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Original Article

The Outcome of the Intravesical BCG Treatment in Naive Positive Tuberculin Skin Test Non-Muscle Invasive Bladder Cancer Patients

Shusit Parnitvitidkun, MD

Department of Surgery, Surin Hosipital, Surin, Thailand

Abstract

Purpose: **To study one-year outcome of intravesical Bacillus Calmette-Guerin (BCG) treatment in patients with non-muscle invasive bladder cancers.**

Materials and Methods: **From May 2008 to August 2009, 12 patients with primary non-muscle invasive bladder cancers were treated with TUR-BT followed by 6 weekly induction courses and maintenance of 3-, 6- and 12-month intravesical BCG treatment for recurrent tumor prophylaxis. Patients were divided into 2 groups: 7 with negative Purified Protein Derivative (PPD) skin test and 5 with positive skin test prior to the intravesical BCG treatment.**

Results: **There was only one recurrent patient in the negative PPD skin test group and 3 patients in positive PPD skin test had recurrence tumors.**

Conclusions: **In patients with primary naïve positive PPD skin test, the intra-vesical chemotherapy should be considered for treatment of primary non-muscle invasive bladder cancers instead of BCG.**

Key words: **BCG (Bacillus Calmette-Guerin), bladder cancer, PPD (Purified Protein Derivative)**

Introduction

Intravesical Bacillus Calmette-Guerin (BCG) therapy for superficial bladder cancer was introduced by Morales and associates in 1976[1]. The results of clinical trials suggest that intravesical BCG is one of the most effective treatments available for patients with superficial bladder cancer[2-5]. Intravesical BCG therapy has been reported to reduce tumor recurrent rates from 60 percent to 10-20 percent when used for prophylaxis[3,4] and to induce the regression of established superficial tumors[6,7], including carcinoma in situ[8,9] in approximately two-thirds of the patients. These results were superior to those achieved with endoscopic resection alone[2,3].

Several factors have been tested as potential prognostic indicators of response to BCG therapy, including purified protein derivative skin testing and granuloma formation in bladder biopsy specimens[10]. Kelly and associates reported in 1985 that there was a 70 percent recurrence rate for patients in whom PPD skin test did not convert to positive, while those who had positive results had a recurrence rate of approximately 20 per cent in the intravesical BCG treatment[11]. In the same year, Lamm DL reported the use of intravesical and percutanous BCG immunotherapy in transitional cell carcinoma patients. Only 4.5 per cent of patients in whom the purified protein derivative skin test results converted from

Correspondence address : *Shusit Parnitvitidkun, MD, Department of Surgery, Surin Hospital, Surin 32000, Thailand; Telephone: +66 4451 1757;Fax: +66 4451 8937;E-mail: shusit.uro@gmail.com*

negative to positive has had recurrent tumor, compared to 32 per cent in patients whose skin test were positive before treatment or failed to convert following treatment[12]. Badalament and associates in 1987 reported the effect of intravesical BCG alone in recurrent superficial bladder tumor patients. Patients with a reactive tuberculin skin test before and after induction BCG had significantly less tumor recurrence than patients with different PPD skin test results[13].

The present study analyzed the outcome of intravesical BCG therapy in primary non-muscle invasive bladder cancer patients with naïve positive tuberculin skin test.

Materials and Methods

Inclusion criteria were patients with primary non-muscle invasive bladder cancer TaG1, multiple lesions not TaG1 single lesion and T1 (2002 TNM classification of urinary bladder cancer and WHO grading 1973) treated with transurethral resection. After the histopathologic results were confirmed, the patients received purified protein derivative skin test. The 0.1 ml intermediate strength purified protein derivative was inoculated to the skin. A positive skin test was defined as an area of induration at least 1 cm in diameter 48 hours after challenge.

Two weeks after the operation, BCG intravesical therapy was performed. Pasteur strain BCG was used, with each ampoule containing 120 mg. with manufacturer specifications of approximately 10^7 colony-forming units per mg. The bladder was catheterized and emptied of urine, and 1 ampoule of BCG was reconstituted in 50 ml. sterile saline and instilled into the bladder. The patients were instructed to retain the vaccine for approximately 2 hours. BCG treatment was administered weekly for 6 weeks and then one on 3, 6 and 12 months. PPD skin test was repeated at the end of 6 weeks induction BCG intravesical treatment in the negative PPD skin test patients. Cystoscopy was done at the 3-month interval for 1 year.

Results

Between May 2008 and August 2009, 12 patients were recruited based on the criteria. Seven patients in negative PPD skin test groups were 4 males and 3 females, age ranged form 53 to 85 years (mean 70.8 years). The other 5 patients with positive skin test were all males, age ranged 39 to 83 years (mean 62.8 years). Routine pre-operative chest X-rays were normal in all patients. The tumor characteristics were as Table 1 & 2.

Table 1 Negative PPD skin test group

Type	Case
TaG2	2
TaG3	3
T1G2	1
T1G3	1

Table 2 Positive PPD skin test group

Type	Case
TaG1	2
TaG2	1
TaG3	1
T1G2	1

In the negative PPD skin test group, the conversions from negative to positive PPD skin test were 3 in 7 patients. The recurrence tumor was found in one patient, T1G3 with non conversion skin test on the 6th month post operation.

In the positive PPD skin test group, the recurrences occurred in 3 of 5 patients. The 2 non-recurrent patients in 1-year follow-up were TaG1 and TaG3. Two out of the 3 recurrent patients (TaG2, T1G2) developed at 3 months and the other one (TaG1) recurred at the end of the year.

Discussion

BCG is the attenuated mycobacterium developed as a vaccine for tuberculosis. It has demonstrated antitumor activity in several different cancers including urothelial carcinoma[1]. The original regimen described by Morales and Colleagues included a percutaneous dose, which was discontinued after success using a similar intravesical regimen by Brosmen[4].

The Southwest Oncology Group (SWOG) reported the most significant impact of maintenance therapy. Patients received a 6-week induction course followed by three weekly instillation at 3 and 6 months and every 6 months thereafter for 3 years. Estimated median recurrence - free survival was 76.8 months in

the maintenance cancer arm and 35.7 months in the control arm (p .001), but only 16% of patients tolerated the full dose-schedule regimen. Most authorities believe that at least 1 year of maintenance therapy is appropriate. The optimal treat schedule and dose for BCG have not been established[14].

According to the European Association of Urology, Guidelines on Ta-T1 non-muscle invasive bladder cancer 2006, the weighting used to calculate recurrence and progression score and probability of recurrence and progression varied with the score. Since the non-muscle invasive bladder cancer TaG1 single lesion (WHO grading 1973) has zero score on recurrence and progression, we excluded this type of tumor in the present study.

In 1981, Lamm and associates[3] reported 51 patients who presented with primary or recurrent biopsy-confirmed transitional cell carcinoma of the bladder within three-year patients were then randomly assigned by closed enveloped of receive standard surgical therapy (control), a standard surgical therapy plus BCG immunotherapy, intravesically and percutanously at weekly intervals for six weeks one to two week after transurethral tumor resection. The results showed that 11 of 24 control patients (46%) developed recurrent tumor compared with 5 of 23 BCG-treated patient (22%) (P = 0.125, Fisher's exact, 0.078 χ^2) Of the five patients who were PPD skin test positive prior to BCG immunotherapy, two developed tumor recurrence. Recurrence occurred only in one among 14 patients who converted from PPD skin test negative to positive[15].

In 1987 Badalament and associates reported maintenance versus non maintenance intravesical BCG therapy of superficial bladder cancer[13]. Ninety three patients with recurrent superficial bladder carcinoma were divided into 2 groups: only intravesical BCG 6 weekly dose group and plus monthly maintenance intravesical BCG 2 years group. PPD positive patients prior to therapy were 43% and 57% in maintenance and nonmaintenance groups respectively. Patients receiving maintenance and nonmaintenance therapy had similar tumor recurrent and progression rates. Patients with a reactive tuberculin skin test before and after induction BCG had significantly less tumor recurrences than patients with different PPD skin test results (p = .02). Tumor progression was not related to tuberculin skin testing[13].

In the group of negative PPD skin test (n = 7), there was only one recurrence in the non converted PPD skin test patient whereas 3 out of 5 positive PPD skin test patients had recurrent tumors. The result of negative skin test group was similar to those in other reports. While the positive PPD skin test group, the outcome was similar to the report of Lamm and associates in 1981 that the experimental group with primary or recurrent transitional cell carcinoma treated with intravesical and percutanous BCG had high recurrence rate[3]. Nevertheless, Badalament et al reported the study of maintenance and non-maintenance only intravesical BCG treatment in recurrent bladder cancer patient, the positive PPD skin test prior to the BCG treatment had a better outcome[13]. According to the recommendation by the Pediatric Society of Thailand, the BCG vaccination is administered for protection against tuberculosis or TB at birth.[16] Most Thai population, therefore, have positive PPD skin test. Furthermore, the variation in the route of BCG treatment and nature of the tumor may explain the different outcomes in our study compared with other studies.

Conclusions

The primary non-muscle invasive bladder cancer patients should be tested with purified protein derivative skin test before induction of the BCG intravesical treatment and the primary naïve positive PPD skin test non-muscle invasive bladder cancer patients should be considered to choose intravesical chemotherapy instead of intravesical BCG therapy.

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