Arab Journal of Urology (2015) 13, 238–243

Arab Journal of Urology
(Official Journal of the Arab Association of Urology)

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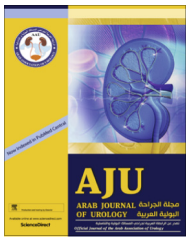

ONCOLOGY/RECONSTRUCTION
ORIGINAL ARTICLE

Low-dose bacille Calmette–Guérin for non-muscle-invasive bladder cancer: Results of a prospective study

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Received 16 February 2015, Received in revised form 23 September 2015, Accepted 24 September 2015

KEYWORDS

BCG;
Bladder cancer;
Low-dose regimen;
NMIBC;
TURB

ABBREVIATIONS

BC, bladder cancer;
CIS, carcinoma in situ;
NMI, non-muscle-invasive;
SWOG, Southwest Oncology Group;
TURB, transurethral resection of the bladder

Abstract ***Objective:*** To evaluate the efficacy and safety of low-dose (45 mg) intravesical bacille Calmette–Guérin (BCG) therapy in the treatment of patients with non-muscle-invasive bladder cancer (NMIBC), as intravesical BCG is the most acceptable adjuvant therapy for NMI transitional cell carcinoma of the bladder. However, in the standard regimen, undesirable effects are the main cause of treatment discontinuation.

Patients and methods: The present study included 37 men with primary NIMBC. All patients underwent complete TURB and 2 weeks later, a 6-week course of 45 mg BCG diluted in 50 mL isotonic saline was instilled into the bladder and retained for 2 h. Patients were evaluated for BCG efficacy (recurrence with or without progression) and safety by documentation of minor and/or major side-effects.

Results: There were no major or severe side-effects and no treatment discontinuations. Local adverse effects occurred in 20 patients, while systemic effects, in the form of fever, occurred in six patients (16.2%). There was recurrence in 14 patients (37.8%) after 18–34 months, with disease progression (muscle invasion) in four (10.8%) after 6–18 months. The recurrence index was 0.39/100 patients/month and the mean (range) tumour-free period was 30.97 (7–36) months.

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Peer review under responsibility of Arab Association of Urology.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.aju.2015.09.005

Conclusion: Low-dose BCG intravesical therapy is an effective adjuvant treatment in NMIBC. However, this needs to be validated in future studies and in comparison with other proposed doses and/or regimens.

Introduction

Bladder urothelial cancer is the fourth most common malignancy diagnosed in American men [1] and worldwide, it is the seventh most common malignancy in men and the seventeenth most common in women. It is estimated that, in 2002, ≈357,000 new cases of bladder cancer (BC) were diagnosed [2].

At diagnosis, most of these cancers are non-muscle-invasive (NMI) lesions. These lesions have a high incidence of recurrence (up to 75%), which requires close monitoring and subsequent intervention [3].

Transurethral resection of the bladder (TURB) is the initial and crucial step in managing NMIBC. The aim of TURB is to establish a histological diagnosis of the tumour; to determine the tumour stage (the pathologist must be able to evaluate the depth of tumour invasion), all clinically important prognostic factors, e.g. grade, number, size, and configuration of the tumour, as well as the presence of carcinoma in situ (CIS); and to completely remove all visible lesions [4].

Intravesical instillation of BCG after initial TURB is intended to prevent tumour recurrence and progression [5] and was first proposed by Morales et al. [6] for the treatment of NMIBC. Since then, BCG therapy has been shown to be the most effective treatment in the prevention of recurrence and progression of NMIBC, especially for high-risk NMIBC [7].

Despite BCG treatment, 30–50% of patients do not respond and ≈15% progress to muscle-invasive disease [8,9]. Various factors might explain the high percentage of BCG failures. First, full compliance with the current protocol is influenced by BCG-associated side-effects. Second, incorrect histological staging of tumours, due to high intra- and interobserver variability among pathologists, may also explain BCG failures [10,11]. Also, an incomplete tumour resection, reported in 20–62% of cases at restaging TURB, might underlie refractory disease [12,13].

Despite the widespread use of intravesical BCG instillation as a standard adjuvant therapy, there are still many questions needed to be answered, e.g., (i) the necessity of maintenance BCG therapy; (ii) the efficacy of low-dose BCG vs standard dose; and (iii) the superiority of combined therapy with BCG [14,15].

The present study was designed to evaluate the efficacy and safety of low-dose (45 mg) intravesical BCG therapy for treating patients with NMIBC.

Patients and methods

This was a prospective study following the tenets of the declaration of Helsinki and was approved by the Institutional Review Board. The present study was conducted in our Urology Department, between March 2010 and January 2014.

In all, 37 men with a mean (SD) age of 54 (5.6) years, with primary NMIBC with low- and intermediate-risk of recurrence and progression were included (Table 1; Ta, five patients; T1, 32; grade 2 in 25 patients and grade 3 in 12). Gross haematuria was the presenting symptom in 31 patients, five presented with recurrent UTI, and one was accidentally discovered during ultrasonography for an unrelated condition.

The procedure commenced with a bimanual examination under anaesthesia, followed by a careful endoscopic examination of the entire urethra and bladder. The size (compared with the diameter of the resection loop), number, and location of tumours, as well as regions of erythema and mucosal abnormalities suggestive of CIS were identified and registered. Tumours were completely

Table 1 Tumour characteristics.

Characteristic	*N* (%)
Bladder tumour	
Primary	37 (100)
Recurrent	0
Tumour number	
1	23 (62)
2–7	14 (38)
>7	0
Tumour size, cm	
<3	29 (78)
⩾3	8 (22)
Associated CIS	1
Tumour stage	
Ta	5 (13)
T1	32 (87)
Tumour grade	
G1	0
G2	25 (67)
G3	12 (33)