10.1016/j.aju.2015.07.002>



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Published online: 05 Apr 2019.



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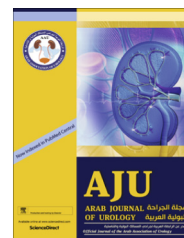
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ONCOLOGY/RECONSTRUCTION
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A comparative study between full-dose and half-dose intravesical immune bacille Calmette–Guérin injection in the management of superficial bladder cancer



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Received 24 April 2015, Received in revised form 6 July 2015, Accepted 13 July 2015
Available online 7 August 2015

KEYWORDS

BCG;
TCC;
Non-muscle-invasive;
Bladder cancer

ABBREVIATIONS

NMIBC, non-muscle-invasive bladder cancer;
CIS, carcinoma *in situ*;
TURBT, transurethral

Abstract Objectives: To determine whether a half-dose of bacille Calmette–Guérin (BCG) can reduce toxicity without affecting its efficacy in the management of non-muscle-invasive bladder cancer.

Patients and methods: From January 2012 to January 2014, 80 patients with superficial bladder cancer and in the intermediate-risk group were simply randomised to receive two different doses of BCG, i.e., a full dose of 90 mg (group A) or a half-dose of 45 mg (group B). There were no significant differences in clinical and pathological characteristics between the groups. At completion of the study, 40 patients could be evaluated in each group.

Results: All patients were evaluated for a follow-up of 12 months after treatment. There was no significant difference in recurrence rate (15 patients, 38%, in group A and 16, 40%, in group B) in the two groups, and no difference in progression rate of the disease, at eight patients (20%) in each group. There were significant differences

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Peer review under responsibility of Arab Association of Urology.



resection of the bladder tumour

between groups A and B in toxicity (grade 1 adverse events, 70% vs. 60%; grade 2, 18% vs. 7.5%, respectively). Grade 3 adverse events were only reported in group A (2.5%).

Conclusion: The half dose of intravesical BCG instillation can reduce the toxicity and side-effects that are associated with the treatment of superficial bladder cancer, without affecting the efficacy of therapy.

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Introduction

World-wide, urothelial bladder cancer is the seventh most common cancer in men and the 17th most common in women, but in developed countries bladder cancer is more common [1]. Most cases are TCC and most new patients (65–75%) have Ta disease (mucosal only), T1 (lamina propria invasion), or carcinoma *in situ* (CIS) [2]. After transurethral resection of the bladder tumour (TURBT) non-muscle-invasive bladder cancer (NMIBC) has a high risk of recurrence and of progression by extension to the muscle layer as a muscle-invasive tumour [3].

BCG immunotherapy provides the most successful protection from recurrence and even reduces the progression of superficial TCC. BCG immunotherapy has been shown in many meta-analyses and randomised clinical trials to provide better protection than chemotherapy [4,5]. BCG therapy is not generally considered to be safe, but has excellent results and the benefits outweigh the risks. About half of patients will have minor ‘cystitis’ symptoms, 25% will have full-blown fever, rigors shivers, etc., and 6% will have severe infections requiring anti-tuberculosis therapy. Overall, 60–70% of patients will benefit. These potential local and systemic toxicities can affect the management, by stopping instillation sessions in up to 30% of patients, or lead to a postponement or decrease in the number and dose of BCG therapy in 55–80% of cases.

Recently there have been many trials to reduce the side-effects of BCG therapy without affecting its efficacy [6]. The aim of the present study was to compare the efficacy and safety of full (standard) and half doses of intravesical BCG administration in patients with NMIBC.

Patients and methods

This prospective study was conducted in 80 patients with histologically confirmed NMIBC (TCC, Ta and T1) of the bladder, in the intermediate-risk group according to European Association of Urology guidelines [4], treated in the outpatient clinic of the Urology Department of Benha University Hospital between January 2012 and January 2014. There were 63 men and 17 women, with

a mean (SD, range) age of 61.9 (8.9, 36–86) years. A histopathological diagnosis, before study entry, was made after TURBT. All patients were assessed according to our local guidelines (full history taken, general and local examinations, laboratory studies and radiological investigations). Under cysto-urethroscopy, TURBT was done until the muscle fibres were visible. Thereafter, biopsies were taken from the tumour base and from all bladder walls and the prostatic urethra (as random biopsies), and examined separately. A single immediate installation of mitomycin was administered after TURBT. Following TURBT, the stage and grade of the tumour were determined using the TNM staging system (2009 system, American Joint Commission on Cancer in combination with the International Union Cancer Consortium) [7]. Only patients with confirmed superficial urinary bladder TCC of intermediate risk were enrolled in this study. We routinely used a second cystoscopy 4–6 weeks after the initial TURBT. Patients with tumour *in situ* (Tis), stage \geq T2, tumour recurrence more than twice, a previous history of instillation of BCG or chemotherapy, active tuberculosis infection, previous BCG sepsis and immunocompromised patients were excluded from the study.

We used immune BCG (designated ‘BCG-T’) which is produced by an Egyptian company for the production of vaccines, an affiliated company of VACERA (www.vacera.com). Immune BCG-T is a suspension of a live attenuated mycobacterium in a stabilising medium. Each 1 mL contains live attenuated BCG 30 mg and a liquid stabiliser medium. The vial contains 3 mL (90 mg BCG), which is the full dose. This immune BCG-T is used only for intravesical instillation and not used as a vaccine.

Patients were divided into two groups by simple randomisation methods, with group A receiving a full dose of BCG (90 mg) and group B the half dose (45 mg).

The study had local ethics committee approval and all patients signed a consent before instillation, and were informed about all possible side-effects for early detection.

Treatment was started 2 weeks after TURBT, ensuring that gross haematuria and UTI were absent before instillation. Treatment was given weekly for 6 weeks. The BCG induction course was repeated if there was a

recurrence. The induction course was followed by three weekly instillations at 3 and 6 months after induction, as a maintenance course.

The treatment results were evaluated every 3 months over a follow-up of 12 months, by urine cytology and diagnostic cysto-urethroscopy. If the tumour recurred during treatment, TURBT was repeated and the patient was kept in the same group, with a close follow-up after a repeated course of the induction therapy. Any adverse event was recorded and graded according to the WHO grading system of BCG adverse effects [8].

The end-points of the study were progression to muscle-invasive disease (stage \geq T2), and the development of grade 4 or severe degree grade 3 adverse effects.

Categorical data were expressed as the number and percentage, and quantitative data as the mean (SD). The chi-squared test, goodness-of-fit test, 'Z' test and Student's *t*-tests were used to determine the significance of differences, with $P < 0.05$ considered to indicate significance.

Results

The tumour characteristics are shown in Table 1; 10 patients (13.5%) were grade 1 and 70 (87.5%) were grade 2; 31 (38.8%) were stage Ta and 49 (61.2%) were T1. The mean (SD, range) tumour size was 3.13 (0.95, 1–5) cm.

There was a recurrence in 31 patients (38.8%), including 15 (37.5%) in group A and 16 (40%) in group B, with no statistically significant difference between the groups in this incidence ($P = 0.82$; Table 2).

In 16 patients (20%) the tumour progressed, with eight in each group. The progression was muscle-invasive alone in all patients, with no distant metastases reported. There was no significant difference between

the groups in the incidence of tumour progression ($P = 1.0$; Table 2).

No toxicity (side-effects) of the drug was reported in 17 patients (21.2%), with four in each group being free of any side-effects (Table 2). The most common grade 1 side-effects were dysuria and frequency, reported in 21 patients in group A (50.5%) and in 16 in group B (40%). The next most common were low-grade fever, in four patients in group A (10%) and six in group B (15%). Haematuria was reported in three patients in group A (7.5%) and two in group B (5%), but it subsided in < 48 h.

The most common grade 2 side-effects included severe dysuria, in five patients in group A (12.5%) and three in group B (7.5%). Haematuria for > 48 h was reported in only one patient in group A, which required a postponement of the next session of BCG instillation. For grade 3 side-effects, only one patient in group A had a severe allergic reaction.

Discussion

Urothelial bladder cancer represents a major global health problem and is the fourth commonest cancer in western countries, but in the last five decades it has been the most common cancer in Egypt [9,10]. The results of the present study are consistent with those reported by Agrawal et al. [11] on 152 patients randomised to receive three different doses of BCG therapy (40, 80 and 120 mg). Their study showed no statistically significant difference in the recurrence rates of the tumour (20%, 25% and 20%, respectively) between the three groups.

In the present study there was a recurrence in 31 patients (38.8%), including 15 in group A and 16 in group B. After TURBT the patients were kept in the same group but with a close follow-up after a repeated course of the induction therapy.

The present results are also comparable with those of several other studies [12–15], reporting that reducing the BCG dose could be an alternative method of BCG

Table 1 The tumour characteristics of the 80 patients.

Variable	<i>n</i> (%)
Site	
Anterior wall	12 (15.0)
Right lateral wall	16 (20.0)
Left lateral wall	34 (42.5)
Base	8 (10.0)
All three	8 (10.0)
Right lateral, posterior	2 (2.5)
N tumours	
One	70 (87.5)
Two	2 (2.5)
Three	8 (10.0)
Stage	
Ta	31 (38.8)
T1	49 (61.2)
Grade	
G1	10 (12.5)
G2	70 (87.5)

Table 2 The overall outcome (efficacy) and the incidence of adverse events in both groups.

Variable	Group, <i>n</i> (%)		Total	<i>P</i>
	A	B		
<i>Outcome (total follow-up)</i>				
Disease-free	16 (40.0)	17 (42.5)	33 (41.2)	0.82
Recurrence	16 (40.0)	15 (37.5)	31 (38.8)	0.82
Progression	8 (20.0)	8 (20.0)	16 (20.0)	1.0
<i>Adverse events</i>				
Grade				
None	13 (32.5)	4 (10.0)	7 (21.2)	0.001
Grade 1	24 (60.0)	28 (70.0)	52 (65.0)	0.15
Grade 2	3 (7.5)	7 (17.5)	10 (12.5)	0.17
Grade 3	0	1 (2.5)	1 (2.5)	0.31
Total	40	40	80	

instillation therapy for NMIBC, with less toxicity and good efficacy. A much larger study by Martinez-Pinerio et al. [16] on 500 patients, comparing a one-third dose with the standard dose, showed that 5 years after treatment the mean (SD) proportion of recurrence-free patients was 70.5 (3.1)% and 70.4 (1.3)% for the standard and decreased-dose groups, respectively, and in 21 patients (11.5%) in the standard group and 33 (13.3%) in the decreased-dose group the tumours became invasive, so the one-third dose had similar results for recurrence and progression. Another study by the same group [17] on 155 patients with high-risk NMIBC treated with two different doses of BCG (81 and 27 mg of Connaught strain) showed that a one-third dose of BCG was as effective as the standard dose against progression and recurrence in patients with high-risk stage T1G3 and Tis superficial TCC. There was disease recurrence in 32 patients (39%) treated with the full dose and in 33 (45%) treated with the low dose. There was tumour progression in 20 patients (24.7%) with the full dose and in 19 (26%) with the lower dose, which agrees with the present results.

Another study [18] confirmed that the half-dose of BCG might be suitable for initial BCG management, for the prophylaxis of superficial bladder cancer recurrence and progression, again in agreement with the present study.

Yari et al. [19] reported on 60 patients with confirmed superficial bladder cancer, randomised into two groups receiving intravesical BCG 120 mg/week for 6 weeks (group 1) or 20 mg mitomycin-C and 60 mg BCG weekly for 6 weeks (group 2). The tumour recurrence rate in group 1 was 32.1% and 11.1% in group 2. Thus the intravesical instillation of half-dose BCG combined with half-dose mitomycin-C seemed to be more effective than the intravesical administration of full-dose BCG, which is partly comparable with our results.

Kumar et al. [20] reported a study on 26 patients with superficial bladder TCC divided in two groups, with instillation of the standard-dose (full dose) 120 mg of BCG (modified Danish 1331 strain) in group A and a low-dose (40 mg) in group B. Urine samples were obtained immediately before and after (2–4 h) BCG therapy. Interleukin-8 was assessed using a commercial ELISA. They reported that five and six patients treated with a full dose and low dose, respectively, had a recurrence and/or progression. There was no significant difference at 4 h in mean interleukin-8 levels in the full- and low-dose groups.

Another study testing the efficacy of a quarter dose of BCG was that by Mack et al. [21], who reported that quarter-dose BCG had a 61% response rate for treating superficial bladder cancer.

Other studies have included high-risk patients when comparing the efficacy of low-dose and standard-dose BCG therapy [22,23]. These confirmed that low-dose

BCG is effective in the management of high-risk superficial bladder cancer and gives similar results to full doses of BCG therapy. However, these results were not comparable with those of Oddens et al. [3], as in their study on 1355 patients the recurrence rate was 46% and progression rate was 8.3% in patients treated with a one-third dose of BCG, while in those treated with full-dose BCG the recurrence rate was 40.8% and progression rate was 7.8%.

An earlier study by Morales et al. [24] suggested that the full dose was necessary to eradicate CIS and was also necessary if a short course of treatment was considered, which differs from the present results.

For toxicity, Pagano et al. [15] reported that the half dose of BCG (75 mg) reduced side-effects, with cystitis in 27% of patients, haematuria in 3%, and fever in 19%, but for the standard dose, cystitis was reported in 91% of patients, haematuria in 43% and fever in 28%. This difference was comparable to that in the present study. Previous studies [22,16] showed decreased toxicity without affecting the efficacy by using a one-third dose of BCG therapy. Also, in other studies [13,14,18], reducing the BCG dose by half significantly reduced toxicity. A similar outcome for local side-effects was also apparent in the present study, where the incidence of mild side-effects like dysuria and frequency in groups A and B was 50.5% and 40%, respectively. Haematuria was the second commonest side-effect, with an incidence of 7.5%, and 5% in groups A and B, respectively; Severe dysuria was reported in five and three patients in group A and B, respectively.

Agrawal et al. [11] used three different doses of BCG therapy (40, 80 and 120 mg; groups A, B and C respectively) and reported that there was a statistically significant difference between group B and C in the incidence of dysuria, with values in groups A, B and C of 30%, 33.3% and 70%, respectively. They reported that the second most common toxicity was urinary frequency, with a statistically significant difference between groups B and C. No patient had haematuria in group A, but 8.3% and 30% of patients in groups B and C had haematuria, respectively, which was statistically significantly different, strongly agreeing with the present results.

Also in the study of Yari et al. [19], dysuria and frequency occurred in 60.7% and 71.4% of patients in group A, while in group B patients the incidence was 40.7% and 44.4%, respectively, which agreed with previous results and was similar to our results.

For systemic symptoms the most common side-effect in the present study was mild to moderate fever, in four patients (10%) in group A and six (15%) in group B. Only one patient in group A had a severe allergic reaction. The results of the present study are consistent with or supported by the results of Yari et al. [19], in which fever occurred in 28.6% of patients, and generalised

symptoms in 32.1% of their group A. In group B, 11.1% of patients had these side-effects.

Similarly, Martinez-Pinerio et al. [17] reported that the proportion of patients with systemic side-effects was also significantly higher in the standard than in the decreased-dose arm (13 of 82, 15.9% vs. four of 73, 5.5%). These results were not comparable with those of Oddens et al. [3], who reported that there were no statistically significant differences in side-effects between the one-third dose and full-dose BCG, and they recommended that intermediate-risk cases should be treated with the full dose for 1 year.

Improving the tolerability of BCG without losing efficacy has been the subject of many recent studies. A dose reduction to a half, one-third, a quarter and a sixth of the standard dose has been investigated [25].

In conclusion, the half dose of intravesical BCG therapy can reduce the toxicity and side-effects associated with the treatment of superficial bladder cancer without compromising the efficacy of therapy.

Conflict of interest

None.

Source of funding

None.

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