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RESEARCH ARTICLE

BCG immunotherapy for non-muscle invasive bladder cancer: is efficacy related to toxicity?

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Abbreviations used: AE, adverse effects; BCG, Bacillus Calmette–Guérin; CIS, carcinoma *in situ*; EAU, European Association of Urology; IQR, interquartile range; NMIBC, non-muscle invasive bladder cancer; TURBT, trans-urethral resection of bladder tumor

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ABSTRACT

OBJECTIVES: To examine the prevalence of local and systemic adverse effects (AEs) associated with Bacillus Calmette-Guerin (BCG) immunotherapy for non-muscle invasive bladder cancer (NMIBC) and to determine if there was any relationship between adverse effects and efficacy of treatment.

PATIENTS AND METHODS: Patients receiving induction intravesical BCG immunotherapy for NMIBC from 1995 to 2013 were identified from a group urology practice. Patients completed an AE scoresheet and an AE was recorded if the patient experienced the symptom at any point in the week following instillation. Patients were dichotomised based on recurrence status (treatment efficacy was defined as non-recurrence) and association with AEs was investigated using univariate Cox regression analysis.

RESULTS: One hundred and fifty eight patients were examined with a mean age of 70.2 years (range 41–88) and a male predominance (125, 79%). The most prevalent local AEs were frequency (107, 68%), dysuria (98, 62%) and nocturia (95, 60%). Malaise (54, 34%), myalgia (41, 26%) and fever (32, 20%) were the most common systemic AEs. Recurrence status was available for 82 patients, with 43 (52%) diagnosed with recurrence. There was no significant relationship between overall AEs and recurrence [hazard ratio (HR) 0.97, $P = 0.57$], or for local (HR 0.99, $P = 0.90$) and systemic (HR 0.88, $P = 0.32$) AEs. Only frequency was significantly associated with reduced recurrence (HR = 0.42, $P = 0.04$).

CONCLUSIONS: AEs due to BCG immunotherapy are common in the induction period with nearly 70% of patients in our cohort experiencing individual symptoms. Local AEs are considerably more prevalent than systemic. Frequency was the only AE to be significantly associated with non-recurrence. Overall, AEs due to BCG instillation treatment were not related to efficacy for NMIBC.

Keywords: adverse effects, bladder cancer, BCG, immunology, uro-oncology

INTRODUCTION

Bladder cancer is the ninth most common malignancy in the world with approximately 70 percent classified as non-muscle invasive bladder cancer (NMIBC) [1,2]. The risk of progression at five years for those classified as high risk NMIBC is as high as 45 percent [3]. Following trans-urethral resection of bladder tumor (TURBT), intravesical instillation of bacillus Calmette-Guerin (BCG) is recommended for this group of high risk patients [4]. BCG immunotherapy has a superior efficacy in reducing the risk of both recurrence and progression of NMIBC compared with TURBT alone or TURBT and chemotherapy [5,6].

Whilst the exact anti-tumor mechanism of intravesical BCG is unknown, it is mostly thought that a significant local immune response is stimulated [7]. Urothelial and bladder cancer cells are infected which stimulates this immune response. Cytokines and a mononuclear cell infiltrate in the bladder wall induce an anti-tumor effect. The tumor cells are enabled to act as both killer cell targets and antigen presenting cells. BCG has a prolonged course of action after instillation and is detected in

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approximately 30% of urine samples at seven days after instillation [8].

A number of both local and systemic adverse effects (AEs) have been associated with BCG instillation. These can range from haematuria, frequency, fever and malaise to rare cases of disseminated infection such as severe sepsis [5,9]. It has been suggested that the same BCG instillation immune response which stimulates anti-tumor activity is the cause of these AEs however this is currently inconclusive [10-13]. Studies have mostly analyzed maintenance treatment or only a limited number of AEs.

The primary aim of our study was to examine the prevalence of local and systemic AEs in the induction period of intravesical BCG instillation and, secondarily, to determine if there was any relationship between adverse effects and the efficacy of BCG instillation.

METHODS

After approval from the institution ethics committee, retrospective analysis of patients receiving intravesical BCG immunotherapy at a group urology practice from 1995 to 2013 was performed. Standard practice was weekly intravesical BCG instillation for six weeks. Only patients having induction episodes of BCG instillation for their first diagnosis of NMIBC were included. The induction episode was defined as the first course of BCG instillation for the patient. Patients receiving less than the desired six BCG cycles in the induction episode were also included. Maintenance BCG courses were excluded from analysis. Demographics such as age and gender were recorded as well as the number of weekly BCG instillations received. Histopathological results were collected from the initial diagnosis. Using tumor stage and presence of carcinoma *in situ* (CIS), patients were stratified into risk-groups as per European Association of Urology (EAU) guidelines [14]. The date of diagnosis, commencement of BCG treatment, recurrence and progression of cancer, and last follow up were also recorded.

The primary objective of this study was to describe the prevalence of AEs in the induction BCG instillation. The AEs were divided into ten local and nine systemic symptoms (total 19) and were collected on a standardized symptom form (**File S1**). This form was routinely given to all patients receiving BCG instillation at our group urology practice. Patients were instructed to record the severity of each AE on a scale from zero to ten for each day in the week following instillation. However due to inconsistent recording of severity, this was unable to be accurately quantified. Therefore an AE was recorded as a binary outcome (yes/no) if a patient reported that symptom at any point in the week following instillation.

The secondary objective was to examine if an association between the presence of BCG instillation-associated AEs and efficacy existed. Efficacy was defined as the non-recurrence of NMIBC. Data on recurrence status was obtained from subsequent histopathology results. Patients with available follow-up data were dichotomized based on recurrence status and baseline characteristics compared. The association between recurrence and AEs were analyzed individually and also analyzed in overall, local and systemic groups. Patients were categorized as having a high (above the median) or low prevalence of AEs.

Statistical analysis was performed using STATA 12. (StataCorp, Texas, USA). Categorical data was analyzed using Fishers' exact or chi-squared test as appropriate. Continuous data was analyzed using a Student's *t*-test or Wilcoxon rank-sum test. Univariate Cox regression analysis was performed to investigate for association between an AE reported and predictors of recurrence.

RESULTS

Identification of our cohort between 1995 and 2013 is displayed in **Figure 1**. There were 200 episodes of induction BCG immunotherapy identified, with 42 episodes subsequently excluded due to being repeat treatments for the same patient. Therefore, the induction episodes of 158 patients were available for evaluation. The mean age was 70.2 years old (range 41–88) with a male predominance (79%). One hundred and thirty six patients (86%) received the standard six BCG instillations with the other 22 receiving less instillations. Discontinuation was commonly due to intolerability. Two patients developed sepsis and were subsequently hospitalized.

The frequency of AEs is shown in **Table 1**. Local symptoms were more common than systemic. The most prevalent local symptoms were frequency (107, 68%), dysuria (98, 62%) and nocturia (95, 60%). A further five AEs, urgency, haematuria, post-micturition pain, bladder pain and genital pain, were reported by more than a quarter of patients. For systemic symptoms, malaise (54, 34%), myalgia (41, 26%) and fever (32, 20%) were most common.

Table 1. Prevalence of adverse effects (*n* = 158).

Adverse effects	*n* (%)
Local adverse effects	
Frequency	107 (68%)
Dysuria	98 (62%)
Nocturia	95 (60%)
Urgency	90 (57%)
Haematuria	57 (36%)
Bladder pain	54 (34%)
Bladder pain during micturition	46 (29%)
Genital pain	41 (26%)
Bladder pain after micturition	33 (21%)
Genital itch	17 (11%)
Systemic adverse effects	
Malaise	54 (34%)
Myalgia	41 (26%)
Fever	32 (20%)
Abdominal pain	21 (13%)
Nausea	19 (12%)
Eye pain	19 (12%)
Arthralgia	16 (10%)
Cough	9 (6%)
Rash	6 (4%)

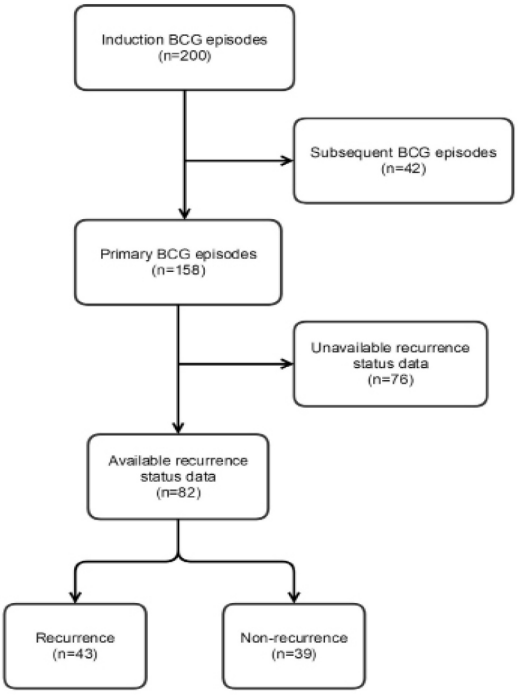

Figure 1. Study population.

There was data on 82 patients for recurrence status (**Table 2**). Of these, 43 (52%) patients were found to have recurrence of NMIBC in the study period. There was no significant difference between recurrent and non-recurrent groups regarding tumor stage, concurrent CIS and EAU risk-group. Groups were also similar in respect to age, gender, completion of six BCG cycles or median time to BCG instillation from diagnosis. Median time to recurrence was 11.1 months and the median follow up time for those with no recurrence was 40.5 months. Similar time to recurrence and number of recurrences was observed between high and low AE groups.

As shown in **Table 3**, there was no significant relationship between overall AEs and recurrence on univariate Cox regression analysis (HR 0.97, $P = 0.57$). Similarly, results were non-significant when analyzing for group local (HR 0.99, $P = 0.90$) and systemic (HR 0.88, $P = 0.32$) AEs. When examining individual AEs, only frequency was significantly associated with a reduced risk of recurrence (HR = 0.42, $P = 0.04$). Multivariate analysis was not performed due to the lack of significant univariate results.

DISCUSSION

In our study, BCG instillation-associated AEs were a common occurrence. As expected due to its direct local mechanism of action, local AEs were found to be more prevalent than systemic. Frequency, dysuria, nocturia and urgency were all experienced by more than half of the patients in the week following instillation. Regarding systemic AEs, greater than 20% of patients experienced malaise, myalgia and fever.

Table 2. Recurrence status ($n = 82$).

	Recurrence ($n = 43$)	Non-recurrence ($n = 39$)	*P* value
Age (mean, 95% CI)	70.2 (67.2–73.4)	70.3 (66.8–73.8)	0.99
Male/Female (*n*, %)	32/11 (74%/26%)	35/4 (90%/10%)	0.09
Tumor stage (*n*, %)			0.61
Ta	16 (37%)	12 (31%)	
T1	16 (37%)	17 (44%)	
Missing	11	10	
CIS (*n*, %)			0.17
Yes	28 (65%)	19 (49%)	
No	14 (33%)	19 (49%)	
Missing	1	1	
EAU risk group (*n*, %)			0.76
Low	7 (16%)	5 (13%)	
High	35 (82%)	32 (82%)	
Missing	1	2	
Completion of 6 cycles (*n*, %)	35 (81%)	33 (85%)	0.78
Time from diagnosis to BCG, months (median, IQR)	1.5 (1.0–1.8)	1.3 (1.1–1.8)	0.92
Time from BCG to recurrence, months (median, IQR*)		–	0.29*
High AEs	9.2 (4.2–26.7)		
Low AEs	12.1 (6.8–42.4)		
Number of recurrences (median, IQR*)		–	0.69*
High AEs	2 (1–3)		
Low AEs	2 (1–3)		

**P* value relates to the comparison between high and low AEs in the recurrence group.

A Cochrane review by Shelley *et al*. [5] has previously assessed the prevalence of BCG instillation-associated AEs. However, within this review of six studies ($n = 585$), there was heterogeneity between individual study populations, treatments and measurements of outcomes. Two studies only analyzed patients with recurrent NMIBC [15,16] while a further two also included patients with low risk NMIBC [17,18]. One of the trials used an eight week treatment compared to the standard six [17] and three gave supplemental intradermal BCG [16,19,20]. While we reported the occurrence of any severity of AE, some studies only recorded AEs intolerability if resulting cessation of treatment [13]. Despite these methodological differences, the prevalence of urinary frequency (68% in our population *vs.* 71%), dysuria (62% *vs.* 67%), fever (20% *vs.* 25%) and nausea (12% *vs.* 8%) were comparable to the Cochrane review. Haematuria (36% *vs.* 23%) and malaise (34% *vs.* 14%) was more prevalent in our cohort. As displayed in **Table 4**, our results of the four most prevalent AEs are also similar to those reported

in the American Urological Association (AUA) NMIBC guidelines [4] and another Cochrane review by Shang *et al*. [21]. Brausi *et al*. have observed a much lower prevalence of 33% for cystitis and 38% for frequency [9]. It is likely that this difference is attributable to variation in definitions between studies.

Table 3. Relationship between recurrence and adverse effects.

	HR (95% CI)	*P* value
Overall AEs	0.97 (0.87–1.08)	0.57
Local AEs	0.99 (0.86–1.15)	0.90
Frequency	0.42 (0.18–0.98)	0.04
Dysuria	0.90 (0.43–1.91)	0.79
Nocturia	0.75 (0.36–1.56)	0.45
Urgency	0.90 (0.40–2.03)	0.81
Haematuria	1.41 (0.60–3.33)	0.44
Bladder pain	0.58 (0.23–1.46)	0.25
Bladder pain during micturition	1.55 (0.67–3.60)	0.31
Genital pain	1.10 (0.45–2.68)	0.83
Bladder pain after micturition	1.51 (0.70–3.29)	0.30
Genital itch	1.90 (0.61–5.98)	0.27
Systemic AEs	0.88 (0.69–1.13)	0.32
Malaise	0.59 (0.22–1.59)	0.30
Myalgia	0.56 (0.20–1.52)	0.25
Fever	0.61 (0.21–1.74)	0.35
Abdominal pain	0.17 (0.02–1.14)	0.07
Nausea	1.21 (0.36–4.08)	0.76
Eye pain	0.44 (0.10–2.02)	0.30
Arthralgia	0.56 (0.12–2.61)	0.46
Cough	1.15 (0.29–4.59)	0.84
Rash	1.83 (0.18–18.5)	0.61

In our cohort, only presence of urinary frequency was significantly associated with non-recurrence (HR 0.42, $P = 0.04$) on univariate analysis. When AEs were examined all together, or in local and systemic groups (**Table 3**), no significant association was found. It has been hypothesized that the acute local inflammatory response which causes AEs is related to the anti-tumor effect caused by BCG [10]. As frequency is the most common local AE in our cohort, this may be the reason that it was the only AE to show a significant correlation with efficacy. Other studies have also investigated the relationship between BCG-associated AEs and efficacy in preventing recurrence. Individual symptoms such as fever, dysuria and frequency have been demonstrated to show association with reduced risk of recurrence [10,12]. Most of these studies evaluated AEs in both the induction and maintenance period and thus these patients were exposed to BCG for longer periods of time. A prospective study found that AEs in the induction period do not predict efficacy nor time to recurrence [13]. Apart from clinicopathologic parameters and BCG-associated AEs, other markers have been investigated to predict response to BCG instillation. Leucocyturia has been associated with an increased severity of AEs and a decreased risk of recurrence [22]. Inflammatory markers, intracellular markers and gene polymorphisms have also been studied with urinary IL-2 the most useful marker in evaluating treatment response currently [23].

To reduce the prevalence of BCG - associated AEs, various measures have been attempted. Dose reduction of one third has been shown to lessen complications however it may result in decreased efficacy with high-risk NMIBC [9,24]. Two recent randomized controlled trials (RCTs) have compared different BCG strains. The Tice and Connaught strains have similar side effects (42% *vs*. 28%, $P = 0.09$) [25] and no difference in intolerability for the Tokyo and Connaught strains (8.1% *vs*. 9.8%, $P = 0.70$) was shown [26]. Andius *et al*. reduced the instillation dwell time to less than 30 min [27]. Decreased fever, chills and dysuria were found while frequency and haematuria were unchanged. Van der Meijden *et al*. randomized patients to receive BCG and isoniazid or BCG alone [28]. For the isoniazid group, there was no reduction in fever or cystitis and cessation of treatment due to systemic side effects was actually more likely to occur (13% *vs*. 7%, $P = 0.02$). Fluoroquinolones may reduce the occurrence of moderate or severe toxicity [29]. Newer techniques under investigation to evaluate efficacy and toxicity include the addition of mitomycin C to BCG as adjuvant intravesical therapy [30]. Currently however, there is no effective preventative method for BCG toxicity.

Limitations include the retrospective nature of our study. Approximately 50% of patients were lost to follow up so their recurrence status was unknown. As the commencement of the study period was a number of years ago, data on recurrence was unable to be collected for all patients due to missing medical records. Complete data on other risk factors for recurrence such as multifocality, lesion size, grade and the use of mitomycin C was not able to be obtained. Secondly, AEs experienced during maintenance BCG episodes were not analyzed due to poorer patient compliance in completing the symptom score sheet. Potentially, more AEs could have occurred in the maintenance period. However, Brausi *et al*. demonstrated that the prevalence of AEs was not greatly increased when analyzing maintenance episodes over three years and therefore the same could be expected of our cohort [9]. Additionally, some AEs in our symptom sheet such as bladder pain and bladder burning were analogous which may have made it difficult for patients to differentiate. We constructed our own BCG instillation symptom questionnaire as there are no standardized published symptom scores for BCG instillation-associated AEs. This questionnaire was unchanged throughout the 19 year study period. While established symptom scores such as the International Prostate Symptom Score and Overactive Bladder Symptom Score may be of some value for local AEs however they do not allow for description of systemic AEs. Other studies have recorded AEs in a similar method to our study while others recorded only a limited range of AEs or defined an AE only if it results cessation of treatment. A BCG adverse event score was created by Saint *et al*. [12] which included an extensive four class classification grid on local and systemic adverse. This shares many similarities to our symptom form. Due to this variation amongst the literature, the development of a standardized symptom score based on the World Health Organization Toxicity Grades would be useful.

In conclusion, adverse effects due to BCG instillation are common in the induction period with nearly 70% of patients in our cohort experiencing individual symptoms. Local adverse effects are considerably more prevalent than systemic. Whilst BCG instillation is generally well tolerated with a high rate of treatment completion, patients should be counseled regarding these potential AEs. In our population, frequency was the only adverse effect to be significantly associated with non-recurrence. Overall, adverse effects due to induction BCG instillation

treatment in our study were not related to efficacy for non-muscle invasive bladder cancer.

Table 4. Prevalence of adverse effects across studies (%).

	Cohort	Shelley *et al.* [5]	AUA guidelines [4]	Shang *et al.* [21]	Van der Meijden *et al.* [28]	Brausi *et al.* [9]
Cystitis/Dysuria	62	67	59 (LUTS*)	54	73	33
Frequency	68	71	–	–	30	38
Haematuria	36	23	29	31	34	39
Fever	20	25	30	–	15	17

*LUTS, lower urinary tract symptoms.

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Supplementary information

File S1. Standardized symptom sheet

Supplementary information of this article can be found online at http://www.bladderj.org/bladder/rt/suppFiles/96.