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ORIGINAL ARTICLE

Single monthly bacillus Calmette-Guérin intravesical instillation is effective maintenance therapy to prevent recurrence in Japanese patients with non-muscle-invasive bladder cancer

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Abstract
Background A series of bacillus Calmette-Guérin (BCG) bladder instillations is the gold standard therapy to prevent recurrence after transurethral resection of bladder tumor (TUR-Bt) of non-muscle-invasive bladder cancer (NMIBC). However, in some cases the outcome is not optimal with the standard 6- to 8-week protocol and therefore interest has focused on additional maintenance therapy. The present study was conducted to assess the utility of single monthly intravesical instillation treatments for up to 1 year in Japanese patients.
Methods A total of 75 stage Ta and T1 patients who had undergone TUR-Bt were retrospectively evaluated, all first receiving 80 mg BCG (Tokyo 172 strain) given once a week, 6–8 times, for primary prophylaxis. Comparison was then made of groups with (group A, 48 patients) and without (group B, 27 patients) additional maintenance BCG therapy given once a month 6–8 times.
Results Recurrence-free survival rates at 5 years in groups A and B were 83.0 and 51.9% ($P = 0.006$), despite the greater proportion of T1 patients and the longer follow-up period in the group A patients. Significant protection against recurrence persisted on multivariate analysis with adjustment for age, stage, grade, and tumor number.
Conclusions These findings indicate maintenance BCG therapy of single intravesical instillations given once a month with our protocol to be definitely effective for prophylactic use, especially in stage Ta patients. Further evaluation of parameters such as the continuance period and dose protocol is warranted.

Keywords Bacillus Calmette-Guérin · Non-muscle-invasive bladder cancer · Intravesical instillation · Maintenance therapy

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Introduction

Intravesical bacillus Calmette-Guerin therapy has found world-wide application for reducing the risk of progression or recurrence in patients with stage Ta, T1 non-muscle-invasive bladder cancer (NMIBC) [1–6]. This therapy is also effective for carcinoma in situ (CIS) [1, 7]. However, with the standard protocol, especially in high-risk stage Ta, T1 NMIBC cases, lesions may recur; thus, maintenance BCG therapy has been introduced as a further control measure.

In 1987, Badalament et al. [8] first evaluated the effectiveness of monthly maintenance BCG therapy in 93 patients with polychronotopic superficial papillary carcinoma and CIS, but differences in tumor reduction, and in recurrence and progression rates between the treatment group and patients not receiving such therapy were not significant. However, in 2000, Lamm et al. [7], in a randomized South West Oncology Group Study, reported the effectiveness of 3-week courses of maintenance instillations of BCG given at 3, 6, 12, 18, and 24 months. Sylvester et al. [1] also showed the efficacy of maintenance BCG treatment for NMIBC and CIS in a meta-analysis of all available data from randomized clinical trials.

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Subsequently, in 2007, Ali-El-Dein [9] reported that single monthly instillations of 120 mg BCG given for 1 year were as effective as 3-week courses of maintenance BCG given at three-monthly intervals, in terms of recurrence and progression rates, and the single instillation regimen had lower toxicity. In line with these findings, BCG maintenance therapy for high-risk stage Ta, T1 NMIBC is recommended in guidelines for Europe and the United States. There are no such guidelines for Japan, and the optimal dose and interval for this treatment have not been standardized in our country [10, 11]. Therefore, we performed the retrospective study reported here to investigate the efficacy of monthly BCG maintenance therapy (80 mg Tokyo 172 strain, given 6–8 times), in a series of Japanese patients, by comparing results in these patients with results in others not receiving such therapy during the same time period.

Patients and methods

From March 1989 to January 2006, 213 patients were treated in our group hospitals with intravesical instillations of BCG (Tokyo 172 strain, purchased from Nihon BCG, Tokyo, Japan) after transurethral resection of bladder tumor (TUR-Bt) for NMIBC. Patients with primary and concomitant carcinomas in situ or bladder cancers with muscle invasion (more than stage pT2) were excluded from the present series, as were those who had undergone previous urinary tract open surgery, or intravesical or general chemotherapy (total number of patients excluded was 138). The remaining 75 patients, who formed the present study cohort, had all initially received 80 mg BCG once a week, given 6–8 times, for prophylaxis. Comparison was then made of two patient groups, with (group A, 48 patients) and without (group B, 27 patients) additional maintenance BCG therapy, consisting of a single intravesical instillation, given once a month 6–8 times. The age range was from 36 to 84 years (average 64) in group A and from 50 to 83 years (average 68) in group B, with male: female ratios of 42:6 (87.5:12.5%) and 24:3 (88.9:11.2%), respectively. All patients had a history of either multifocal and/or recurrent stage Ta or T1 papillary urothelial carcinoma (UC) (Ta:T1 = 16:32 in group A and Ta:T1 = 14:13 in group B), without any other concurrent malignancies or active tuberculosis infection. Tumor grades were G1/G2/G3 = 11 (22.9%)/26 (54.2%)/11 (22.9%) in group A and G1/G2/G3 = 3 (11.1%)/17 (63.0%)/7 (25.9%) in group B, and number of tumors were single/2–3/4 or more = 16 (33.3%)/13 (27.0%)/19 (39.7%) in group A and 6 (22.2%)/7 (25.9%)/14 (51.9%) in group B. Numbers of recurrences before the initial BCG treatment were none/1/2 = 26 (54.1%)/19 (39.6%)/3 (6.3%) in group A and 17 (63.0%)/8 (29.6%)/2 (7.4%) in group B. The follow-up periods ranged from 38 to 146 months (average 102) in group A, and from 42 to 125 months (average 66) in group B, the value for the maintenance treatment group being significantly longer ($P = 0.002$, U-test). Patient characteristics are summarized in Table 1.

BCG maintenance administered 6–8 times, in line with the literature, was decided by the attending doctor or after group discussion according to the condition and/or coexisting diseases for each patient. BCG treatment was terminated before the course of 8 instillations could be performed in a number of patients, but a minimum of 6 instillations was performed in all. The patients were asked to refrain, where possible, from urination within 2 h 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 patients prior to BCG instillation and also at other times when considered appropriate.

Follow up was performed once a week during weekly treatment periods, and then every 1–3 months after the cessation of treatment, depending on the patient's situation. Progression was defined as progression to muscle-invasive disease [1], and progression was also regarded as recurrence. Recurrence-free survival was defined as the period elapsed between the last BCG induction instillation and recurrence or progression.

Table 1 Patients' characteristics

	Maintenance (+)	Maintenance (−)	P value
Number of patients	48	27	
Age (years)	64 (36–84)	68 (50–83)	0.507 (U-test)
Gender	42:6:0	24:3:0	0.999 (Fisher's exact test)
Grade (1:2:3)	11:26:11	3:17:7	0.452 (χ^2 test)
Stage (Ta:T1)	16:32	14:13	0.116 (χ^2 test)
Number of tumors (1:2–3:4↑)	16:13:19	6:7:14	0.515 (χ^2 test)
Number of recurrences (0:1:2)	29:16:3	17:8:2	0.938 (χ^2 test)
Observation period (months)	102 (38–146)	66 (42–125)	0.002 (U-test)

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 [12].

Univariate statistical analysis was accomplished using Fisher's exact test, and multivariate analysis was conducted with Cox's proportional hazard model. Cumulative (non-recurrence, progression-free survival) 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 as statistically significant. All the statistical analyses were performed using SPSS Version 17 (SPSS, Chicago, IL, USA).

Results

Recurrence-free survival rates at 5 years in groups A and B were 83.0 and 51.9% [$P = 0.006$, log-rank (Mantel-Cox)], despite the greater proportion of T1 patients and the longer follow-up period in group A patients. Kaplan–Meier curves showed an obvious difference between the two groups (Fig. 1). Comparing Ta and T1 stage differences, there was a significant difference in recurrence-free survival only in group A ($P = 0.005$, Fig. 2a), with group B showing $P = 0.376$ (Fig. 2b). Comparing groups A and B, log-rank analysis showed a significant difference for Ta ($P = 0.004$, Fig. 2c), but not for T1 ($P = 0.057$, Fig. 2d). According to age distribution, there was a significant difference in group A ($P = 0.023$), only solitary (single) cancer cases were significantly different between the existence of maintenance treatment ($P = 0.008$), and no recurrent case has significant difference in maintenance cases ($P = 0.037$). However, there was no significant difference between groups A and B in gender or tumor grade.

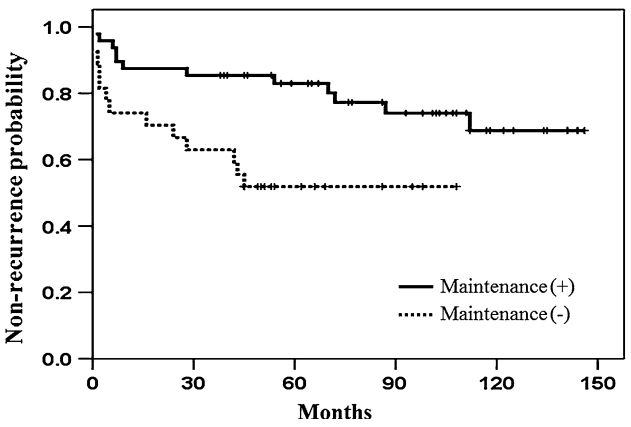

Fig. 1 Recurrence-free survival curves comparing patients with and without maintenance bacillus Calmette-Guérin (BCG) treatment

Progression-free survival rate curves for group A (maintenance BCG treatment) and group B (no additional maintenance) showed no significant difference.

Most of the patients experienced irritative voiding symptoms including pain on urination, and increased urinary frequency during induction treatment. Gross hematuria and temperature elevation (38°C or higher) were found at incidence rates of less than 30% in each group, but there were no severe adverse events. There was no arthritis, tuberculous infection, or other rare adverse events during BCG treatment in any of the patients.

Table 2 shows the results of the univariate and multivariate analyses of the maintenance BCG treatment. Significant protection against recurrence was shown on maintenance treatment ($P = 0.009$) in the univariate analysis, and in the multivariate analysis, the significant protection against recurrence persisted with adjustment for stage ($P = 0.015$) and maintenance treatment ($P = 0.002$).

Discussion

Our present retrospective data demonstrated that additional maintenance BCG therapy, consisting of a single intravesical instillation, given once a month, 6-8 times, was effective for Japanese NMIBC patients with Ta lesions. Although only borderline significance was demonstrated for T1 cases ($P = 0.057$), we consider this indicative of NMIBC given the relatively small number of cases, and generally our data are in line with the findings of Koga et al. [10], who investigated the efficacy of 4 maintenance instillations after BCG induction therapy for Ta/T1/CIS. Our data are also in line with the findings of Hinotsu et al. [11], who followed the same 3-week 3-month regimen as that of Lamm et al. [7]; this latter maintenance protocol was recommended in the guidelines for high-risk NMIBC in the West [7], but the completion rate in the study reported by Lamm et al. [7] was less than 50%, and this area is still controversial. Problems with patient compliance were not encountered with the same protocol in Japan [11]. All the patients in our group A were given 6 monthly instillations, but in some, further instillations were contraindicated because of adverse side effects. In the study reported by Koga et al. [10], with only four instillations, there was no problem with completion. Whether the strain of BCG might exert an influence is a question for future research, although both Lamm et al. and Hinotsu et al. used the same Connaught strain [7, 11].

The sources of bladder cancer recurrence are considered to be preclinical lesions, persisting CIS, and implantation

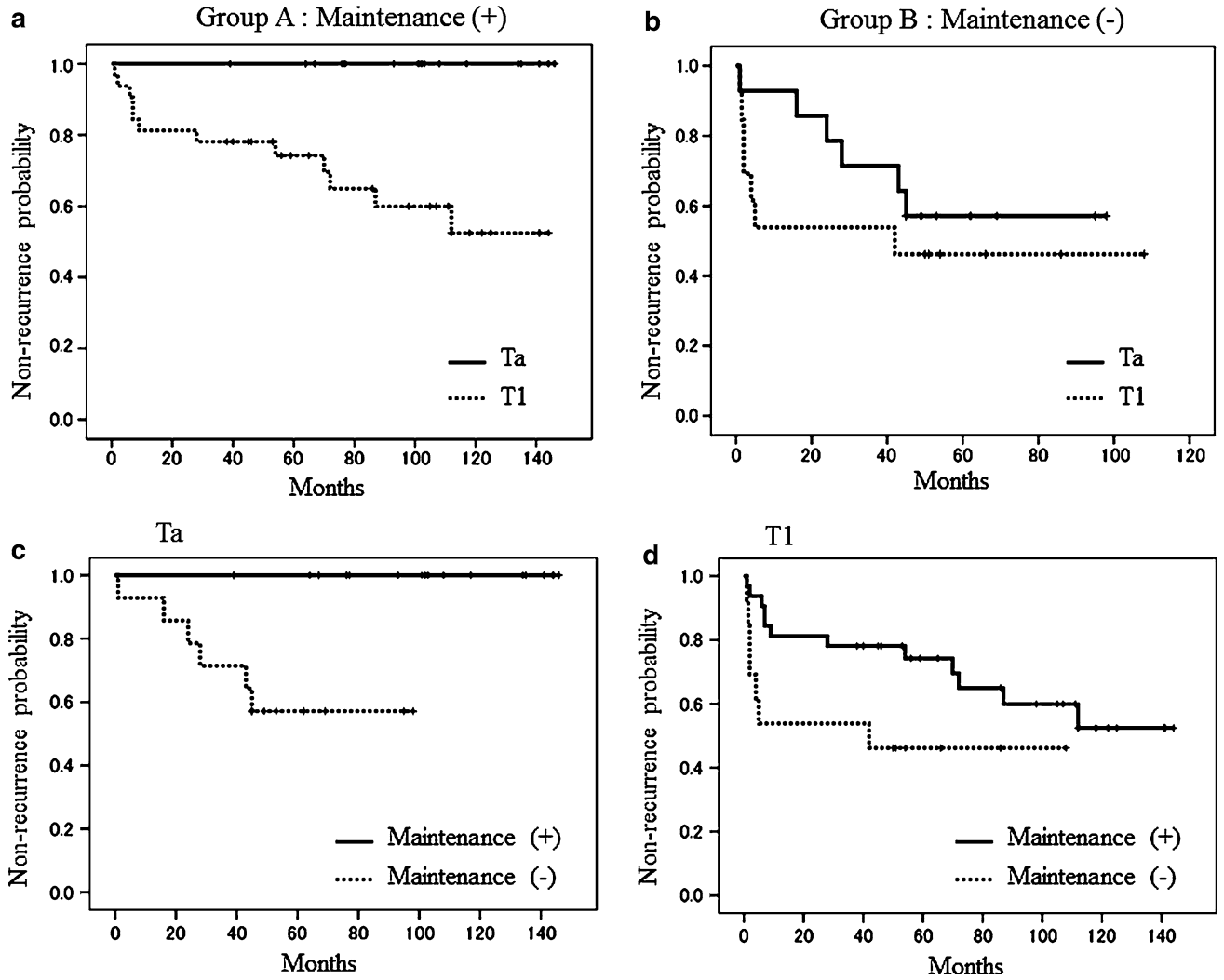

Fig. 2 Recurrence-free survival curves stratified by stage according to presence and absence of BCG maintenance treatment. Comparison of Ta and T1 stage differences: **a** group A, **b** group B. Comparison of groups A and B: **c** Ta, **d** T1

Table 2 Results of the analyses of maintenance bacillus Calmette-Guérin (BCG) treatment

Category	Univariate[a]		Multivariate[b]		
	P value	Hazard ratio	*P* value	Hazard ratio	95% Confidence interval (CI)
Age	0.196	1.312	0.289		
Gender	0.935	1.052	0.647		
Grade	0.392	1.3	0.514		
Stage	0.053	2.473	0.015*	3.182	1.252–8.088
Number of tumors	0.915	0.975	0.962		
Number of recurrences	0.518	1.217	0.131		
Maintenance	0.009*	0.334	0.002*	0.269	0.117–0.616

* Significantly different

[a,b] Cox proportional hazards model

during TUR-Bt. Previously, we reported the efficacy of repeated BCG therapy for control [5, 13]. In deciding the optimal BCG maintenance therapy protocol, a good completion rate, reflecting tolerability of adverse effects, is of primary importance.

In an editorial comment in *European Urology* in 2008, Herr [14] argued that we have not yet generated sufficient evidence to support the efficacy of BCG maintenance therapy for bladder cancer. However, our retrospective data, together with small-scale prospective trials conducted

in Japan [10, 11], clearly show that very high patient compliance is feasible, with very positive results regarding recurrence. Further broad-based investigations are now necessary to generate consensus as to the best protocol for guidelines in Japan and other countries in Asia.

In conclusion, our findings show that BCG maintenance therapy, consisting of a single intravesical instillation given once a month according to our protocol, is definitely effective for prophylactic use, especially for patients with stage Ta NMIBC.

Conflict of interest None declared.

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