Original Article

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Symptoms of Bacillus Calmette-Guerin Cystitis in Bladder Cancer Patients according to Tuberculosis Sequelae by Chest Radiography

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Purpose: Bacillus Calmette-Guerin (BCG) vaccination has been administered to most infants at birth in Korea; however, tuberculosis (TB) remains extant. TB can leave sequelae on chest radiography according to the immune response of the host. We investigated the symptoms of cystitis after intravesica instillations in bladder cancer, depending on the TB sequelae on chest radiography.

Materials and Methods: One hundred forty-two patients with non-muscle invasive bladder cancer (NMIBC) underwent transurethral resection and intravesical BCG therapy for bladder cancer. Patients received a BCG induction course—with or without a maintenance course—and were divided into the two groups: Group A, which included patients with visible sequelae of TB on chest radiography (n=31) and group B, which included patients without visible sequelae of TB (n=111). Cystitis symptoms of BCG intravesical therapy were compared between the two groups. The recurrence and progression rates of bladder cancer were also analyzed.

Results: The overall rate of cystitis symptoms was 32.3% (10/31) in group A and 33.3% (37/111) in group B. One patient in group A and three in group B did not complete the treatment course due to severe cystitis symptoms (p=0.876). Pyuria was reported when cystitis symptoms occurred in 80% (8/10) in group A and 56.8% (21/37) in group B. The recurrence and progression rates were not different between the two groups.

Conclusions: Our results show that there was no significant difference of cystitis symptoms in accordance with the presence of TB sequelae in chest radiography when BCG instravesical therapy for NMIBC was performed.

Keywords: Cystitis; BCG vaccine; Tuberculosis; Radiography; Administration, intravesical

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INTRODUCTION

Korea is considered to have an intermediate tuberculosis (TB) burden [1,2]. The incidence of TB, including at extra-pulmonary sites, was 78.5 per 100,000 people in 2012 [2]. Regardless of the vaccination status or treatment status, chest radiography indicates the presence of sequelae for TB [3]. Cell-mediated immunity is the major host defense mechanism against TB through macrophages and T lymphocytes [3,4]. When host factors prevail, gradual healing with the formation of parenchymal scars results [3]. Therefore, the presence of sequelae on chest

radiography demonstrates previous exposure to TB. However, in some cases, there is no presence of sequelae after successful treatment of TB infection [5]. Although not clearly understood thus far, the immune response of the host is thought to be important for the formation of sequelae on chest radiography.

Bacillus Calmette-Guerin (BCG) vaccination is a routine method for TB prevention and is also used to prevent recurrence and progression in high-risk non-muscle invasive bladder cancer (NMIBC) by intravesical instillation [6,7]. Most adverse events with respect to intravesical BCG are local reactions due to immune stimulation required for the eradication of cancer cells [8]. Within 24 to 48 hours of BCG instillation, cystitis symptoms, including transient hematuria, dysuria, urgency, and frequency, are most common [9]. Systemic reactions to BCG, including fever, pneumonitis, and miliary TB, are very rare [8,9].

We hypothesize that there may be a difference in the host factor for TB, and the presence of sequelae in chest radiography is a phenomenon reflecting such difference. Moreover, these host factors could eventually affect the local response to BCG intravesical instillation. Based on this, we evaluated the difference of adverse events, especially cystitis symptoms that is representative of local reaction after BCG instillation for NMIBC between patients with stable TB sequelae and those without sequelae by chest radiography. Additionally, the recurrence and progression of bladder cancer were analyzed to identify the differences in the effectiveness of intravesical BCG instillation based on the findings of chest radiography.

MATERIALS AND METHODS

We retrospectively analyzed 142 bladder cancer patients, who underwent transurethral resection of bladder cancers and intravesical BCG instillation, using medical records between 2001 and 2012. This study protocol was reviewed and approved by the institutional review board of the Inje University Busan Paik Hospital (IRB no. 15-0219). Patients without residual tumor and with a diagnosis of pathologic Ta or T1 stage were included. BCG was instilled intravesically after tumor resection, according to the following inclusion criteria: i) pathologic T1 disease, ii) high grade or grade 3, iii) carcinoma in situ, iv) two or more tumors, and (v) recurrent, large (>3 cm) pathologic Ta disease. Patients with any of the following were excluded: i) history of muscle-invasive bladder cancer (pathologic T2 or above stage), ii) history of radiotherapy for bladder cancer, iii) incomplete resection of bladder cancer, and iv) recurrence within 3 months after resection (indicative of residual tumor). The TNM classification and World Health Organization grading system (2004) were used for pathologic staging and tumor grading.

BCG vaccine, which consists of *Mycobacterium bovis* and produced by Oncotice (Merck Sharp & Dohme Corporation, Kenilworth, NJ, USA), was prepared for instillation by dissolving one vial in 50 ml of normal saline. After emptying the bladder using a Nelaton catheter, the prepared solution was instilled into the bladder through the catheter. Patients were instructed to retain the suspension for 2 hours if possible. An induction course with weekly BCG instillation for 6 weeks was performed in all patients. Following the induction course, a maintenance course involving weekly BCG instillation at 3, 6, 9, 12, 18, 24, and 36 months was performed, according to the decision of the clinician.

Chest radiography was performed in all patients for serial cancer staging. If chest radiography showed unclear results, high resolution computed tomography was performed and the patient was referred to a pulmonologist to confirm TB inactivity [10]. Following a confirmation of TB status, patients were divided into two groups: Group A, which included patients with visible sequelae of TB on chest radiography and group B, which included patients without visible sequelae. Patients who revealed active TB were excluded.

Basic demographics and clinical characteristics, including age, sex, pathologic T stage, grade, and tumor size, as well as nature (multiplicity and morphology) were analyzed in both groups. The type and incidence of cystitis symptoms were also compared between the two groups during the course of BCG induction. Cystitis symptoms were defined as transient hematuria, dysuria, urgency, and frequency after BCG intravesical instillation. The recurrence rates and progression rates were compared using a log-rank test. Kaplan-Meier survival curves were constructed to assess recurrence-free survival. IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA) was used for statistical analyses, and a value of $p<0.05$ was considered to indicate statistical significance.

RESULTS

Thirty-one patients (group A) had visible sequelae of TB on chest radiographs, and 111 patients (group B) had no sequelae. There were no significant differences in the characteristics of patients—except for age—between the two groups. Moreover, tumor characteristics—including pathologic T stage, grade, size, multiplicity and morphology—also did not differ (Table 1).

Table 1. Characteristics of groups A and B

Characteristic	Group A (n=31)	Group B (n=111)	p-value
Age (y)	72 (47-79)	63 (35-86)	0.005
Sex			0.327
Male	27 (87.1)	88 (79.3)	
Female	4 (12.9)	23 (20.7)	
Pathologic T stage			0.651
Ta	9 (29.0)	37 (33.3)	
T1	22 (71.0)	74 (66.7)	
Grade			0.837
Low	21 (67.7)	73 (65.8)	
High	10 (32.3)	38 (34.2)	
Tumor size (cm)			0.920
≤3	14 (45.2)	49 (44.1)	
>3	17 (54.8)	62 (55.9)	
Tumor number			0.110
Single	9 (29.0)	50 (45.0)	
Multiple	22 (71.0)	61 (55.0)	
Morphology			0.254
Papillary	26 (83.9)	101 (91.0)	
Nodular	5 (16.1)	10 (9.0)	
Recurrence	7 (22.6)	35 (31.5)	0.334
Progression	2 (6.5)	8 (7.2)	0.884

Values are presented as median (range) or number (%).
Group A: patients with visible sequelae of tuberculosis (TB) on chest radiography, group B: patients without visible sequelae of TB on chest radiography.

Table 2. Comparison of adverse events between groups A and B

Adverse events	Group A (n=31)	Group B (n=111)	p-value
Cystitis symptoms[a]	10 (32.3)	37 (33.3)	0.910
Anti-TB medication treatment[b]	1 (3.2)	1 (0.9)	
Prostate TB granuloma[c]	0 (0)	1 (0.9)	
Discontinuation of BCG therapy	1 (3.2)	3 (2.7)	0.876
Pulmonary TB	0 (0)	0 (0)	

Values are presented as number (%).
Group A: patients with visible sequelae of TB on chest radiography, group B: patients without visible sequelae of TB on chest radiography, BCG: bacillus Calmette-Guerin, TB: tuberculosis.
[a]This means persistent urinary symptoms as like dysuria, urgency, frequency and hematuria more than 24 hours after BCG instillation. [b]The patients included who treated anti-TB medication due to fever and prolonged cystitis symptoms even after 48 hours despite of supportive care. [c]Prostate TB granuloma was diagnosed pathologically by prostate needle biopsy.

A total of 47 patients experienced cystitis symptoms on urination, including transient hematuria, dysuria, urgency, and frequency during the induction course of BCG intravesical instillation. There were no statistically significant differences in the incidence of cystitis symptoms between the two groups (Table 2). One of them in each group received an anti-TB drug due to continuous urination symptoms despite supportive treatment. BCG treatment was discontinued in one patient in group A and three patients in group B, according to patients' wishes due to intolerable cystitis symptoms despite medication. One patient in group B was diagnosed with prostate TB granuloma after prostate needle biopsy. No patients were reported to have toxicities above grade 3. Moreover, active pulmonary TB was not detected in any patient.

Table 3 demonstrated the differences in characteristics of patients with cystitis symptoms between the two groups. Patients in group B had more papillary bladder tumor than those in group A, with statistical significance (p=0.004). Urine analysis and culture were performed in patients with cystitis symptoms when the symptoms first occurred (Table

Table 3. Characteristics of patients with cystitis symptoms between groups A and B

Characteristic	Group A with cystitis symptoms (n=10)	Group B with cystitis symptoms (n=37)	p-value
Age (y)	66.5 (47-77)	62.8 (39-82)	0.386
Sex			0.083
Male	10 (100.0)	28 (75.7)	
Female	0 (0)	9 (24.3)	
Pathologic T stage			0.852
Ta	3 (30.0)	10 (27.0)	
T1	7 (70.0)	27 (73.0)	
Grade			0.487
Low	5 (50.0)	23 (62.2)	
High	5 (50.0)	14 (37.8)	
Tumor size (cm)			0.820
≤3	5 (50.0)	20 (54.1)	
>3	5 (50.0)	17 (45.9)	
Tumor number			0.056
Single	2 (20.0)	20 (54.1)	
Multiple	8 (80.0)	17 (45.9)	
Morphology			0.004
Papillary	6 (60.0)	35 (94.6)	
Nodular	4 (40.0)	2 (5.4)	
Recurrence	2 (20.0)	8 (21.6)	0.911
Progression	1 (10.0)	2 (5.4)	0.598

Values are presented as median (range) or number (%).
Group A: patients with visible sequelae of tuberculosis (TB) on chest radiography, group B: patients without visible sequelae of TB on chest radiography.

Table 4. Results of urine analysis between groups A and B, from the patients with cystitis symptoms

Results of urine analysis	Group A with cystitis symptoms (n=10)	Group B with cystitis symptoms (n=37)	p-value
Symptoms with pyuria	8 (80.0)	21 (56.8)	0.180
Symptoms without pyuria	2 (20.0)	16 (43.2)	
Positive urine culture	0 (0)	2 (5.4)	0.452

Group A: patients with visible sequelae of tuberculosis (TB) on chest radiography, group B: patients without visible sequelae of TB on chest radiography.

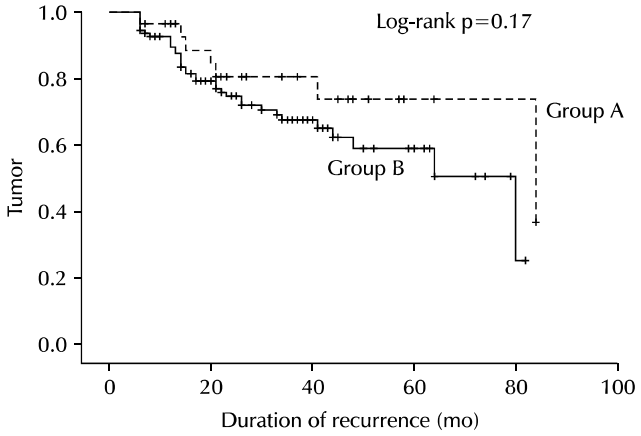

Fig. 1. Results of log-rank test regarding recurrence-free survival in groups A and B. Group A: patients with visible sequelae of TB on chest radiography, group B: patients without visible sequelae of TB on chest radiography.

4). In group A patients with cystitis symptoms, 80% (8 of 10) showed pyuria (5>HPF of white blood cell in microscopic exam); and 56.8% (21 of 37) of patients in group B with cystitis symptoms showed pyuria. However, there was no statistically significant difference between the two groups. Only two patients in group B with cystitis symptoms showed positive results of urine culture, but organism was not clearly identified due to a very small count of colonies.

The median follow-up periods were 41.8 (7-96) and 36.7 (6-90) months in patients of group A and group B, respectively. The recurrence rate was 22.6% in group A and 31.5% in group B (p=0.334). The progression rate was 6.5% in group A and 7.2% in group B (p=0.884; Table 1). Estimated overall median recurrence free survival was 67.7 months (95% confidence interval, 55.4-80.0) in group A and 55.7 months (48.7-62.6) in group B (p=0.17, Fig. 1).

DISCUSSION

Intravesical BCG instillation is generally accepted as the treatment of choice for carcinoma in situ and for the prevention of recurrence or prevention in cases of high-risk NMIBC after transurethral bladder cancer resection. The European Association of Urology currently recommends BCG maintenance therapy for at least one year [11]. The most widely used maintenance schedule is based on the Southwest Oncology Group (SWOG) regimen and is comprised of once weekly for six weeks for induction treatments followed by treatment once weekly for three weeks at 3, 6, 9, 12, 18, 24, 30, and 36 months after tumor resection [11-13]. Our institution has also been using the SWOG regimen, including maintenance therapy, for BCG instillation in NMIBC patients. The present study evaluated the symptoms of cystitis and other complications during a first 6-week induction period. The data is not shown, but toxicity with systemic complications was not shown during the period of maintenance treatment.

The precise mechanism underlying the effects of BCG in bladder cancer is unknown. However, the main mechanism of action involves a stimulation of innate immunity and an induction of an adaptive immune response to clear the residual cancer cells [14]. The immune response to BCG is comprised of two steps after intravesical instillation. First, BCG attaches to the bladder cancer cells within the urothelium by binding to the extracellular proteins, such as fibronectin and integrin [15]. BCG is then taken up by the bladder cancer cells, leading to an antitumor response mediated by various pro-inflammatory cytokines [16]. This immunologic reaction results in the induction of an adaptive immune response via T lymphocytes and killer cells activated by the presentation of mycobacterial antigens. This process leads finally to cancer cell destruction [14-16].

Intravesical BCG instillation can cause local and systemic adverse events due to immune reaction. Most adverse events are local, but systemic complications can also develop. In an early study, only 5% of patients had systemic complications, including severe events, such as sepsis and miliary tuberculosis [8,13]. Major trials have shown that both efficacy of maintenance BCG and minimization of adverse events were important for patients to complete BCG treatment [17,18]. Reducing the incidence of adverse

events is important for enhancing the efficacy and tolerability of BCG instillation, despite the majority of complications being local [19]. Therefore, it is important to control cystitis symptoms occurring during BCG intravesical instillation.

Efforts to reduce BCG toxicity by the administration of anti-TB drugs, such as Isoniazid (INH) or the antibiotic ofloxacin, or by a reduction of BCG doses, have been advocated. INH administration does not decrease BCG toxicity and is instead associated with liver toxicity; hence, prophylactic INH is not recommended [17,20]. Ofloxacin reduces local adverse events in the short term, but its long-term effect is unknown to date [21]. The EORTC trial 30,911 reported that reducing the dose of BCG (one-third of the full dose) and shortening the maintenance period to one year may decrease BCG toxicity and enhances tolerability. However, the oncologic efficacy was inferior to that of the full dose and three-year maintenance [20,22,23]. Most adverse events occurred within one year after BCG instillation; therefore, the occurrence of systemic adverse events is dependent on the host factors, not on the number of instillations [7,12,19]. Therefore, the host factors are also important to consider in controlling the adverse events of intravesical BCG instillation for NMIBC.

In Korea, vaccination against TB using BCG is a common method, and most people are exposed to TB during their life time unintentionally [24]. However, vaccination does not result in the formation of antibodies in all exposed people; they can become infected with TB, despite vaccination [25]. Host immunity is known to be the most important factor for whether TB is activated or becomes latent [24,25]. In this sense, sequelae of TB on chest radiography can be an indirect indication of immune response of the host.

We postulated that the host immunity to TB might influence the efficacy and toxicity of BCG instillation for NMIBC which uses the immune response in the bladder. This postulate is established from the assumption that the individual's host factor may be different from TB exposure response as previously described. Therefore, we thought that the difference of sequelae in chest radiography indirectly reflects the host immune status related to TB. Based on this assumption, we expected a different efficacy and adverse events in patients with tuberculosis sequelae on chest radiography, who had undergone BCG treatment for bladder cancer. However, no such differences between the two groups were detected. The present study showed that the incidence of cystitis symptoms were similar between the two groups. Although not statistically significant, pyuria tended to be more common in patients with sequelae of TB in chest radiography. It is likely that this relationship will be better explained if long-term studies are conducted with a larger cohort. Among patients with cystitis symptoms, cancers with papillary morphology were observed more in patients without visible TB sequelae than patients with TB sequelae in chest radiography. On the other hand, cancers with nodular morphology showed the opposite result. These results were statistically significant ($p=0.004$). However, the total number of subjects was small, and there was no evidence for correlation between the morphologies of cancer and local response after BCG intravesical instillation. Thus, the authors concluded that this was not a meaningful outcome that is consistent with the results of the present study.

The present study has several limitations. First, the number of patients and observation period were inadequate for generalization. Second, the study was not randomized or prospective. Third, the present study assumed that the host immunity was restricted to TB and did not reflect the general immune status at the time of BCG injection. However, we confirmed that BCG intravesical instillation for NMIBC would be safe and useful, regardless of the TB sequelae on chest radiography, retrospectively.

CONCLUSIONS

In conclusion, there was no difference in the adverse events associated with cystitis symptoms, the most bothersome and common symptoms of patients with BCG instillation for NMIBC according to the presence of tuberculosis sequelae by chest radiography. Moreover, the efficacy of BCG instillation does not appear to differ. However, if immunological studies are added based on the tendency of differences in the degree of inflammation in the urine test, it would help BCG treatment with better tolerance depending on individual immune status.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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