



Platinum Priority – Bladder Cancer

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Bacillus Calmette-Guérin Without Maintenance Therapy for High-Risk Non–Muscle-Invasive Bladder Cancer

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Abstract

Background: Bacillus Calmette-Guérin (BCG) is the standard intravesical treatment of high-risk noninvasive (Ta, T1, Tis) bladder cancer. Maintenance BCG is recommended for maximum efficacy.

Objective: We compared our results in a large cohort of high-risk bladder cancer patients who received BCG without maintenance with published results from randomized maintenance BCG trials.

Design, setting, and participants: A cohort of 1021 patients underwent restaging transurethral resection for high-risk (Ta, T1, Tis) bladder cancer.

Intervention: Patients received a 6-wk induction course of BCG therapy. Responding patients did not receive maintenance BCG. Relapsing patients were eligible for retreatment with BCG. All patients were followed for a minimum of 5 yr.

Measurements: End points were 5-yr tumor- and progression-free survival rates. **Results and limitations:** Of 816 complete responders to induction BCG, 2- and 5-yr recurrence-free survival rates were 73% and 46%, respectively. The progression-free survival rate was 89%. Progression-free survival time was 56 mo (95% confidence interval, 55–58 mo). Thirty-two percent of the patients required another course of BCG therapy. We cannot exclude that maintenance BCG may benefit patients beyond 5 yr over induction BCG alone and selective BCG retreatments.

Conclusions: Our results with BCG treatment without maintenance of patients with high-risk non–muscle-invasive bladder cancer compare favorably with trials in which comparable patients received maintenance BCG.

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1. Introduction

Intravesical bacillus Calmette-Guérin (BCG) is the standard treatment after transurethral resection (TUR) of high-risk non–muscle-invasive bladder cancer. Since it was first introduced by Morales et al in 1976 [1], randomized trials have shown that BCG therapy reduces the frequency of

tumor recurrences and prevents or delays stage progression better than TUR alone [2,3] or topical chemotherapy [4,5]. Most practice guidelines recommend maintenance BCG for 1–3 yr [6,7], whereas it is optional in others [8]. The widespread use of maintenance BCG is based on a single, albeit large, trial [9], and a meta-analysis of published results from selected trials suggests that tumor progression

is reduced only among patients receiving maintenance BCG therapy [10]. However, we showed that induction BCG alone delayed progression and improved 5-yr [11] and 10-yr [12] cancer-specific survival. We also showed that maintenance BCG added no benefit to induction BCG [13], which was confirmed in four subsequent negative randomized trials [14]. Two additional small studies have recently been published; one showed no significant advantage to maintenance BCG [15], whereas the other demonstrated improved recurrence-free survival over induction BCG alone [16]. Adding to the confusion, a recent review did not appear to show significant differences in the cumulative incidence of recurrence or progression between patients receiving BCG alone or BCG with maintenance therapy [17].

Maintenance BCG is associated with cumulative toxicity. Only 16% of patients in the Southwest Oncology Group (SWOG) trial were able to complete the 3-yr maintenance schedule [9], and we found that only 36% of patients were able to tolerate 2 yr of monthly BCG instillations [13]. One study, however, claimed that 80% of patients completed a 3-yr maintenance regimen and only 20% became intolerant [18]. We do not use maintenance BCG because of poor compliance and negative results from the randomized trial in our patient population and prefer to retreat responding patients who later relapse with another 6 wk of BCG, sparing them undue toxicity.

Maintenance BCG benefits only patients who respond to induction BCG. Several reviews, a meta-analysis, and results from randomized multicenter studies were published recently, showing outcomes of responding patients receiving maintenance therapy [19–23]. We compare our results in patients with high-risk non-muscle-invasive bladder cancer who were treated with BCG without maintenance.

2. Patients and methods

A cohort of 1021 consecutive patients with bladder cancer was evaluated from 1995 to 2006. They underwent restaging TUR and were found to have high-risk non-muscle-invasive bladder cancer (high-grade Ta, T1, and/or Tis). They then received six weekly instillations of Connaught strain (81 mg) BCG therapy and were evaluated for response after 3 and 6 mo by cystoscopy, urine cytology, and TUR biopsy. No patients received maintenance BCG therapy. A complete response was defined as a negative biopsy and urine cytology by 6 mo. Patients were followed every 3–6 mo with cystoscopy, repeat TUR as necessary, and urine cytology. Each patient was entered into a database, and clinical information was updated prospectively at each follow-up evaluation. Patients who recurred with non-muscle-invasive disease after 6 mo were eligible to receive another BCG induction course. Patients who recurred and underwent cystectomy before objective evidence of tumor progression were considered treatment failures. Patients who were upstaged to muscle invasion (T2) on restaging TUR or who underwent immediate cystectomy without receiving BCG were excluded from analysis.

Patients who responded completely to induction BCG are the focus of this report. End points were recurrence-free and progression-free survival. Tumor recurrence was defined as any tumor on biopsy or positive urine cytology during follow-up examinations. Progression was defined as a muscle-invasive tumor or metastasis. We constructed Kaplan-Meier curves for cancer-free survival times. The institutional review board approved the study.

3. Results

Of the 1021 patients evaluated and treated, 816 (79%) had a complete response to induction BCG therapy (784 patients had no tumor at both 3- and 6-mo evaluations, and 32, or 23% of 141 patients positive at 3 mo, became negative by 6 mo without another course of BCG). Table 1 shows the patient and tumor characteristics. They represent a cohort at high risk for tumor recurrence and tumor progression owing to high-grade, high-volume papillary or solid urothelial tumors, often associated with carcinoma in situ. All patients received a 6-wk induction of BCG, and 32% were retreated with another 6-wk course of BCG for tumor relapse during the minimum follow-up period of 5 yr. Sixty-seven patients (8%) underwent cystectomy for recurrent T1 cancers; they are evaluated as treatment failures. Of note, 107 patients (13%) developed upper tract tumors within 5 yr.

Figure 1 shows the recurrence-free survival of patients who responded initially to induction BCG therapy. The 2-yr recurrence-free survival rate was 73% (221 patients [27%] recurred), and after 5 yr, 46% remained free of recurrence

Table 1 – Patient characteristics

Patients, <i>n</i>	816
Sex, No. (%)	
Male	597 (73)
Female	219 (27)
Age, yr	
Median (range)	64 (21–93)
Tumor type, No. (%)	
Ta	416 (51)
T1	400 (49)
Grade, No. (%)	
High grade	780 (96)
Low grade*	36 (4)
Carcinoma in situ (Tis), No. (%)	
Yes	505 (62)
No	311 (38)
Disease extent, No. (%)	
Solitary/primary	57 (7)
Multiple/primary	90 (11)
Multiple/recurrent**	669 (82)
Restaging TUR pathology, No. (%)	
T0	392 (48)
Tis	165 (20)
Ta	192 (24)
T1	67 (8)
Prior intravesical chemotherapy, No. (%)	
Yes	155 (19)
No	661 (81)
BCG courses, No. (%)	
1	816
2	187 (23)
3	73 (9)
BCG maintenance	0
Minimum follow-up, 5 yr, No.	816

TUR = transurethral resection; BCG = bacillus Calmette-Guérin.

* T1 tumors.

** One or more recurrent tumors within prior 6 mo.

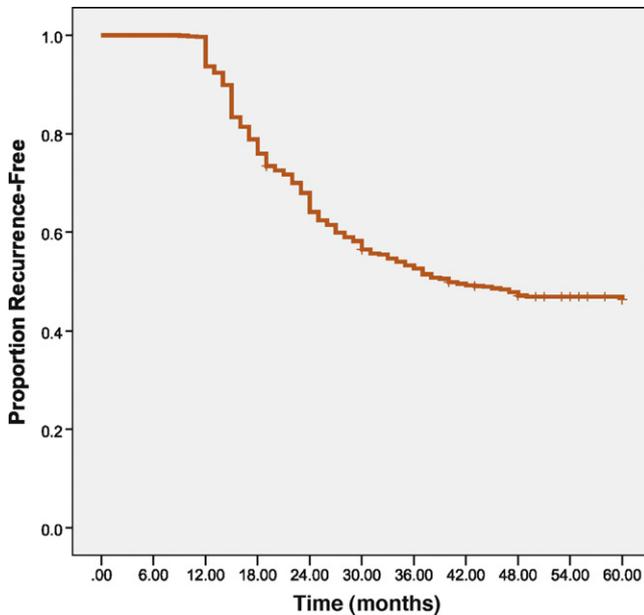


Fig. 1 – Five-year recurrence-free survival of 816 patients after complete response to bacillus Calmette-Guérin therapy.

(438 patients [54%] experienced at least one tumor recurrence). The median time to recurrence was 41 mo (95% confidence interval, 39–42 mo).

Figure 2 shows 5-yr progression-free survival among the 816 patients, who were followed for at least 5 yr without maintenance BCG but selectively retreated with a 6-wk course of BCG for noninvasive tumor relapse. Five-year progression-free survival was 89%; 93 patients (11%) progressed. The median time to progression has not been reached. None of the patients progressed between 3 and 6 mo after BCG therapy, and only one progressed to muscle

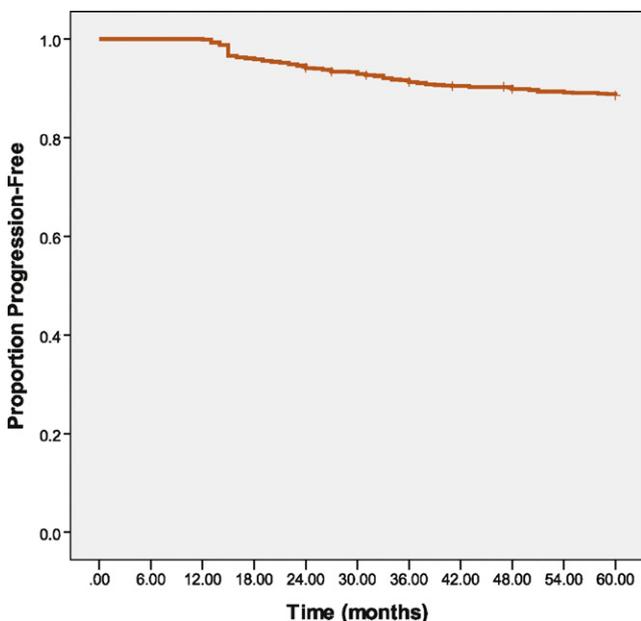


Fig. 2 – Five-year progression-free survival of 816 complete responders to bacillus Calmette-Guérin therapy.

invasion before 12 mo. A total of 33 patients (32% of progressors and 4% overall) died of urothelial cancer.

4. Discussion

The major finding of our study is that of 816 patients with high-risk non-muscle-invasive bladder cancer who underwent restaging TUR and had a complete response to induction BCG therapy, 27% recurred within 2 yr and half recurred by 5 yr, 11% progressed, and 4% died of urothelial cancer without receiving maintenance BCG therapy. Maintenance BCG was not used in favor of retreatment with BCG as needed upon relapse, which was required in 32% of patients. The fact that each patient had a second-look TUR may have contributed to the favorable results because the majority had residual disease resected before receiving BCG therapy. Quality of TUR, however, remains an unquantifiable variable and is usually poorly defined in intravesical trials.

How do these results compare with randomized trials using maintenance BCG? We restricted our comparisons to published raw data (provided in tables and figures) from prospective or randomized studies that included high-risk patients who responded initially to induction BCG therapy and then received a maintenance BCG regimen. The SWOG study reported that 56% of patients (108 of 192 on the maintenance arm) had a recurrence (similar to our 54% having recurrences), but they showed 5-yr recurrence-free survival in 60% of patients receiving the three plus three maintenance schedule [9], 14% higher than our 46% 5-yr recurrence-free survival rate. The SWOG trial had less progression with maintenance, although it was defined subjectively as “worsening” disease, which occurred in 87 of 192 patients (45%), substantially more than our objective progression rate of 11% in 5 yr without maintenance BCG. Including our 67 cases undergoing early cystectomy because of “worsening” disease with the 93 “objective” progressors, the overall progression rate using this definition is still lower at 20% among patients not receiving maintenance BCG than those in the SWOG trial.

In an individual patient data meta-analysis of randomized trials comparing intravesical mitomycin C (MMC) with BCG, Malmstrom et al reported a 32% reduction in risk of recurrence on maintenance BCG compared with MMC, and there was a 28% risk increase for BCG without maintenance [19]. However, only 23% of the patients were high risk, and the raw data show that 42.6% of 711 patients recurred on no maintenance compared with 43.2% of 726 patients on BCG maintenance over a median follow-up time of 4.4 yr. The progression rate was 11%, identical to our experience. In another mature trial that included 281 patients (42% high risk) treated with BCG plus maintenance, 37% recurred, 12% progressed, and 5% died of bladder cancer [21]. A third trial reported a 2-yr recurrence-free survival rate of 72% on maintenance, and 10.4% progressed to muscle invasion [22], similar to our results of 73% and 11%, respectively, and a comprehensive review of multiple trials showed 24-mo recurrence-free survival rates varying between 54% and 89% [20]. A recent study comparing BCG maintenance with BCG

plus interferon reported 2-yr recurrence-free survival rates of 63% and 55%, respectively [23], which are not superior to our 2-yr or 5-yr results without maintenance BCG.

5. Conclusions

The authors of the studies just cited conclude that maintenance BCG is crucial for efficacy. The raw data in high-risk patients, however, does not seem robust enough to justify such a strong conclusion that every patient should receive maintenance BCG. Admitting that maintenance BCG may prevent a few more recurrences than induction BCG alone, relapsing patients can be salvaged with retreatment rather than exposing all patients to the toxicity associated with maintenance. The important end point of progression in these randomized trials appears to be similar in maintenance and nonmaintenance patients and identical to progression rates in our patients, of whom only a third required retreatment for tumor recurrence. We accept a slightly higher recurrence rate to avoid overtreatment of many patients, and we do not agree that maintenance BCG is necessary to prevent or delay life-threatening tumor progression.

We believe another multicenter prospective randomized trial is needed to settle the issue whether maintenance BCG is truly effective, and we would be glad to participate in such a trial.

Author contributions: Harry W. Herr had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Herr.

Acquisition of data: Herr.

Analysis and interpretation of data: Herr, Dalbagni, Donat.

Drafting of the manuscript: Herr.

Critical revision of the manuscript for important intellectual content: Herr, Dalbagni, Donat.

Statistical analysis: Herr.

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