



BRIEF REPORT

Trend of Frequency and Outcome of Reactive Arthritis in Japanese Patients with Bladder Cancer following Intravesical BCG Therapy over the Last 20 Years

Yoshinori Taniguchi^{1*}, Hirofumi Nishikawa¹, Yasuhiko Yoshinaga², Eri Amano¹, Shigeto Kobayashi³ and Yoshio Terada¹

¹Department of Endocrinology, Metabolism, Nephrology and Rheumatology, Kochi Medical School Hospital, Kochi University, Nankoku, Japan

²Rheumatic Disease Centre, Kurashiki Medical Center, Kurashiki, Japan

³Department of Rheumatology, Juntendo-Koshigaya Hospital, Koshigaya, Japan

*Corresponding author: Yoshinori Taniguchi, MD, Department of Endocrinology, Metabolism, Nephrology and Rheumatology, Kochi Medical School Hospital, Nankoku, 783-8505 Japan, Tel: +81-88-880-2343, Fax: +81-88-880-2344, E-mail: taniguchiy@kochi-u.ac.jp



Abstract

Reactive arthritis (ReA) is a sterile arthritis occurring in a genetically predisposed individual, secondary to an extra-articular infection, usually of the gastrointestinal or genitourinary tract. Intravesical instillation of Bacillus Calmette-Guerin (iBCG) is used as an effective immunotherapy of bladder cancer. Despite of the clinical efficacy, ReA could develop as adverse event and the frequencies are known as about 0.5 to 1% in Western countries and 2.0% in Japan. However, the trend of frequency and outcome of iBCG-induced ReA in Japanese patients have not been assessed in multi-centre studies. Herein, Japanese patients who received iBCG ($n = 555$) for bladder cancer from March 1997 to February 2017 were retrospectively assessed. Of the 555 cases, ReA was revealed in 11/555 (2.0%). Although the protocol of iBCG therapy was not statistically different over the 20 years, but a half dose of iBCG was used in 2007 to 2017 more than in 1997 to 2007. Despite the increase of the use of half dose of iBCG in 2007 to 2017, the overall frequency of iBCG-induced ReA was not significantly different between from 1997 to 2007 and from 2007 to 2017 (2.1% and 1.9%, respectively). This suggests that the development of iBCG-induced ReA was dose-independent. Furthermore, all iBCG-induced ReA, even if revealing sacroiliitis, did not progress to chronic peripheral arthritis type and spondyloarthritis over the last 20 years.

Keywords

Reactive arthritis, BCG, Bladder cancer, Incidence, Trend, Outcome

Brief Report

Reactive arthritis (ReA) is a sterile arthritis occurring in a genetically predisposed individual, secondary to an extra-articular infection, usually of the gastrointestinal or genitourinary tract [1,2]. Intravesical instillation of Bacillus Calmette-Guerin (iBCG) is used as an effective immunotherapy of bladder cancer [3]. In contrast to the clinical efficacy, ReA could develop as adverse event and the frequencies are known as about 0.5 to 1% in Western countries [4-7]. We recently reported about the clinical characteristics and the frequency 2.0% of iBCG-induced ReA in patients with bladder cancer in Japan [8,9]. However, the trend of frequency and outcome of iBCG-induced ReA in Japanese patients have not been assessed in multi-centre studies.

Herein, the clinical findings of Japanese patients who received iBCG ($n = 555$ [250 and 305 in Kochi Medical School Hospital and Kurashiki Medical Center, respectively]) for bladder cancer from March 1997 to February 2017 were retrospectively assessed, with specific attention to patients with ReA. Especially, iBCG-induced ReA patients diagnosed from 1997 to 2007 were compared with iBCG-induced ReA diagnosed from 2007 to 2017 because of the change of using iBCG dosage, and

Table 1: Background of enrolled patients.

	Total
Number of patients received iBCG therapy	555 cases
Male/Female ratio	438/117 cases
Mean age \pm SD (years)	72 \pm 10
T stage of bladder cancer (Tis/Ta/T1/T2)	158/209/158/30 cases
Cellular atypism (G1/G2/G3)	146/283/126 cases

iBCG: intravesical Bacillus Calmette-Guerin; Tis: carcinoma *in situ*; Ta: noninvasive papillary cancer; T1: invasion to submucosa; T2: invasion to muscle layer; G1: low-grade; G2: low-grade and high-grade; G3: high-grade cancer.

Table 2: Dosage of iBCG and trend of frequency of iBCG-ReA between 1997-2007 and 2007-2017.

	1997-2007 (187 cases)	2007-2017 (368 cases)
iBCG dose (Immunobladder [®])	80 mg/dose in 143/187 cases; 40 mg/dose in 44/187 cases; 80 mg/dose in 3 developed cases 40 mg/dose in 1 developed case	80 mg/dose in 102/368 cases; 40 mg/dose in 266/368 cases; 80 mg/dose in 2 developed cases; 40 mg/dose in 5 developed cases
Frequency	4/187 cases (2.1%)	7/368 (1.9%)

ReA: Reactive Arthritis; "developed case" means case developed ReA.

Table 3: Outcome of iBCG-ReA between 1997-2017.

Outcomes	1997-2017 n (%), total 11 cases
Recovery	11/11 cases (100%)
Relapse	0/11 cases (0%)
Spondyloarthritis	0/11 cases (0%)

ReA: Reactive Arthritis; Recovery is defined as maintenance of remission; Relapse is defined as flare of arthritis.

we studied the trend of frequency. Furthermore, we also assessed outcomes of iBCG-induced ReA patients over the 20 years. This study was approved by the Ethics Committee and conducted in accordance with the Declaration of Helsinki.

Patients' mean age was 72 \pm 10 years and male/female ratio was 438/117. As background of 555 patients received iBCG, T stage of bladder cancer (Tis/Ta/T1/T2) was 158/209/158/30 cases, respectively, and moreover, cellular atypism (G1/G2/G3) was 146/283/126 cases, respectively (Table 1). ReA was diagnosed according to the Berlin diagnostic criteria for ReA [10]. Of the 555 cases, ReA was revealed in 11/555 (2.0%) as shown in previous report [9]. There were no significant relationships between T stage of bladder cancer, cellular atypism and development of iBCG-induced ReA. Although the protocol of iBCG therapy was not statistically different over the 20 years, but a half dose of iBCG was used in 2007 to 2017 more than in 1997 to 2007. Despite the increase of the use of half dose of iBCG in 2007 to 2017, the overall frequency of iBCG-induced ReA was not significantly

different between from 1997 to 2007 and from 2007 to 2017 (2.1% and 1.9%, respectively) ($p = 0.13$) (Table 2). Finally, we assessed the outcome of iBCG-induced ReA once improved after treatment with oral prednisolone, celecoxib and isoniazid. All iBCG-induced ReA patients, even if with sacroiliitis, did not progress to chronic peripheral arthritis type and spondyloarthritis (SpA), especially pure axial SpA, as outcomes (Table 3).

As shown in our recent report, the frequency of iBCG-induced ReA in the Japanese population was 2.0% [9], greater than the 0.5-1% reported in the Western countries [4-7]. Recently, it has been reported that the time to revisit the concept of ReA is coming [1]. Recent report from French group compared ReA patients between 2002 and 2012 with ReA patients between 1986 and 1996 and concluded that while the incidence of *Chlamydiae trachomatis* has decreased, new microbes including BCG, *Mycoplasma* and *Strongyloides stercoralis* were found to be involved [11]. However, the trend of frequency and outcome of iBCG-induced ReA in Japanese patients have never been assessed. The present study demonstrates that overall frequency of iBCG-induced ReA in Japan was stable, despite the tendency of difference of iBCG dosage. iBCG dosage might be independent on the onset or etiology of iBCG-induced ReA. The number of iBCG therapy for bladder cancer is increased now, and therefore the increase of BCG-related ReA will continue in future.

Some cases of iBCG-induced ReA could develop to chronic peripheral arthritis type and SpA in the Western countries, although the frequencies were unknown [4]. On the other hand, no progression from iBCG-induced ReA to SpA, especially pure axial SpA, was observed in the present study, even if revealing sacroiliitis. Recent report showed 92% of HLA-B27 positive ReA patients developed SpA compared with 10% of HLA-B27 negative patients in the 2002-2012 cohort [11]. This might indicate that no progression to SpA in iBCG-induced ReA patients in the present study might be caused by the low rate (0.3%) of positivity for HLA-B27 in the Japanese population [12].

This study has several limitations. This was a retrospective study performed in only a limited number of Japanese patients at two centers. The evaluation of iBCG-induced ReA before and after treatments could have been conducted prospectively in a larger number of patients.

In conclusion, the trend of frequency of iBCG-induced ReA in Japan has been stable, despite the difference of iBCG dosage. Furthermore, all iBCG-induced ReA did not progress to chronic peripheral arthritis type and SpA over the last 20 years.

Key Points

The trend of frequency of iBCG-induced ReA has been stable and could be iBCG dose-independent. Fur-

thermore, all iBCG-induced ReA did not progress to chronic peripheral arthritis type and SpA over the last 20 years in Japan.

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Conflict of Interest

None.

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