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Bacillus Calmette-Guérin Failure in Patients with Non–Muscle-invasive Urothelial Carcinoma of the Bladder May Be Due to the Urologist's Failure to Detect Urothelial Carcinoma of the Upper Urinary Tract and Urethra

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Abstract

Background: Various reasons exist for so-called bacillus Calmette-Guérin (BCG) failure in patients with non–muscle-invasive urothelial bladder carcinoma (NMIBC).
Objective: To explore whether urothelial carcinoma of the upper urinary tract (UUT) and/or prostatic urethra may be a cause for BCG failure.
Design, setting, and participants: Retrospective analysis of 110 patients with high-risk NMIBC repeatedly treated with intravesical BCG, diagnosed with disease recurrence, and followed for a median time of 9.1 yr.
Intervention: Two or more intravesical BCG induction courses without maintenance.
Outcome measurements and statistical analysis: Primary outcome was pattern of disease recurrence (BCG failure) within the urinary tract categorised into UUT and/or urethral carcinoma (with or without intravesical recurrence), and intravesical recurrence alone. Secondary outcome was survival. Predictors of UUT and/or urethral carcinoma and the effect of pattern of disease recurrence on cancer-specific survival were assessed with multivariable Cox regression analysis adjusting for multiple clinical and tumour characteristics.
Results and limitations: Of the 110 patients, 57 (52%) had UUT and/or urethral carcinoma (with or without intravesical recurrence), and 53 (48%) had intravesical recurrence alone. In patients with UUT and/or urethral carcinoma, bladder carcinoma in situ (Tis) before the first and second BCG course was present in 42 of 57 (74%) and 47 of 57 (82%) patients, respectively. On multivariable analysis, bladder Tis before the first and/or second BCG course was the only independent predictor of UUT and/or urethral carcinoma. Of the 110 patients, 69 (63%) were alive at last follow-up visit, 18 (16%) had died due to metastatic urothelial carcinoma, and 23 (21%) had died of other causes. Pattern of disease recurrence within the urinary tract was not an independent predictor of cancer-specific survival. Main study limitations were retrospective design and limited power for survival analysis.
Conclusions: In our patients with high-risk NMIBC *failing* after two or more courses of intravesical BCG, UUT and/or urethral carcinoma was detected in >50% of the cases during follow-up. The vast majority of these patients had bladder Tis before the first and/or second BCG course. In patients experiencing the so-called BCG failure, a diagnostic work-up of UUT and prostatic urethra should always be performed to exclude urothelial carcinoma before additional intravesical therapy or even a radical cystectomy is considered.

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1. Introduction

Intravesical bacillus Calmette-Guérin (BCG) is currently considered the first-line treatment with curative intent for carcinoma in situ (Tis) and in an adjuvant setting after transurethral resection (TUR) of intermediate- and high-risk non–muscle-invasive urothelial carcinoma of the bladder (NMIBC) [1–3].

However, approximately 50% of patients treated with BCG experience intravesical disease recurrence and/or progression, which is commonly referred to as BCG *failure*. This definition encompasses heterogeneous classes of patients, ranging from those who abandon treatment due to side effects to patients who never respond to BCG to those who have recurrence after a variable disease-free period [4].

While research in the past years has focused on prognostic stratification of these patients and evaluation of optimal treatment for intravesical recurrence, little attention has been directed towards identifying possible reasons for so-called failure. Patients failing after repeat intravesical BCG courses may have urothelial carcinoma in the upper urinary tract (UUT) or in the prostatic urethra that has remained undetected and untreated by intravesical BCG and, as such, perpetuates disease recurrence [5].

Based on this premise, in the present study we evaluated a cohort of patients with high-risk NMIBC and disease recurrence after two or more intravesical BCG induction courses with primary interest on rate of UUT and/or urethral carcinoma and secondary focus on long-term oncologic outcome.

2. Materials and methods

2.1. Patients

We retrospectively identified from our prospectively maintained institutional database all patients with NMIBC who received two or more courses of six weekly intravesical BCG instillations each between February 1983 and June 2012 and had disease recurrence (BCG failure). Of 120 patients, three with incomplete clinical and/or pathologic data and seven with irregular follow-up were excluded. A total of 110 patients formed the basis for the present analysis.

The rationale for considering patients receiving two or more BCG courses was to have a well-defined population sufficiently exposed to BCG, since it is known that in nonsensitised patients, 6 wk (ie, the duration of a single intravesical BCG course) is insufficient to build up a delayed-type hypersensitivity reaction and to generate an immune response to subsequent BCG exposure [6]. Typically, sensitised patients experience inflammatory local and/or systemic side effects, whose occurrence has been reported to be associated with improved outcome [7,8].

2.2. Treatment

Indications for intravesical BCG were primary or secondary Tis, Ta G3, and T1 G2/3 tumours, and multiple recurrent Ta G2 tumours. The second (or further) BCG course was given to patients with disease recurrence (positive urine cytology or biopsy) detected either immediately at the first follow-up visit after the last BCG course or later on after a disease-free interval.

A complete resection of all visible tumours (if any) was performed. A repeat TUR of the resection site excluding residual tumour or muscle invasion was performed in T1 and/or G3 tumours 2 wk after the initial TUR. UUT tumours were excluded with either excretory urography, computed tomography, or magnetic resonance imaging in all patients before the first BCG course and before the subsequent ones only if not already performed within the last 12 mo.

BCG induction treatment was generally commenced within 2 wk from TUR. A treatment course consisted of six weekly instillations with either 120 mg BCG Pasteur (Immun BCG Pasteur F; Institut Pasteur, Paris, France) or 81 mg BCG Connaught (ImmuCyst; Sanofi Pasteur MSD AG, Baar, Switzerland) or 81 mg BCG Tice (OncoTICE; Organon, West Orange, NJ, USA) dissolved in 50 ml 0.9% saline and retained in the bladder for 2 h. Strain type was given according to availability. No BCG maintenance therapy was administered.

2.3. Follow-up

After each intravesical BCG course, patients were followed either at our institution or by their referring urologist with a standard protocol including cystourethroscopy and bladder barbotage cytology every 3 mo for the first 3 yr and every 6 mo for the following 2 yr, and yearly urinalysis thereafter. UUT imaging was performed 1 and 3 yr after treatment with either excretory urography, computed tomography, or magnetic resonance imaging. Follow-up for patients undergoing a radical cystectomy (RC) during the follow-up was conducted as previously reported [9].

In case of positive bladder barbotage cytology without visible intravesical tumour, UUT and/or urethral carcinoma was searched for, as shown in Figure 1. If bladder tumours were found, they were completely resected, and a bladder barbotage cytology was obtained after TUR immediately before transurethral catheter removal. If the cytology results were positive, the same scheme already outlined was followed. Patients with proven or suspected recurrent disease were re-referred to our centre for further work-up or treatment.

2.4. Outcome measures

Primary outcome was pattern of disease recurrence (BCG failure) within the urinary tract, categorised into UUT and/or urethral carcinoma (with or without intravesical recurrence), and intravesical recurrence alone. Diagnosis was always confirmed cytologically and/or histologically. Diagnosis of UUT Tis was made by the following criteria: (1) urothelial cells of malignant type in urine cytology obtained after forced diuresis and confirmed in urine obtained after selective retrograde UUT catheterisation; and (2) no detectable lesions on UUT imaging [10]. For the diagnosis of urethral Tis, a positive barbotage cytology of the urethra was followed by confirmatory multiple cold-cup urethral biopsies. Patients were classified as having UUT and/or urethral carcinoma also if the tumour was incidentally detected in the ureter and/or prostatic urethra/prostatic ducts on definitive pathology at the time of a RC. Tumour stage and grade were assigned according to the 2002 TNM classification and 1973 World Health Organisation system, respectively.

Secondary outcome was cancer-specific survival (CSS), which was calculated as time from start of the first BCG course to death from systemic progression of urothelial carcinoma. Alive patients without systemic progression were censored at date of last follow-up visit; patients dying of competing causes before systemic progression were censored at date of death.

2.5. Statistical analyses

The analysis was based on intention to treat. Continuous variables were non-normally distributed and are reported as median with interquartile range (IQR) and full range. Differences in patient and