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Urologic Oncology: Seminars and Original Investigations 30 (2012) 259–265

UROLOGIC ONCOLOGY

Original article

Results of long-term follow-up of patients with superficial bladder carcinoma treated with intravesically applied bacillus Calmette-Guerin vaccine according to the schedule of 6 weekly + 6 monthly instillations

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Received 25 November 2009; received in revised form 8 February 2010; accepted 10 February 2010

Abstract

Background: The efficacy of bacillus Calmette-Guerin (BCG) immunotherapy in the prevention of local recurrence and disease progression in patients with superficial bladder cancer is very well documented. This study reports the effect of BCG on disease-specific and overall survival.

Patients and methods: In this retrospective trial, we have analyzed 170 patients with stage Ta and T1 superficial bladder cancer. Patients in the control group (87 patients) we followed-up only (median follow-up of 119 months) and treated surgically or with other oncologic modalities when progression of disease was diagnosed. The BCG group consisted of 83 patients treated with 6 weekly followed by 6 monthly instillations, and they have been followed-up of median 124 months.

Results: Patients receiving BCG had statistically significant better 10-year disease specific survival (83% vs. 69%, $P = 0.03$). At the same time point, the local recurrence rate was 48 % and the progression rate 19% for patients treated with BCG, while 77% ($P < 0.001$) and 38% ($P = 0.007$) were results in control group. Despite numerically better in the BCG group, overall survival is not significantly different in the 2 groups ($P = 0.14$).

Conclusion: BCG immunotherapy significantly increases the disease-specific survival in patients with superficial bladder carcinoma.

Keywords: BCG immunotherapy; Bladder carcinoma; Disease-specific survival; Transurethral resection

1. Introduction

At first diagnosis, 70% to 80% of patients with bladder cancer present as superficial disease or non-muscle-invasive urothelial neoplasia following the new terminology [1]. According to the TNM classification, superficial bladder tumors include tumors that invade mucosa (Ta), lamina propria (T1), and carcinoma in situ (CIS) [2]. Transurethral resection is a diagnostic and therapeutic standard in the initial phase of treating the superficial carcinoma of the bladder. For smaller tumors, as well as solitary tumors of lower grade, this method may be curative. However, in most cases, the tumor resection alone does not prevent subsequent recurrence and disease progression, which can occur in 50% to 80% and 4% to 30%, respectively, 3 years after initial resection [3].

For this reason, following tumor resection, different agents, mainly chemotherapeutics and immunomodulators, are applied intravesically to reduce the probability of recurrences and progression. Since 1976, when Morales et al. first reported reduction of recurrence rate after BCG instillations following tumor resection, BCG vaccine was established in clinical practice as the most effective agent that can change the course of the disease [4]. Numerous studies

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1078-1439/$ – see front matter © 2012 Published by Elsevier Inc.
doi:10.1016/j.urolonc.2010.02.007

proved its efficacy and advantages compared to other agents [5–8]. However, there are still unresolved issues in the treatment of the superficial carcinoma of the bladder, such as optimal treatment schedule and treatment duration, patient selection, long term results and impact on survival.

Based on the fact that we have such a unique patient population (single institution, control group without treatment with BCG, long-term follow-up), we were in a position to investigate the real impact of BCG on superficial bladder carcinoma history. In our previous publication, we have analyzed the impact of a 6+6 BCG schedule on prevention of local recurrence and progression after 5 years of follow-up [9]. Now, our goal is to present the results of the impact of the 6+6 BCG scheme on the disease-specific survival of patients with superficial bladder carcinoma after a median follow-up time of 10 years.

2. Patients and methods

Two hundred seventy patients with superficial bladder carcinoma were admitted to the Split University Hospital between February 1989 and May 1994. Out of these, 170 patients had histologically proven stage Ta and T1 superficial transitional cell carcinoma and were eligible for intravesical BCG instillation treatment. The inclusion criteria for the therapy were presence of any of the following: recurring tumor, multiple tumors, involvement of lamina propria (T1 stage disease), and moderately or poorly differentiated tumor (grades II-III). All patients underwent complete transurethral resection of the tumor, which established histologic type, grade, stage, and absence of muscle invasion. Tumors were staged according to the TNM system of The Union Internationale Contre le Cancer and tumor grade by the Mostofi system [2,10]. The protocol of immunoprophylaxis with BCG consisted of 6 weekly plus 6 monthly instillations, modification of protocol published by de Kernion et al. [11].

Prophylaxis consisted of bladder instillations of 120 mg of Pasteur strain 1173 (Torlak, Belgrade, Yugoslavia) in the concentration of 75 mg/ml suspended in 50 ml of saline, in the first 2 years of the study. In the 1992–1994 period, 3 ml of the Stamm-Connaught strain "Imumcyst" (Connaught Laboratories Ltd., Ontario, Canada) was used in the concentration of 27 mg/ml suspended in 50 ml saline. These two different strains were compatible [7]. Instillations were performed after the bladder was catheterized and completely drained. We ensured not to insert any air or cause trauma or bleeding during catheterization. The patients were instructed to lie down for 2 h and change position every 30 min to allow maximal contact of the suspension with the bladder mucosa.

Instillations began 2 to 3 weeks after transurethral resection. After 6 weekly instillations and 1 month break when cystoscopic examination and urine cytology were done, 6 monthly instillations were applied. Out of 80 patients designated to receive BCG, 79 received planned treatment and only 1 received 6 weekly and 5 monthly instillations.

Intravesical BCG instillations were offered to all patients, of whom 80 underwent the treatment (BCG group) whereas the remaining 90 patients were not treated, and they have been followed-up only (control group). Two patients in the treatment group and 6 in the control group were lost from follow-up. The control group consisted of patients who did not receive the BCG vaccine; most of them due to its shortage during a time of war in Croatia but to a smaller degree also due to refusal by the patient. In the BCG group, there were 14 patients with recurrent tumors and 66 with primary tumor, whereas in the control group all patients had a primary tumor.

Follow-up consisted of cystoscopic examination every 3 months with urine cytology and mucosal biopsies of all overt or suspicious areas in the first year. Thereafter, same procedures have been applied at the 6-month intervals. An excretory urogram was done once per year.

Two patients in the BCG group were diagnosed with another primary carcinoma (colon and stomach carcinoma). After that we lost them from follow-up. Another 3 patients crossed over from the control group after receiving a "6+6" scheme of the BCG because of multiple recurrences. Consecutively, in the final analysis of the treatment outcome, 83 patients were included with median duration of follow-up of 124 months (from 17 to 193).

In the control group, the median duration of follow-up was 119 months (from 28 to 209). Six patients received BCG vaccine intravesically after recurrent tumor resection. Three of them received the "6+6" scheme of BCG immunoprophylaxis, and we added them to the BCG group. Another 3 patient received 6 weekly instillations and after that they were lost from follow-up, so we included them in our analysis until they received BCG immunoprophylaxis. Consecutively, we analyzed the course of disease in 87 control patients.

For statistical analysis, we used SPSS ver. 15.0 (SPSS Inc., Chicago, IL) software package. We chose $P < 0.05$ level to determine the statistical significance of all analyses. In case of noncensored data, the groups were compared with χ^2 test (categorical variables) and Student's t-test (metric variables). The recurrence and progression rates (events per person-years) were compared using large-sample one-sample binominal test for incidence rates. The Kaplan-Meier method was used to obtain disease-free survival curves for the groups, which were compared by log-rank test.

3. Results

The two groups of patients were similar with respect to the retrospective nature of the study (Table 1). Patients receiving BCG did have more recurrent tumors, smaller tumors, less T1 lesions, and more often multiple tumors. BCG treated patients had statistically significantly lower