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Original article

Purified protein derivative skin test reactions are associated with clinical outcomes of patients with nonmuscle invasive bladder cancer treated with induction bacillus Calmette-Guérin therapy

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Abstract

Objectives: To investigate the relationship between purified protein derivative (PPD) skin test reactions before bacillus Calmette-Guérin (BCG) therapy and the clinical outcomes of BCG-naïve nonmuscle invasive bladder cancer patients treated with adjuvant BCG therapy.

Materials and methods: A total of 288 nonmuscle invasive bladder cancer patients subjected to the PPD skin test before BCG therapy were included. PPD skin test reactions were categorized into 3 groups: positive, slightly positive, and negative. The presence of an induration was positive. If an induration was absent, erythema of 10 mm or more and less than 10 mm corresponded to slightly positive and negative, respectively.

Results: A total of 66 (22.9%), 149 (51.7%), and 73 (25.3%) patients exhibited a positive, slightly positive, and negative to PPD skin test, respectively. The 5-year recurrence-free survival rate of patients with positive PPD skin test reactions was 89.4 ± 4.1%, which was significantly higher than those of patients with slightly positive (65.5 ± 4.2%, $P = 0.001$) and negative reactions (56.4 ± 6.6%, $P < 0.001$). A multivariate Cox regression analysis revealed that a positive PPD skin test reaction was independently associated with tumor recurrence (hazard ratio of 0.233, $P < 0.001$), but not with stage progression. The incidence of fever persisting for more than 2 days or fever of ≥38°C was significantly higher in patients with a positive PPD skin test reaction (18.2%) than in patients with slightly positive (8.7%) and negative PPD skin test reactions (4.1%).

Conclusions: The PPD skin test reactions before BCG therapy may predict clinical outcomes following BCG therapy and help clinicians counsel patients exhibiting strong therapeutic effects with BCG therapy and potentially major BCG-related side effects.

Keywords: Bacillus Calmette-Guérin; Immunotherapy; Purified protein derivatives; Treatment outcome; Urinary bladder neoplasms

1. Introduction

Nonmuscle invasive bladder cancer (NMIBC) accounts for 75% of all cases of bladder cancer [1]. The major goals of treating NMIBC patients are to prevent recurrence and muscle-invasive disease progression. Current guidelines recommend treatment strategies for NMIBC according to risk stratification [2–4]. Adjuvant bacillus Calmette-Guérin (BCG) therapy following the transurethral resection of bladder tumor (TURBT) is recommended for intermediate- to high-risk NMIBC patients. The clinical efficacy of BCG therapy has been established [5,6]; however, some practical issues are associated with BCG therapy, such as optimal treatment schedules not being established and clinical biomarkers to select patient populations that obtain clinical benefits from BCG therapy not existing.

The purified protein derivative (PPD) skin test has been used to evaluate the tuberculosis status of NMIBC patients before adjuvant BCG therapy [7] and reveals the signature of previous exposure [8]. Previous studies reported that patients with a positive PPD skin test reaction before BCG therapy exhibited a better response to BCG therapy than those with a negative reaction [8,9]. These studies only

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included a small number of patients and a detailed description of BCG-related side effects, another side to the immunological response, was not provided. The relationship between PPD skin test reactions and the clinical outcomes of NMIBC patients has not yet been elucidated in detail. Therefore, we herein examined the relationship between PPD skin test reactions before BCG therapy and clinical outcomes, namely, oncological outcomes and the occurrence of side effects, in a large number of BCG-naïve NMIBC patients.

2. Materials and methods

2.1. Patient selection

A total of 643 patients with primary NMIBC were administered adjuvant intravesical BCG therapy after TURBT at our institute between 1987 and 2015. Among these patients, we excluded those who did not receive a PPD skin test before BCG therapy, those who were suspected of having active tuberculosis, and those who received maintenance BCG therapy. Finally, we identified 288 patients with primary NMIBC who were treated with an induction course of BCG therapy during the study period. A retrospective study was then conducted on the 288 patients to evaluate the effect of PPD skin test reactions on the clinical outcomes of adjuvant induction BCG therapy. This study was approved by the Institutional Review Board of Keio University Hospital.

2.2. Treatment and follow-up

All surgical specimens obtained from TURBT were histologically confirmed to be urothelial carcinoma, and tumors were graded according to the 1973 WHO grading system [10]. We performed adjuvant induction BCG therapy for patients with intermediate- or high-risk NMIBC according to current clinical guideline [2]. About 1 to 2 weeks before the start of adjuvant BCG therapy, the PPD skin test was performed by injecting 0.1 ml of tuberculin PPD (Japan BCG Laboratory, Tokyo, Japan) into the inner surface of the forearm. PPD skin test reactions were assessed approximately 48 hours after the injection. The injection site was inspected visually under good light, and the presence of erythema (reddening of the skin) and an induration (hard, dense, raised formation) were confirmed. If an induration was suspected, its margins were detected using fingertips. Erythema and induration measurements were recorded in mm. If an induration was absent, it was recorded as 0 mm. The presence of other findings, such as double erythema, blistering, or necrosis, was also recorded. Patients were classified into 3 groups according to their PPD skin test reactions: negative, slightly positive, and positive. The presence of an induration was positive. If an induration was absent, erythema of 10 mm or more and less than 10 mm corresponded to slightly positive and negative, respectively [11]. Patients with double erythema, blistering, or necrosis were suspected of having active tuberculosis, then excluded from this study.

The intravesical instillation of BCG was initiated 4 to 5 weeks after TURBT and continued weekly for 6 to 8 weeks. Patients were treated with either the Tokyo-172 strain (Immunobladder, Japan BCG Laboratory) or Connaught strain (ImmuCyst, Sanofi, Paris, France). The BCG Tokyo-172 strain was solely used until October 2003, at which time the BCG Connaught strain was approved for the treatment of NMIBC in Japan. From October 2003 to September 2012, the use of BCG Tokyo-172 or Connaught strain depended on the attending physician's preference. BCG Tokyo-172 have solely used again after September 2012, since supply of BCG Connaught strain was stopped.

All patients were routinely assessed with urine cytology and cystoscopy every 3 months for the first 2 years after TURBT, every 6 months for the next 3 years, and then every 6 to 12 months thereafter. Computed tomography was performed annually for the first 5 years and then every 1 to 2 years thereafter in order to evaluate extravesical lesions. Tumor recurrence was defined as a new tumor appearing in the urinary bladder after adjuvant BCG therapy. Stage progression was defined as the development of histologically confirmed muscle invasion (pathological stage equal or greater than pT2) or lymph node or distant metastasis detected by imaging modalities.

2.3. BCG-related side effects

Side effects during BCG therapy were classified as minor and major, according to our previous study [12]. Macroscopic hematuria and lower urinary tract symptoms, improving within 48 hours with no subsequent recurrence, were considered to be minor, whereas those persisting for more than 48 hours were considered to be major side effects. Low-grade fever subsiding within 2 days was considered to be a minor side effect, whereas fever persisting for more than 2 days or fever of $\geq$38°C was considered to be a major side effect. Other side effects such as epididymitis, prostatitis, and systemic infection were classified as major side effects.

2.4. Statistical analysis

The following factors were collected and analyzed for each individual patient: age, sex, tumor grade, pathological T category, tumor multiplicity, presence of concurrent carcinoma in situ, PPD skin test reactions (positive, slightly positive, or negative), the BCG strain (Tokyo-172 or Connaught), and side effects occurring during adjuvant BCG therapy. The categorical and continuous variables of the different groups were compared using the chi-squared test and Mann-Whitney *U* test, respectively. Recurrence-free survival (RFS) and progression-free survival (PFS) rates were