RESEARCH COMMUNICATION

Intravesical Bacillus Calmette-Guérin (BCG) Instillation for Primary and Recurring T1G3 Bladder Cancers

Takehiko Okamura[1*], Hidetoshi Akita[1], Ryosuke Ando[1], Yasunori Kawai[2], Keiichi Tozawa[2], Kenjiro Kohri[2]

Abstract

Instruction: With T1G3 bladder cancer, it remains unresolved whether the best treatment option is bladder preservation or total cystectomy. To assess the feasibility of the first option, we performed a clinical evaluation of the efficacy of intravesical instillation of bacillus Calmette-Guérin (BCG) for prevention of T1G3 bladder cancer recurrence after transurethral resection of bladder tumor (TUR-Bt). Methods: A total of 30 patients with T1G3 bladder cancers received 6 to 8 weekly instillations of BCG followed in some cases by further applications at monthly intervals. Results: Recurrence occurred in 13 cases. There were 6 patients with progression, total cystectomy being performed for 5 of these. Further BCG-including treatments were performed in 7 patients, and all of them were alive at the end of the follow-up period. Finally, bladder preservation proved successful in 24 of 30 cases. Conclusion: Intravesical instillation of BCG in high-risk T1G3 cases, including additional BCG treatment, proved effective and satisfactory in our series. Therefore, this option warrants emphasis with regard to its relative merit compared to total cystectomy.

Keywords: Intravesical instillation - bacillus Calmette-Guérin - T1G3 bladder cancer

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Introduction

BCG is an effective immunotherapy to reduce recurrence from resected papillary urothelial carcinoma of the bladder; the treatment has been used for more than 30 years. Moreover, BCG immunotherapy markedly improves the outcome of high-risk non-muscular invasive bladder cancers, including T1G3 lesions (Sylvester et al., 2002). With the latter, it remains to be resolved whether the best treatment option is bladder preservation treatment or total cystectomy. If conservative bladder therapy is carried out before cystectomy, the risk of progression is commonly thought to increase proportionally with a narrowing window of opportunity. A significant proportion of such patients may fail to respond to BCG therapy; their tumors not only persist or recur but may also become invasive or metastatic (Saint et al., 2003; Sylvester et al., 2006). In our experience, however, bladder preservation is possible in selected patients even in high-risk cases (Okamura et al., 2010). Therefore, it is very important to determine the most appropriate use of BCG against T1G3 high-risk bladder cancers by analyzing long-term retrospective data. In the present study, we therefore performed a clinical evaluation of the efficacy of intravesical instillation of BCG to prevent T1G3 bladder cancer recurrence after TUR-Bt treatment.

Materials and Methods

From August 1986 until January 2006, a total of 30 consecutive patients with T1G3 bladder cancers were treated in our group hospitals with intravesical instillations of BCG (Tokyo 172 strain purchased from Nihon BCG Manufacturer, Tokyo) after TUR-Bt. Patients with primary or concomitant carcinomas in situ or bladder cancers with muscle invasion (more than stage pT2) were excluded, together with those who had undergone previous urinary tract open surgery or general chemotherapy. The age range was from 50 to 83 years (average 67.0 years). The male: female ratio was 28:2 (93.3%:6.7%). There were 24 primary cases and 6 recurrent cases, 7 with single and 23 with multiple tumors. Follow-up periods varied between 14 and 125 months (average, 66.1 months). All the patients received a BCG instillation of 40, 60 or 80mg suspended in 40ml of physiological saline or distilled water once a week for up to 6 to 8 weeks, and then in some cases another 6 to 8 applications at one-month intervals. BCG dosage and selection of patients who should be on maintenance therapy were decided by the attending doctor or after group discussion according to the condition and/or coexisting disease of each patient (40mg : 60mg : 80mg=3 (10.0%) : 1 (3.3%) : 26 (86.7%)). BCG treatment was terminated in a number of cases before the course of 6 instillations

*[1]Department of Urology, J.A. Aichi Anjo Kosei Hospital, Anjo, [2]Department of Nephro-Urology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan. *For correspondence: hiko2546@sf.commufa.jp*

could be concluded, but a minimum of 4 applications was performed in all patients. The patients were asked to refrain, when possible, from urination within two hours of the instillation and were monitored for bladder irritation, temperature change and other clinical symptoms. A tuberculin reaction, 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 to 3 months after cessation of treatment, depending on the patients' condition. If tumors recurred after the initial treatment, further courses of BCG treatment in association with surgery or a different modality were chosen depending on the patients' condition and tumor status. The affected patients were again followed-up by surgery and further treatment, with up to a total of 3 courses of BCG therapy in addition to the initial treatment in tolerant cases, as we previously reported (Bracken et al., 1981). Progression was defined as change to muscular invasive disease (Pagano et al., 1991).

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".

Figure 1:Non-recurrence rate: Primary or Recurrent

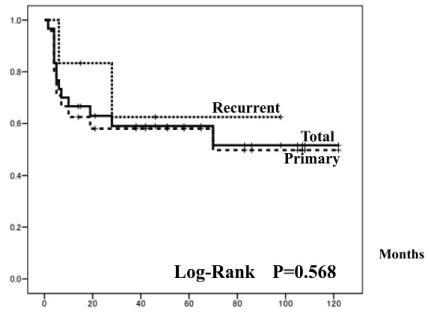

Figure 1. Non-Recurrence rates. The non-recurrence curve for all cases and comparative non-recurrence curves for the primary and recurrent all 30 cases. Five- and 10-year non-recurrence rates were 59.0% and 51.6%, respectively

Figure 2:Non-recurrence rate : Single or Multiple

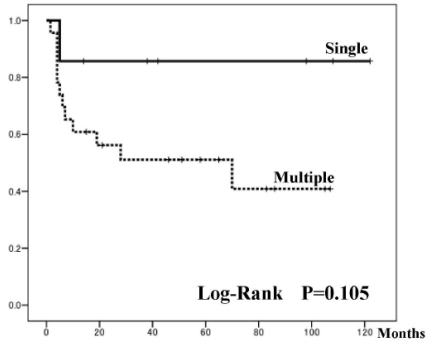

Figure 2. Comparative Non-Recurrence Curves of Single and Multiple-Lesion Cases. Multiple-Lesion Cases Seemed to Have a Worse Outcome, but no Significant Difference was Observed Because of the Small Number of Patients in Each Group

Results

Recurrence occurred in 13 cases with intervals from the operation ranging from 1.5 to 70 months (average of 12.9 months). Among them were 2 cases with a more than 3-year interval. The non-recurrence curve for all cases and comparative non-recurrence curves for the primary and recurrent cases are shown in Figure 1. Five- and 10-year non-recurrence rates were 59.0% and 51.6%, respectively. There were only 6 recurrent cases and there was no significant difference between the primary and recurrent groups. Comparative non-recurrence curves for single and multiple-lesion cases are shown in Figure 2. Multiple-lesion cases appeared to have a worse outcome, but, again, no significant difference was observed because of the small number of patients in each group. Further BCG treatment was again performed unless muscle invasive change had occurred. There were 6 patients with

Table 1. Summary of 13 Recurrent Cases. Eight Patients were Cancer Free After Additional TUR-Bt and Intensive Bladder Instillation of Combinations of Anti Cancer Drugs or Chemotherapy Combined with BCG

Progression Interval	Treatment after recurrence	Alive/dead
-	Repeated TUR Total cystectomy	alive
-	TUR→BCG	alive
4M	Progression→ Total cystectomy	alive
6M	Progression →Radiation→Urinary diversion	alive
-	TUR→BCG	alive
7M	Progression → Total cystectomy	alive
-	TUR→Chemo→BCG→TUR→ACD BI→Chemo→BCG	alive
-	TUR→BCG→TUR→BCG	alive
-	TUR→BCG	alive
-	TUR→BCG→ACD-BI	alive
99M	TUR→BCG→TUR→ACD-BI→TUR→BCG→TUR→BCG	alive
4M	Chemo→Progression→Total cystectomy	alive
5M	Progression→Total cystectomy	dead

ACD-BI : Anti Cancer Drug Bladder Instillation

confirmed progression.

Total cystectomy was performed in 4 of the 6 progressive cases, and in one with repeated recurrence (not progression), and 4 patients remained cancer free after the operation, although one died later because of further recurrence. Radiation therapy to the bladder and urinary diversion was performed in one progressive case because of the patient's poor condition, but the patient was still alive at the end of the follow-up period. A summary of results for 13 recurrent cases is shown in Table 1. Eight patients were cancer free after additional TUR-Bt treatment and intensive bladder instillation of a combination of anti cancer drugs or chemotherapy combined with BCG. Many different treatment options were selected in individual cases depending on the attending doctors, but as an end result, bladder preservation using BCG treatment proved successful in 24 of 30 T1G3 cases.

Discussion

It is well known that urothelial carcinomas presenting as T1G3 non–muscle-invasive lesions are high-risk because of the possibility of progression to muscle-invasive or metastatic disease (Patard et al., 2002). The most difficult point is to decide which patients should be treated using a conservative approach and which should undergo radical cystectomy (Morales et al., 1976), because most individuals would naturally prefer not to undergo an invasive operation. BCG treatment is the most reliable tool in a conservative approach to cancer control.

In this retrospective study, only one patient had died of cancer at the end of the long-term follow-up period, although all 30 patients were T1G3 high-risk cases. Moreover, bladder preservation was successful in 24 selected recurrent cases who received more than one course of BCG treatment. Generally, with cystectomy, the 5-year prognosis for survival of high-risk T1G3 is up to 90% (Stöckle et al., 1987; Bracken et al., 1981,; Pagano et al., 1991; Amling et al., 1994; Freeman et al., 1995; Gontero et al., 2010) but quality of life is reduced. Most attending doctors are very familiar with the use of BCG and know the details of its adverse effects and how they can be minimized. In our present series, adverse effects were mostly prevented, and BCG treatment could be performed a large number of times.

We have reported previously that a repeated course of BCG was successful in selected patients (Okamura et al., 1996). We believe that the most important aspect of the treatment is to perform BCG instillation as many times as possible in individual cases, if the clinical data show that it is tolerated and there is no evidence of tumor progression. The second most important point is to change the plan immediately and perform open surgery if BCG is not effective in high-risk T1G3 cases. Furthermore, critical clinical variables, such as the presence of an associated CIS or an early BCG failure (Lamm, 2000; Saint et al., 2003; Sylvester et al., 2006; Patard et al., 2002; Fernandez-Gomez et al., 2008), which have been defined as factors related to progressive tumor growth, must be considered before making a decision to continue BCG therapy (Lamm, 2000; Patard et al., 2002; Saint et al., 2003; Sylvester et al., 2006; Fernandez-Gomez et al., 2008). Given the lack of reliable prognostic and predictive tumor markers, laboratory research is definitely warranted to identify candidate biomarkers for clinical behavior. In this regard, p53 has been widely studied, but the results are not conclusive enough to make clinical decisions in T1G3 disease (Lacombe et al., 1996; Schmidt-Dräger et al., 2000; Esuvaranathan et al., 2007; Palou et al., 2009; Shariat et al., 2009). In our series, some tumors appear to have become BCG resistant. Such examples should be utilized to confirm histopathological diagnosis and further investigate molecular aspects in the future.

In conclusion, at present there is no defined treatment option for T1G3 cases, and evidence for the respective benefits of immediate open surgery and BCG intravesical instillation is thus a high priority. Our present results are therefore important in suggesting that all eligible patients should undergo this latter option as a first-line therapy. In conclusions intravesical instillation of BCG in high-risk T1G3 cases, including additional BCG treatment in non-progressive recurrent cases, was effective and satisfactory in our series. Therefore, in discussions with patients this treatment option warrants emphasis in regard to its relative merit compared to total cystectomy, focusing on maintaining a good quality of life.

References

Amling CL, Thrasher JB, Frazier HA, et al (1994). Radical cystectomy for stages Ta, Tis and T1 transitional cell carcinoma of the bladder. *J Urol*, **151**, 31-6.

Bracken RB, McDonald MW, Johnson DE (1981). Cystectomy for superficial bladder cancer. *Urology*, **18**, 459-63.

Esuvaranathan K, Chiong E, Thamboo TP, et al (2007). Predictive value of p53 and pRb expression in superficial bladder cancer patients treated with BCG and interferon-alpha. *Cancer*, **109**, 1097-105.

Fernandez-Gomez J, Solsona E, Unda M, et al (2008). Prognostic factors in patients with non-muscle-invasive bladder cancer treated with bacillus Calmette-Guérin: multivariate analysis of data from four randomized CUETO trials. *Eur Urol*, **53**, 992-1002.

Freeman JA, Esrig D, Stein JP, et al (1995). Radical cystectomy for high risk patients with superficial bladder cancer in the era of orthotopic urinary reconstruction. *Cancer*, **76**, 833-9.

Gontero P, Bohle A, Malmstrom PU, et al (2010). The role of bacillus Calmette-Guérin in the treatment of non-muscle-invasive bladder cancer. *Eur Urol*, **57**, 410-29.

Lacombe L, Dalbagni G, Zhang ZF, et al (1996). Overexpression of p53 protein in a high-risk population of patients with superficial bladder cancer before and after bacillus Calmette-Guérin therapy: correlation to clinical outcome. *J Clin Oncol*, **14**, 2646-52.

Lamm DL (2000). Preventing progression and improving survival with BCG maintenance. *Eur Urol*, **37**, 9-15.

Morales A, Eideger D, Bruce AW (1976). Intracavitary bacillus Calmette-Guérin in the superficial bladder tumor. *J Urol*, **116**, 180-3.

Okamura T, Akita H, Hashimoto Y, et al (2010). Non muscle invasive bladder cancer cases initially failing to respond to bacillus Calmette-Guérin intravesical instillation therapy. *Curr Urol*, **4**, 18-24.

Okamura T, Tozawa K, Yamada Y, et al (1996). Clinicopathological evaluation of repeated courses of intravesical bacillus

Calmette-Guérin instillation for preventing the recurrence of initially resistant superficial bladder cancers. *J Urol*, **156**, 967-71.

Pagano F, Bassi P, Galetti TP, et al (1991). Results of contemporary radical cystectomy for invasive bladder cancer: a clinicopathological study with an emphasis on the inadequacy of the tumor, nodes and metastases classification. *J Urol*, **145**, 45-50.

Palou J, Algaba F, Vera I, et al (2009). Protein expression patterns of ezrin are predictors of progression in T1G3 bladder tumours treated with nonmaintenance bacillus calmette-guérin. *Eur Urol*, **56**, 829-36.

Patard JJ, Rodriguez A, Leray E, et al (2002). Intravesical bacillus Calmette-Guérin treatment improves patient survival in T1G3 bladder tumors. *Eur Urol*, **41**, 635-42.

Saint F, Salomon L, Quintela R, et al (2003). Do prognostic parameters of remission versus relapse after bacillus Calmette–Guérin (BCG) immunotherapy exist? Analysis of a quarter century of literature. *Eur Urol*, **43**, 351-61.

Sanchez-Carbayo M, Cordon-Cardo C (2007). Molecular alterations associated with bladder cancer progression. *Semin Oncol*, **34**, 75-84.

Schmidt-Dräger BJ, Goebell PJ, et al (2000). p53 immunohistochemistry as a prognostic marker in bladder cancer: playground for urology scientists? *Eur Urol*, **38**, 691-700.

Shariat SF, Bolenz C, Godoy G, et al (2009). Predictive value of combined immunohistochemical markers in patients with pT1 urothelial carcinoma at radical cystectomy. *J Urol*, **182**, 78-84.

Shariat SF, Lotan Y, Karakiewicz PI, et al (2009). p53 Predictive value for pT1-2 N0 disease at radical cystectomy. *J Urol*, **182**, 907-13.

Stöckle M, Alken P, Engelmann U, et al (1987). Radical cystectomy--often too late? *Eur Urol*, **13**, 361-7.

Sylvester RJ, van der Meijden AP, LammDL (2002). Intravesical bacillus Calmette-Guérin reduces the risk of progression in patients with superficial bladder cancer: a meta analysis of the published results of randomized clinical trials. *J Urol*, **168**, 1964-70.

Sylvester RJ, van der Meijden AP, Oosterlinck W, et al (2006). Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol*, **49**, 466-77.