Original Article

Weekly intravesical bacillus Calmette-Guerin (BCG) alternating with epirubicin in Ta and T1 urothelial bladder cancer: An approach to decrease BCG toxicity

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Abstract

Context: Bacillus Calmette-Guerin (BCG) therapy is the standard treatment for nonmuscle-invasive bladder cancer (NMIBC). However, its toxicity is a major concern.

Aim: If we reduce the number of BCG doses by half and replace the second half with epirubicin, we may have a lower toxicity while maintaining the same efficacy of BCG. To test this hypothesis, we conducted this study as an update of our previous report.

Setting and Design: The study included 607 patients with Ta and T1 NMIBC between January 1994 and December 2008.

Materials and Methods: After transurethral resection of bladder tumor (TURBT), the patients received weekly doses of 120 mg BCG alternating with 50 mg epirubicin for six weeks (three weekly doses of each). Maintenance was given. Recurrence, progression rates, and toxicity were assessed. End points were progression, recurrence, and cancer-specific survival.

Results: A total of 532 patients were eligible for evaluation (mean age: 58 years; median follow-up: 45 months). Of these, 291 (55%) were free, 157 (29.5%) showed recurrence, and 84 (15.8%) showed muscle-invasive progression. Toxicity developed in 221 patients. These were mild in the majority (167), whereas 10 developed hematuria, 30 severe cystitis, and five systemic complications. The rate of permanent therapy discontinuation was 3.8%.

Statistical Analysis Used: SPSS package version 16 and Kaplan-Meier curves were used to evaluate survival.

Conclusions: Reducing the frequency of BCG instillations by half and replacing the second half with epirubicin results in a similar efficacy and a lower toxicity compared with historical cases receiving BCG alone. However, further trials are required to support these results.

Key Words: Bacillus Calmette-Guerin, epirubicin, nonmuscle-invasive bladder cancer, Ta, T1, toxicity

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INTRODUCTION

Bacillus Calmette-Guerin (BCG) is the adjuvant treatment of choice for recurrence prophylaxis of nonmuscle-invasive bladder cancer (NMIBC). However, its toxic local and systemic effects are limitations against its wide use by urologists.[1] Intravesical chemotherapeutic agents, such as epirubicin, are also effective in NMIBC. Although the efficacy of these agents

is not comparable to that of BCG, they have the advantage of being less toxic.[2,3]

There have been many trials aimed at maintaining the efficacy and reducing the frequency and severity of toxic and side effects of BCG by dose reduction.[4-7] However, it was suggested that the standard dose may be more effective in high-risk, multiple, tumor *in situ* (TIS)-associated Ta and/or in cases of NMIBC with a history of previous treatment.[5,8,9] Furthermore, in some studies, dose reduction was not associated with a subsequent reduction of side effects.[10,11]

We hypothesized that if we reduced the number of BCG doses by half and replaced the second half with intravesical epirubicin, we may have a lower toxicity profile while maintaining the efficacy of BCG alone. Therefore, we tested this hypothesis in a prospective randomized trial in 1999 and found that the new therapeutic regimen (alternating immunochemotherapy) had the same efficacy and a lower toxicity than BCG alone.[12]

Herein, an update of our experience with this new regimen in NMIBC, including a larger number of patients over a longer follow-up, is presented.

MATERIALS AND METHODS

The preliminary study idea and design was approved by the local Urology Council (representing the Research Ethics Committee). This prospective study was conducted on 607 patients with histologically proven Ta and T1 bladder urothelial cancer, between January 1994 and December 2008. The inclusion criteria included grade 2 or 3, stage T1, rapid recurrence within six months of initial resection, multicentricity, tumor size equal to or more than 3 cm, associated unifocal carcinoma *in situ* (CIS) and/or positive postoperative urinary cytology. Exclusion criteria included follow-up less than 18 months, multifocal CIS, and patient death from a known disease unrelated to bladder cancer.

Initially the patients were evaluated by urinalysis, urine culture, serum creatinine, fasting blood sugar level, complete blood count, chest X-ray, excretory urography, and bladder wash for cytology. Complete transurethral resection of the bladder tumor (TURBT) was carried out in all patients. After TURBT, the patients received weekly doses of 120 mg BCG (Pasteur strain) alternating with 50 mg epirubicin for six weeks (single drug per week, i. e., three weeks with BCG and three weeks with epirubicin as shown in Figure 1). Maintenance was given for one year as monthly doses of BCG alternating with epirubicin.[12] As of March 2003, all the patients routinely received a single instillation of 50 mg of epirubicin in the first six hours after TURBT.

The patients were followed every three months during the first two years and every six months thereafter. Clinical manifestations of disease recurrence and/or progression and complications of the intravesical therapy were noted. Evaluation at each visit is detailed in our previous report.[12] In cases of recurrence of the tumor while still in the NMIBC stage, the same protocol was repeated. If there was a failure for the second time in six months, cystectomy was indicated.

The number of patients developing recurrence or muscle-invasive progression during follow-up is referred to as recurrence or progression rate, respectively. It is expressed as a percentage of the total number of patients. The recurrence rate per 100-patient months is defined as the number of recurrences divided by the number of follow-up in months and multiplied by 100.

Recurrence, muscle-invasive progression, time to recurrence or progression, and/or death from bladder cancer were considered as the end points of the study. Kaplan-Meier survival curves were used to estimate disease-free survival.

RESULTS

Seventy-five patients were excluded from the evaluation. Of these, 60 had a follow-up in less than 18 months and 15 died from a definite disease unrelated to bladder cancer. Therefore, 532 patients (454 males, 78 females) were eligible for evaluation. Mean age ± standard deviation (range) in this cohort was 58 ± 12 years (23-85). Follow-up ranged from 18 to 177 months (median 45).

The tumor characteristics in this cohort are shown in Table 1. The stage of the tumor was T1 in 517 patients and unifocal CIS was present in only 11 patients.

During follow-up, recurrence developed in 157 patients (29.5%) and muscle-invasive progression was noted in 84 patients (15.8%). The five-year disease-free survival (no recurrence or progression) and progression-free survival ± standard error values were

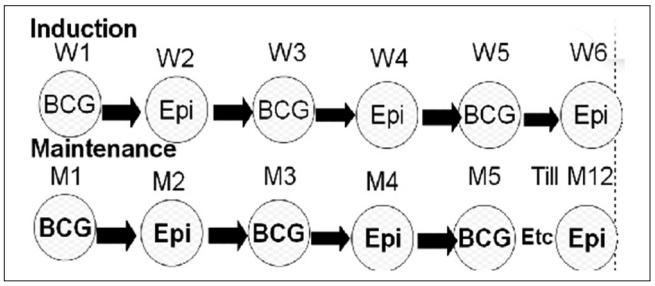

Figure 1: Diagrammatic representation of the induction and maintenance schedules of sequential immunochemotherapy with BCG and epirubicin (Epi). W1, W2, etc refer to week 1, week 2, etc; M1 refers to month 1

57% ± 2% and 83% ± 2%, respectively. The recurrence rate per 12-patient months was 0.1. The mean intervals to first recurrence and to progression were 18 and 20 months, respectively. The disease-free survival in the study group is shown in Figure 2. The actuarial five-year progression-free survival rate was higher for grades 1 and 2 than grade 3 (100, 86, and 58%, respectively; log rank $P \leq 0.001$).

The complications and side effects of therapy are shown in Table 2. These side effects were noted in 221 patients (41.5%). Toxic episodes developed in only 4.5% of the instillations. Most of these complications (167; 31.4%) were mild irritative voiding symptoms (mild frequency, urgency, burning micturition) and/or low grade fever and malaise and did not necessitate therapy discontinuation. Ten patients developed hematuria without the need for blood transfusion, 12 had reduced bladder capacity, and five systemic complications. Of the 12 patients with reduced bladder capacity, seven improved on conservative treatment with antituberculous drugs for six months and regained normal capacity, whereas five developed fibrotic contracted bladder and were treated with cystectomy.

Side effects developed after the fourth dose in 190 patients. Temporary and permanent therapy discontinuation due to toxicity was observed in 34 and 20 patients, respectively.

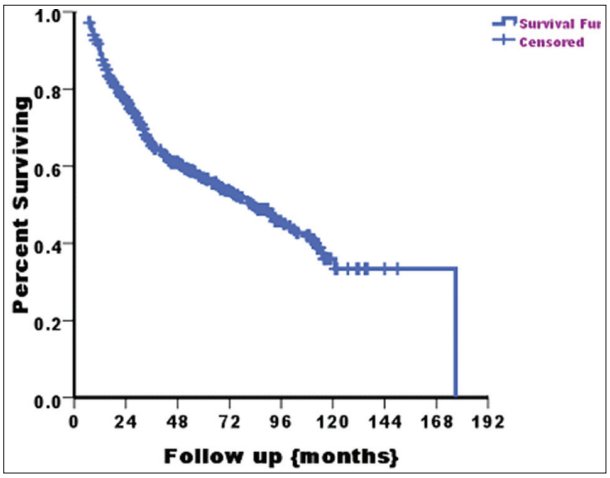

Figure 2: Kaplan-Meier curve showing disease-free (recurrence- and progression-free) survival in the study cohort

Table 1: Tumor characteristics of the 532 patients eligible for evaluation

Variable	No. of patients	%
Stage		
pTa	15	3
pT1	517	97
Associated CIS (unifocal)		
Yes	11	2
No	521	98
Grade		
G1	57	11
G2	380	71
G3	95	18
Multiplicity		
Single	273	51
Multiple	259	49
Tumor size		
Less than 3 cm	240	45
3 cm or greater	292	55
Tumor configuration		
Papillary	482	91
Solid or others	50	9
Recurrence history		
Primary	465	87
Recurrent	67	13
Recurrence at 3 months (1st check cystoscopy)		
No	457	86
Yes	75	14

DISCUSSION

In the current study as well as in our previous trial, we proved that this alternating therapy has a lower toxicity and a similar efficacy as compared with historical controls receiving BCG alone.[1,12,13] Since 1994, this alternating therapy has become the standard of care for Ta and T1 NMIBC in our hospital.

Efficacy

It has been proved in both randomized controlled trials (RCTs) and in meta-analyses that intravesical BCG is the most effective agent for recurrence prophylaxis of NMIBC.[14,15] In the study of Han and Pan, the recurrence rate in 2,342 patients was 40.5% compared with 49.7% in patients not receiving BCG.[14] In addition, Malmstrom *et al.* found that BCG with maintenance was more effective than mitomycin C both in patients previously treated and those not previously treated

Table 2: Toxicity and side effects of alternating bacillus calmette-guerin and epirubicin in the study cohort

Parameter	No. of patients	%
*Overall side effects	221	41.5
Mild symptoms	167	31.4
Mild irritative symptoms (frequency, burning micturition)	151	28.4
Low-grade fever, malaise+nausea	16	3
Local toxic effects		
Severe cystitis	30	5.6
Hematuria	10	1.9
Reduced bladder capacity (fibrotic contracted bladder)	12 (5)	2.3 (0.9)
Tuberculous prostatitis	1	0.2
Epididymo-orchitis	1	0.2
Therapy discontinuation		
Temporary	34	6.4
Permanent	20	3.8
Systemic toxicity**		
Fever	5	0.9
Toxic hepatitis	1	0.2
BCG sepsis	1	0.2
Allergic penile skin reaction	1	0.2
Toxic episodes/total no. of instillations	406/9018	4.5

*More than one side effect developed in 9 patients,**Eight systemic complications developed in 5 patients

with chemotherapy.[15] In these studies, the recurrence rates in BCG arms are comparable to those observed in our trial and this further proves that the efficacy of this alternating therapy is as effective as BCG alone.

The mean interval to first recurrence and all recurrence and progression parameters reported in this study are actually a continuation of the same results of the previous trial.[12]

The rationale for choosing intravesical epirubicin alternating with BCG has been stated before.[12] The toxic effects of epirubicin are less frequent and less severe than those of BCG and it is also effective, though not comparable to BCG, in NMIBC.[16]

Toxicity

The most important result of the current therapeutic regimen is the lower rate of toxic and side effects compared with those of BCG alone.[13] Furthermore, the overall toxicity rate, the rate of severe cystitis, and hematuria in this study are lower compared with some studies using a reduced BCG dose.[17,18] Overall toxic effects may develop in more than 90% of the cases.[13] However, they are mostly in the form of reversible mild irritative bladder symptoms or low-grade fever and malaise, and only 5% of the patients show severe toxicity.[1,13] Severe systemic BCG reactions may be explained by exaggerated immune response or active BCG tuberculous infection, and life-threatening reactions such as BCG sepsis occur most probably due to systemic absorption. The rate of systemic toxicity in our series is low (<1%) and compares favorably with other trials using BCG alone.[1,13,19]

One of the most important indicators of BCG toxicity is the necessity to stop the drug temporarily or permanently because of severe toxicity. Therapy discontinuation due to severe toxicity has been reported by Koga *et al*. in nine of 123 patients treated with BCG, a rate which is comparable to that found in the current study.[13] Furthermore, the discontinuation rate in the current study is lower than the rates reported in some trials using BCG alone.[20,21] Saint *et al*. and Takeda *et al*., respectively, reported 39 and 13% rates of BCG discontinuation.[20,21] Toxicity is a cumulative effect that usually occurs after the first two doses, and if it occurs once, the probability becomes higher in the subsequent doses.[22] This observation goes hand in hand with our findings with only one exception, that is, most of the side effects in our series developed after the fourth dose.

Dose and schedule

In principle, the mechanism of action of BCG and BCG-induced local immune response are not known exactly, and therefore improvements in the rational choice of the dose and schedule are not yet well defined.

The usual dose of 120 mg of Frappier (Pasteur) strain and the six weekly instillations were empirically determined by Morales and associates.[23] Strategies to decrease the side effects while maintaining the same efficacy of BCG therapy included reduction of the dose, dwell time, or number of doses.[5-11,24-26]

Limitations of reduction of bacillus calmette-guerin dose

Although reduction of BCG dose is an accepted method to reduce BCG toxicity, some limitations have been noted.[4-9,24] Reduction of BCG dose to a third of the usual dose was as effective as and less toxic than the classical dose in the study of the Spanish (CUETO) group, in both intermediate and high-risk NMIBC.[5,24] However, these authors stated, in their earlier report, that patients with multifocal tumors fared better with the standard dose and a trend toward better recurrence rates in patients with high-risk tumors was observed.[5] Therefore, in this study and others, it was suggested that the standard dose may be more optimal in high-risk, multiple, TIS-associated Ta and/or in cases of NMIBC with history of previous treatment.[5,8,9] Furthermore, at least in some trials, dose reduction did not achieve a subsequent reduction in toxicity.[10,11]

Reduction in dwell time

Reducing the dwell time to 30 minutes or less has been advocated as an alternative to dose reduction in patients showing severe BCG toxicity.[25] However, the maintained efficacy of the BCG may be related to the earlier standard doses, which were associated with pronounced side effects. Furthermore, prospective randomized trials are needed to support this issue.

Decrease in the number of bacillus calmette-guerin doses

There have been a few clinical trials that investigated the use of fewer BCG instillations or alternation of BCG with a chemotherapeutic agent.[26-29] The results of these trials support the results of the current trial. A modified induction BCG course with a two-week interval between instillations has been tried and shown to be effective with a lower toxicity profile.[26] In addition, Zlotta *et al*. stated that the maximal peripheral immune response to BCG therapy had already manifested after four-weekly instillations in most patients.[27]

Based on the observation that a high BCG-induced Th1/Th2 cytokine ratio was associated with effective antitumor activity, De Boer and associates stated, in a mouse model, that a modified schedule composed of only two BCG instillations, administered in week 1 and week 6, showed at least the same level of Th1 cytokines, compared to the six-week course.[28] At the same time, lower responses for the Th2 cytokines and a positive effect on the Th1/Th2 ratio were observed.[28]

Rintala and associates tried an alternating combination of BCG and mitomycin C for prophylaxis against recurrence of stages Ta and T1 bladder cancer and stated that this combination was superior to historical controls treated with BCG alone in terms of toxic effects.[29]

Maintenance bacillus calmette-guerin

We elected to use monthly maintenance rather than the three-weekly schedule because the latter was more toxic in our experience.[30]

Limitations

The study did not include an epirubicin-free arm with the same reduced number of BCG doses (half the number of the standard doses) and did not include a pure BCG arm (six weekly doses). However, in the first study, a pure BCG arm was included. In addition, the follow-up was relatively short in some patients (18 months), although the median follow-up was 45 months.

CONCLUSIONS

The efficacy and toxicity of alternating intravesical BCG and epirubicin in the current study have maintained and supported the results of our initial report. Reduction of the frequency of intravesical BCG instillations by half and replacement of the second half with epirubicin result in a similar efficacy as compared to historical cases treated with BCG alone. In addition, the frequency and severity of toxic and side effects have been lower in this regimen. These results further support the fact that the ideal dose and regimen of intravesical BCG for the treatment of NMIBC is yet to be well defined. However, these results need to be consolidated by other trials performed at multiple centers.

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