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Short Communication

Treating high-grade T1 bladder cancer in the elderly. Is intravesical instillation of BCG worth?

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Background and aims. The mechanism of action of intravesical Bacille Calmette-Guerin (BCG) is supposed to be linked to the efficiency of the immune system. Since senesce could negatively affect the immune system efficiency, BCG efficacy in the elderly has been questioned. The present study aimed to determine whether elderly patients (≥ 70y) with high-grade T1 bladder cancer (BC) benefit from adjuvant intravesical instillation of BCG.

Methods. Study population consisted of 183 patients (median age 79y); 65 received BCG, both induction and one-year maintenance, and 118 did not. Follow-up consisted of urine cytology and cystoscopy every 3 months for the first two years, every 6 months for the third year, and then yearly. Chest/abdomen computed tomography was performed every year to rule out upper tract or metastatic disease.

Results. Mean follow-up was 45 months (range 1-177). Kaplan-Meier plots pointed out that treated patients had significantly better recurrent-free survival (RFS) and progression-free survival (PFS) than the untreated ones. The 40-month cancer-specific survival was 86.2% in treated and 79.7% in untreated patients, but such difference was not statistically significant. Multivariate Cox's proportional hazard regression analysis pointed out that BCG treatment was the only significant independent predictor of RFS and PFS. There was no serious BCG-related adverse reaction; 2 (3.1%) patients suffered moderate flu-like or lower urinary tract symptoms that resolved with symptomatic treatment.

Conclusions. Intravesical BCG proved to be safe and beneficial in elderly patients with high-grade T1 BC. Age per se should not be considered a contraindication to such treatment.

Key words: BCG, Elderly, Bladder cancer, T1, High grade/G3

INTRODUCTION

Bladder cancer (BC) is a common urologic malignancy and its incidence increases with age, exposure to environmental or occupational carcinogens, and smoking habit [1]. Indeed, BC overall incidence increases abruptly from a very low age-standardized rate of 2.3 in patients < 65y to a 51.1 rate in patients ≥ 65y [2]. Due to the increase in average life expectancy, treating BC in elderly people is becoming a major clinical issue.

Approximately 75% of cases present as non muscle-invasive BC (NMIBC); according to EAU guidelines, those at high risk and some of those at intermediate risk should receive adjuvant intravesical instillations of Bacillus Calmette-Guèrin (BCG) after transurethral resection of the bladder tumor (TURBT) [3].

The mechanism of action of BCG is supposed to be mediated by influx of immune cells into the bladder wall [4]. Specifically, BCG would promote activation and migration of immune cells into bladder wall, exploding

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an antitumoral effect mediated by the interaction between antigen presenting cells and lymphocytes Th1. This leads to priming of CD8+ cytotoxic T-cells, activation of Natural Killer cells, and release of inflammatory cytokines such as Interferon [INF]-gamma, Interleukin [IL]-12 and tumor necrosis factor [TNF]-alfa [2]. Therefore, like for other urological cancers [5,6], the clinical response to intravesical BCG administration seems to be linked to the efficiency of the immune system [7].

Senesce has been reported to negatively affect the immune system efficiency [8] and, therefore, to have a potential negative effect on BCG efficiency. Indeed, current EAU Guidelines point out that BCG efficiency is reduced in patients ≥ 70 years old [3], thus making treatment of such patients quite challenging. In clinical practice, this often leads to elderly patients with high-risk NMIBC to receive no adjuvant treatment after TURBT or, in some cases, to undergo immediate cystectomy, a major surgery with a significant impact on patients' quality of life as well as a significant risk of complications [9].

The present study aimed to determine whether elderly patients (≥ 70 years) with high-grade T1 BC benefit from adjuvant intravesical instillation of BCG.

MATERIALS AND METHODS

We retrospectively analyzed our prospectively maintained NMIBC database to identify patients with high-grade T1 BC (according to 2004 WHO grading) aging ≥ 70 years. After TURBT, all patients were offered adjuvant treatment by intravesical instillations of BCG, initially Pasteur strain, 75 mg in 50 mL saline, and later on RIVM strain, 81 mg in 50 mL saline. Patients who accepted received the classical six-week induction cycle and underwent bladder biopsies/TUR 5-8 weeks after having completed it. Those who responded to the induction cycle underwent maintenance according to EAU Guidelines [3]. Those who refused adjuvant BCG underwent follow-up.

Follow-up consisted of urine cytology and cystoscopy every 3 months for the first two years, every 6 months for the third year, and then yearly. Chest and abdominal computed tomography was performed at initial diagnosis and then every year to rule out upper tract or metastatic disease. Tumor recurrence was defined as pathological evidence of disease at bladder biopsy or TURBT, whereas tumor progression was defined as pathological shift to muscle invasive disease at bladder biopsy or TURBT or imaging techniques demonstrating recurrent bladder cancer and distant metastasis likely related to it.

Two senior pathologists unaware of clinical data reviewed all specimens including agreement with the latest WHO Classification of Tumors of the Urinary System and Male Genital Organs [10] and the 2010 TNM staging system [11].

The study was approved by the Internal Review Board.

Statistical analysis

Continuous data are reported as means ± standard deviations (SD) or median values as appropriate; those with normal distribution according to the Skewness and Kurtosis test were compared by Student's t-test whereas those with a non-parametric distribution were compared by the Mann-Whitney U-test. Differences in rates were compared by the chi-square test or the Fisher's exact test. Univariate analysis of disease free survival (RFS), progression free survival (PFS) and cancer specific survival (CSS) was carried out using the Kaplan-Meier method, with differences among groups being tested for significance using the Log-rank test. Univariate and multivariate Cox's proportional hazard regression analysis was carried out to test the impact of clinical variables on RFS, PFS and CSS. Significance was set at $p < 0.05$. Statistical analysis was carried out using the MedCalc 16.8 Software (MedCalc, Ostend, Belgium) and STATA SE 14.

RESULTS

Between January 2005 and June 2018, a total of 199 patients aging ≥ 70 were diagnosed with high-grade T1 BC. Their median age at diagnosis was 79 years (range 70-96). One hundred-eight patients underwent restaging trans-urethral resection (Re-TUR) whereas 91 refused it; residual/recurrent BC was found in 57 (52.7%), muscle-invasive (T2) BC in 6 (5.5%), and no residual tumor in 45 (41.8%). The 6 patients with T2 disease and the 4 with high-grade T1 and concomitant Carcinoma in situ (CIS) at Re-TUR underwent cystectomy. Of the remaining 189 patients, 71 underwent BCG induction therapy whereas 118 patients refused it. Six patients did not complete BCG induction cycle due to recurrent cystitis or poor compliance, thus were excluded.

Study population therefore consisted of 183 patients, 65 treated and 118 not treated with BCG; their clinical characteristics are reported in Table I. Their median follow-up was 45 (1-177 months).

Kaplan-Meier plots pointed out that treated patients had significantly better RFS and PFS (Fig. 1). Of the 40 patients who progressed, 22 underwent cystectomy; eventually, 18 patients died because of their BC. The 40-month CSS was 86.2% in treated and 79.7% in untreated patients ($p = 0.274$) and Kaplan-Meier plots confirmed that such difference in CSS was not statistically significant (Fig. 1).

Table I. Patient's and clinical characteristics.

	BCG (n. 65)	No BCG (n. 118)	P-value
Age, mean (SD)	77.1 (± 5.5)	80.1 (± 5 .4)	0.004
Male gender, n (%)	56 (86.1%)	104 (88%)	0.698
Size tumor > 3 cm, n (%)	19 (29.2%)	40 (33.8%)	0.002
Primary tumor, n (%)	52 (80%)	92 (77.9%)	0.747
Single tumor, n (%)	39 (60%)	58 (49.1%)	0.234
CIS, n (%)	3 (4.6%)	6 (5%)	0.888
Re-TUR, n (%)	47 (72%)	52 (44%)	0.029

CIS: carcinoma in situ; BCG: Bacillus Calmette-Guérin; Re-TUR: Restaging Transurethral Resection.

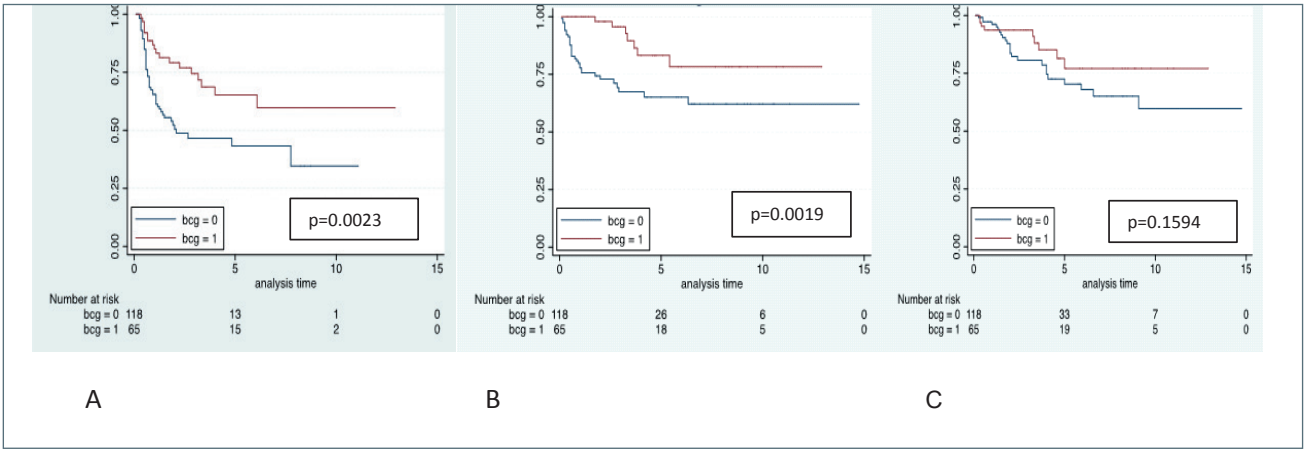

Figure. 1. Kaplan Meier curves for Recurrence Free Survival (A), Progression Free Survival (B) and Cancer Specific Survival (C) between seventy years old patients undergone to BCG therapy and those with no treatment (difference in RFS and PFS are issue from these curves; BCG therapy give an important disease free survival gain in patients ≥ 70 years old).

At univariate Cox's proportional hazard regression analysis, Re-TUR and BCG treatment were the only significant predictors of RFS and PFS, whereas age, sex, tumor presentation, size and number, CIS, presence of muscle in the first sampling had no predictive value (Tab. II). At multivariate analysis, BCG treatment remained a statistically significant independent predictor of both RFS and PFS whereas Re-TUR significantly predicted PFS but not RFS (Tab. III).

No serious BCG-related adverse reaction (AR) was observed. Two (3.1%) patients suffered mild ARs consisting in flu-like symptoms (fever, malaise) lasting < 24 hours, mild bladder pain and moderate low urinary tract symptoms of the storage phase (nocturia, frequency, urgency). All reactions resolved with symptomatic treatment, namely paracetamol 1 gr twice-a-day, within two days.

DISCUSSION

The present study pointed out that elderly (≥ 70 year-old) patients with high-grade T1 BC benefit from adjuvant BCG treatment in terms of RFS and PFS.

The question of BCG efficacy in the elderly has been raised by a few studies theorizing that senesce may deteriorate the innate and adaptive immune systems [4 7] thus leading to a reduced response to BCG treatment. Evidence is to date controversial. In a large study on 805 patients, Herr et al. [12] reported no difference in initial response to BCG; 5-year cancer free rate was 25% in patients ≥ 70 years compared with 37% in patients < 70 years but there was no difference in PFS and CSS. This study however included both Ta and T1 high-grade tumors and excluded patients with early failure. Margel et al. [13] compared patients < 75y with those ≥ 75y and found no difference in RFS but a statistically significant ($p < 0.001$) difference in PFS. Cox multivariate proportional hazard regression analysis demonstrated that age was the most significant independent predictor of progression (HR 2.1) followed by BCG maintenance (HR 0.8). However, this study included both low-grade and high-grade tumors, Ta, T1 and CIS, and no survival curves adjusted for prognostic factors were provided. Finally, Oddens et al. [14] reported that, at mean follow-up of 9.2y, age did not affect RFS but patients > 70y had a worst PFS and CSS than those < 70y. However, also

Table II. Cox univariate proportional hazards regression analysis of possible confounding variables.

	Recurrence free survival		Progression free survival		Cancer specific survival	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Male gender	0.60 (0.27-1.30)	0.196	0.89 (0.34-2.27)	0.810	1.24 (0.47-3.24)	0.652
Primary	0.81 (0.47-1.38)	0.435	1.36 (0.60-3.09)	0.455	0.96 (0.42-2.23)	0.942
Single	0.89 (0.56-1.43)	0.652	0.83 (0.43-1.56)	0.560	1.64 (0.81-3.30)	0.163
Tumor size (> 3 cm)	1.16 (0.59-2.30)	0.656	1.42 (0.49-4.14)	0.514	4.03 (0.85-19.1)	0.078
CIS	0.27 (0.03-1.98)	0.200	0.64 (0.08-4.70)	0.664	0.89 (0.12-6.54)	0.906
Muscle*	1.06 (0.59-1.90)	0.837	1.06 (0.49-2.30)	0.881	1.00 (0.43-2.31)	0.990
Re-TUR	0.59 (0.37-0.95)	0.030	0.38 (0.19-0.73)	0.004	0.28 (0.12-0.63)	0.002
BCG	0.44 (0.26-0.76)	0.003	0.29 (0.13-0.67)	0.004	0.58 (0.27-1.25)	0.165

Anyone EORTC factors affect the outcome. CIS: carcinoma in situ; BCG: Bacillus Calmette-Guérin; Re-TUR: Restaging Transurethral Resection; *Presence of muscle in the sample on first TURBT.

this study has the limitations of having included both low-grade and high-grade tumors, stage Ta and T1.

Findings from the above-mentioned studies, particularly the latter, have led to questioning the opportunity of offering BCG to patients with high-grade NMIBC. The present study did not aim to determine whether age impacts on BCG efficacy but rather how should we treat elderly patients with high-grade T1 BC. Findings were clear. BCG treatment provided significant benefit in terms of RFS and PFS at the price of a low rate of mild ARs. BCG treatment provided a non-significant benefit in CSS; this could be due both to the small number of events and careful follow-up having avoided delays in cystectomy in case of progression. Like for other common urological conditions, case volume [15], tailoring treatment to patients clinical conditions and wise clinical judgment [16-18] all play an essential role. Indeed, a previous study [19] testing BCG treatment in elderly patients reported better CSS in patients who received BCG than in those who did not; unfortunately, also this study suffered the limitations of having included both low-grade and high-grade tumors, stage Ta and T1.

Another relevant yet controversial question is BCG toxicity in the elderly. Heiner et al. [20] pointed out that BCG complications were significantly (p = 0.001) more common in elderly patients, thus recommending to treat such patients by BCG induction only or even by "other" intravesical agents. Racioppi et al. [21] found that elderly patients had more early complications but the rate of severe complications did not vary with age. However, they recommended administering the BCG induction cycle biweekly in the elderly patients to reduce the risk of complications. Finally, a recent large study [22] on patients randomized to receive 3 years BCG maintenance pointed out no impact of age on treatment side effects or discontinuation.

In the present study, treatment discontinuation during the induction cycle occurred in 8.5% (6/71) of our elderly patients. There was no discontinuation during maintenance, somehow suggesting that patients who stand the induction cycle are likely to easily stand maintenance. ARs during maintenance were uncommon (3.1%) and always minor. It is worth mentioning that all patients had their bladder emptied by placing a soft urethral catheter and that all were carefully instructed to drink 2 liters fluids over the following 12 hours in order to better eliminate potential BCG residuals. Whether such measures could be responsible for our low rate of adverse reactions however remains to be demonstrated.

A strong point of our study was having focused on a very homogeneous cohort of patients with high-grade T1 BC and having taken into account available prognostic factors such as sex, primary tumor, concomitant CIS, tumour size and number, as well as Re-TUR.

One potential study limitation was the use of an arbitrary cut-off of 70 years but, in view of previous studies [12 14], this seemed to be appropriate. Another was

Table III. Cox multivariate proportional hazards regression models of possible confounding variables.

	Recurrence free survival		Progression free survival		Cancer specific survival	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Re-TUR	0.68 (0.42-1.08)	0.108	0.43 (0.22-0.85)	0.016	0.38 (0.15-0.95	0.124
BCG	0.48 (0.27-0.83)	0.009	0.34 (0.14-0.77)	0.011	0.81 (0.3-1.12)	0.174

BCG treatment is a significant independent predictor of RFS and PFS. Whereas Re-TUR predicted PFS but not RFS. BCG: Bacillus Calmette-Guérin; Re-TUR: Restaging Transurethral Resection.

not having assessed the impact of other potential predictors of disease outcome, including smoking habits [23] and molecular markers having proved to be reliable in this setting [24-32], but they are not routinely assessed and a dedicated analysis seemed to be beyond the scope of this clinical study.

In conclusion, elderly (≥ 70y) patients with high-grade T1 BC seem to benefit from adjuvant BCG treatment. Given the low rate of mild ARs, age per se should not be considered an absolute contraindication to such treatment.

Conflict of interest

The authors declare no conflict of interest.

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