RESEARCH ARTICLE

Are there Time-period-related Differences in the Prophylactic Effects of Bacille Calmette-Guérin Intravesical Instillation Therapy in Japan?

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Abstract

Objective: The guidelines on indications for prophylactic use of Bacille Calmette-Guérin (BCG) against non-muscle-invasive bladder cancer (NMIBC) have changed over the years. In order to assess the impact on outcome, the present retrospective comparison of BCG efficacy by time period with Japanese patients was conducted. Patients and Methods: A total of 146 cases of NMIBC treated with BCG since February 1985 were retrospectively evaluated. All patients received 80 mg of BCG (Tokyo 172 strain) six to eight times a week for prophylactic use. Comparison was made among three historical groups (Group A: 1980's, 39 cases; Group B: 1990's, 61 cases; Group C: 2000's, 46 cases). Results: In total, recurrence was seen in 55 of the 146 cases (37.7%), and progression in 14 (9.6%), 1 patient dying of cancer. These overall results were similar to those outlined in previous reports. However, the outcomes of this time-period-based analysis indicated a tendency for a shorter time to recurrence in patients after 2000, although a log-rank test showed no significance (P=0.229). Seven of the cases featuring progression (i.e., half of all such cases) were among the 46 Group C patients (15.2%). Excluding these progressive cases, there was no significant difference among the remaining 132 patients in the three groups. Conclusion: This study results revealed a tendency for a lower non-recurrence rate after 2000 in our series. This could stem from a number of factors, including changes in BCG indication criteria and the evolution of histopathological diagnostic criteria.

Keywords: Bacille Calmette-Guérin - non-muscle-invasive bladder cancer - time period - Japanese patients

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Introduction

BCG intravesical instillation therapy has been the gold standard option for NMIBC in the two decades (Smith et al., 1999; Oosterlinck et al., 2001; http://www.nccn.org; http://www.uroweb.org; http://www.auanet.org; Schwaibold et al., 2006). Initially, no generally accepted guidelines were available, and there was no risk classification. However, a first guideline for BCG indication was published by the American Urological Association (AUA) (Smith et al., 1999), and subsequently many similar guidelines were issued by the European Association of Urology (EAU) (Oosterlinck et al., 2001) and the National Comprehensive Cancer Network (NCCN), with change year by year (http://www.nccn.org; http://www.uroweb.org; http://www.auanet.org). In particular, options for prophylactic use of BCG against NMIBC have been revised, because of modification in pathological diagnostic classification, introduction and building a consensus regarding re- trans urethral resection (TUR) procedures (Sivalingam et al., 2005; Schwaibold et al., 2006; Maurizio et al., 2012), and other technical or mechanical improvements. However, there have been no publications concerning variation in outcome due to change in the guidelines for BCG application. We therefore conducted a retrospective comparison to clarify differences in BCG efficacy by time period.

Patients and Methods

A total of 146 cases of NMIBC treated with BCG (Tokyo 172 strain purchased from Nihon BCG Manufacturer, Tokyo) after trans urethral resection of bladder tumor (TUR-Bt) since February 1985 were retrospectively evaluated, all with follow-up observation periods of more than three years (38 to 164 months (average 75.7)). Patients with primary and concomitant carcinomas in situ or bladder cancers with muscle invasion (more than stage pT2) were excluded from the present series, together with those undergoing previous urinary tract open surgery, or given intravesical or general chemotherapy. All the patients initially received 80mg

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BCG 6-8 times once a week for prophylaxis. The age range was from 36-85 (average 66.7), with a male: female ratio of 126:20 (86.3%:13.7%). All patients had a history of either multifocal and/or recurrent stage Ta or T1 papillary urothelial carcinoma (UC) (Ta:T1=71:75, without any other concurrent malignancies or active tuberculosis infection. Tumor grades were G1/G2/G3=35(24.0%)/84(57.5%)/27(18.5%), and numbers were single/2-3/4 or more =36(24.7%)/41(28.0%)/69(47.3%). Recurrence and non-recurrence cases were 68(46.6%) and 78(53.4%) respectively, before the initial BCG treatment. The 146 cases were divided into three historical groups (Group A: 1980's, 39 cases; Group B: 1990's, 61 cases; and Group C: 2000's, 46 cases), for inter-comparison.

BCG treatment was terminated before the course of 6-8 instillations could be performed in a number of cases, but a minimum of 4 applications was performed in all. The patients were asked to refrain where possible from urination within two hours of the instillation and were monitored for bladder irritation, temperature change and other clinical symptoms. A tuberculin test, blood examinations, chest X-rays, cystoscopy and urinary cytology were conducted in all cases prior to BCG instillation and also at other times when considered appropriate.

Follow up was performed once a week during the weekly treatment periods, and then every 1-3 months after cessation of treatment, depending on the patients' situation. Recurrence with progression was defined with reference to muscle invasive disease (Schwaibold et al., 2006). Recurrence free survival was defined as the period elapsed between the last BCG induction instillation.

Surgically resected materials were routinely fixed in 10% buffered formalin and embedded in paraffin for sectioning and histopathological assessment of hematoxylin and eosin stained sections. Tumor grading and staging were performed with reference to the 3rd edition of the "General Rules for Clinical and Pathological Studies on Bladder Cancer of the Japanese Urological Association and the Japanese Society of Pathology ".

Univariate statistical analyses were accomplished using Fisher's exact test, and multivariate analyses were conducted with Cox's hazard model. Cumulative non-recurrence rates were estimated using the Kaplan-Meier method, and the significance of differences between curves was tested by the Log-rank test. A value of $p<0.05$ was considered statistically significant. Simple linear regression analysis was used to determine the correlation coefficient between the period of BCG treatment and clinical variables. All the statistical analyses were performed using SPSS Version 17.

Results

In total, recurrence was seen in 55 of the 146 cases (37.7%). Three and 5 year recurrence free rates were 69.9% and 64.7%. This result was similar to those outlined in previous and recent reports (Okamura et al., 1996; Smith et al., 1999; Oosterlinck et al., 2001; Martínez-Piñeiro et al., 2005; Margel et al., 2007; Ojea et al., 2007; Sylvester et al., 2011; Maurizio et al., 2012; Cho et al., 2012; Librenjak et al., 2012; Meijer et al., 2012; Segal et al., 2012). Patient characteristics of each group are summarized in Table 1. Instillation time was decreased from the 1990's, dose was reduced, T1 stage was decreased, and multiple tumor cases increased over the three time periods, all demonstrating significant alteration. Figure 1 illustrates recurrence free

Table 2. Prospective BCG Treatment Study References Published in Japanese Patients

Publish	Entrée year	No of patients	References
1994	1982	22	Acta Urol Jpn 40:873
1989	1984	44	Jpn J Urol 80:1459
1993	1984	50	Jpn J Urol 84:656
1993	1984	52	Jpn J Urol 84:656
1995	1985	37	Int Urol and Nephrol27:723
1995	1985	37	Int Urol and Nephrol27:723
1990	1985	23	Jpn J Urol 81:1459
1991	1985	33	Jpn J Urol 82:290
1994	1986	103	Ann Soc BCG BRM Imm18:79
1993	1986	45	Ann Soc BCG BRM Imm17:39
1993	1987	34	Acta Urol Jpn 39:987
1992	1988	34	Ann Soc BCG BRM Imm16:79
1996	1992	20	Nishinihon J Urol 58:538
1997	1992	13	Ann Soc BCG BRM Imm 21:87
1997	1992	13	Ann Soc BCG BRM Imm 21:87
2003	1996	39	Int J Urol 10:183
2003	1996	41	Int J Urol 10:183
2001	1996	50	Urol Int 67:289
2009	1997	106	Acta Urol Jpn 55:175
2006	1998	40	Urology67:545
2008	1999	396	Int J Urol 16:279
2011	2004	83	BJU Int 108:187

Table 1. Patients' Characteristics of BCG Treatment in Three Different Age Groups

Categories		1980's N=39	1990's N=61	2000's N=46	p-value
Age	Median (Range)	67(36-85)	67(44-83)	68.5(50-83)	0.27
Gender	Male : Female	32:07:00	55:06:00	39:07:00	0.483
Instillation time	≤5 : 5<	0:39	9:52	3:43	0.028*
Dose	40mg : 60mg : 80mg	0:00:39	1:02:58	21:07:18	0.000*
Grade	G1 : G2 : G3	13:18:08	12:35:14	10:31:05	0.212
Stage	pTa : pT1	12:27	27:34:00	32:14:00	0.001*
Single/Multiple	Single : Multiple	13:26	15:46	7:39	0.148
Number of tumors	1 : 2-3 : 4 or more	13:10:16	15:25:21	8:06:32	0.002*
Primary/Recurrent	Primary : Recurrent	21:18	29:32:00	18:28	0.391
Risk	Low : Intermediate : High	2:29:08	4:43:14	1:40:05	0.378

*significantly different

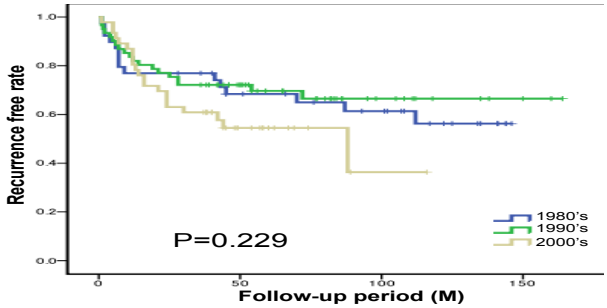

Figure 1. Recurrence Free Survival Curves After BCG Treatment by Decade.

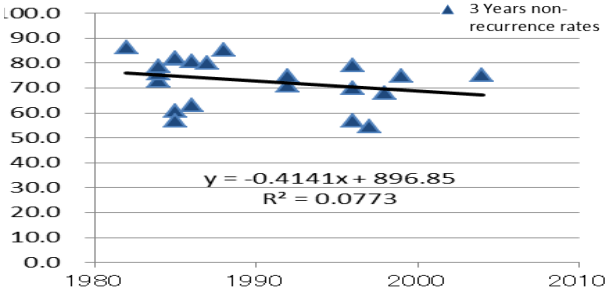

Figure 2. Analysis of the Correlation between the Year of Starting BCG Treatment and 3-year non-recurrence Survival from the 22 References Published in Japanese Patients.

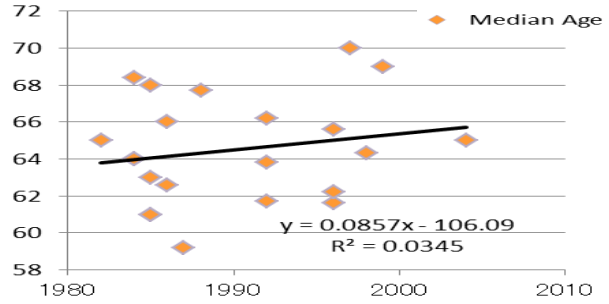

Figure 3. Median age distribution of Japanese patients' literatures by age.

curves after BCG treatment by decade. Three and 5 year recurrence free rates were 76.9 % and 68.4% in the 1980's, 72.1% and 69.6% in the 1990's, and 60.9% and 54.5% in the 2000's. The outcomes of this time-based analysis indicated a tendency for a shorter time to recurrence in patients after 2000, although a log-rank test showed no significance (P=0.229). Patients' age was separated to 50 or less, 51-60, 61-70, 71-80, 81 or more, and analyzed for each decade, and statistical analyses indicated a negative role for age only in the 1990's (P=0.077 in 1980's, P=0.019 in 1990's, and P=0.224 in 2000's) although low numbers limited the power of the analysis. Grade distribution was almost the same in each decade. Stage variation showed a tendency for decrease in recent years. There were no differences tumor multiplicity, episodes of recurrence, and risk categories, comparing across decades.

Progression with recurrence was seen in 14 cases (9.6%), and 1 patient died of cancer. Seven of the cases of progression (i.e., half of all such cases) were among the 46 Group C patients (15.2%). Excluding these progressive cases, there were no significant differences among the remaining 132 patients in the three groups.

Discussion

In our study, the results indicated a tendency for a lower non-recurrence rate since 2000, which might be related to differences in the background characteristics, like greater average numbers of tumors per case, increased low dose cases in the 2000's. We believe that this finding is the first such report in the literature concerning BCG intravesical instillation therapy.

Clearly, a number of factors might account for our findings. In the 1980's, BCG was introduced as a promising treatment option for recurrent NMIBC (the initial term being superficial bladder cancer). Therefore BCG became used worldwide, but many severe adverse effects were reported, including anaphylactic shock, arthritis, Reiter's syndrome, general tuberculosis infection, and contracted bladder. In view of this evidence, applied doses have been reduced (Ojea et al., 2007; Yoneyama et al., 2008) as was also shown by our data. However, most dose-dependent comparisons showed not variation in efficacy with the dose (Martínez-Piñeiro et al., 2005; Sylvester et al., 2011). BCG indication criteria have also been changed so that more strict attention to the selected patients has been given year by year in the US and other countries (AUA, EAU, NCCN guidelines) (http://www.nccn.org; http://www.uroweb.org; http://www.auanet.org). Japan also has changed the applied criteria (bladder cancer practice guideline: Japanese Urological Association: 2009). Our analysis of 22 BCG bladder instillation papers dealing with Japanese patients (Tachibana et al., 1989; Yamamoto et al., 1990; Yabusaki et al., 1991; Ozono et al., 1992; Ao et al., 1993; Kano et al., 1993; Tachibana et al., 1993; Irie et al., 1994; Tanaka et al., 1994; Takashi et al., 1995; Ao et al., 1996; Ozono et al., 1997; Tozawa et al., 2001; Irie et al., 2003; Hinotsu et al., 2006; Kikuchi et al., 2009; Segawa et al., 2009; Hinotsu et al., 2011) revealed a similar tendency for lower 3-year non-recurrence with year of starting BCG treatment as found here (see Fig. 2).

Change of histopathological bladder cancer grading and staging criteria could clearly exert an influence and the distinction between high malignant potential and non-invasive low malignant potential tumors has received more emphasis. Consequently, the name of superficial bladder cancer has been changed to NMIBC and in Japan the pathological classification modified from T1a and T1b to T1 only in the 1990's. However, in our series the more recent cases were more likely to be Ta rather than T1, contrary to expectation from the lower non-recurrence rate.

Increasing patient age is another possible factor and in our series, patients' age overall was significantly different between recurrence and non-recurrence cases (P=0.023). In fact patients' age at BCG application has shown a tendency of increase in the 22 Japanese papers we analyzed (Tachibana et al., 1989; Yamamoto et al., 1990; Yabusaki et al., 1991; Ozono et al., 1992; Ao et al., 1993; Kano et al., 1993; Tachibana et al., 1993; Irie et al., 1994; Tanaka et al., 1994; Takashi et al., 1995; Ao et al., 1996; Ozono et al., 1997; Tozawa et al., 2001; Irie et al., 2003; Hinotsu et al., 2006; Kikuchi et al., 2009; Segawa et al., 2009; Hinotsu et al., 2011). Fig 3 shows a

tendency for increase in more elderly patients receiving BCG treatment over time. There have been published several papers of less efficacy of BCG for elderly patients including our own report (Joudi et al., 2006; Kohjimoto et al., 2010; Okamura et al., 2010; Margel et al., 2011). This point could be supportive in our speculation.

To increase the efficacy of BCG maximally, BCG treatment recommendation or guideline could be more soften for the patients with multiple recurrent low grade tumors, who refused surgery, or who cannot perform surgery for severe complications, because many urologists have been used to adverse effects of BCG these days. On the other hand, long-term outcome of efficacy treated with high-risk NIBC has been reported as poor prognosis, and the author suggested that rethinking the paradigm shift of this disease very recently (Thomas et al., 2012).

In conclusion, This study results revealed a trend showing a low non-recurrence rate since 2000 in Japan. This is thought to stem from a number of factors, including changes in BCG indication criteria and the evolution of histopathological diagnostic criteria.

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