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Original Article

Clinical experience with BCG alone versus BCG plus epirubicin

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Abstract

Background: Bacillus Calmette–Guérin (BCG) and epirubicin have both been shown to be effective in the treatment of superficial bladder cancer. We studied whether the alternating combination of these agents could improve the efficacy with tolerable side-effects in the treatment of high-risk superficial bladder tumors.

Methods: Forty-one patients with high-risk superficial bladder transitional carcinoma were included in this study. Twenty-one patients were randomized into the BCG group and 20 patients were treated with sequential BCG and epirubicin. The patients were followed for 9–24 months (mean 18 months). Recurrence rates, median time to the first recurrence, progression rate and complications were compared.

Results: Fifteen percent of the patients in the BCG and epirubicin group and 19% of the patients in the BCG alone group developed tumor recurrence. Tumor progression was observed in 4.7% and 10% in the BCG/epirubicin group and the BCG alone group, respectively. Median time to first recurrence was 11 months for the BCG/epirubicin group and 16 months for the BCG group ($P > 0.05$). Three patients in the BCG/epirubicin treatment group developed serious side-effects, which necessitated antituberculosis treatment.

Conclusion: Because the efficacy of combination was no better than the standard treatment and the alternating combination seemed to be related to a higher incidence of side-effects, this study albeit small, does not recommend combination therapy of BCG and epirubicin in high risk patients with superficial bladder cancer.

Key words bladder cancer, intravesical chemotherapy, intravesical immunotherapy.

Introduction

Epirubicin and Bacillus Calmette–Guérin (BCG) have been shown to be effective in the prophylactic treatment of superficial bladder cancer. Although it has been proven that both agents effectively decrease the recurrence rate, the effect on progression rates are still debatable. Randomized, prospective trials have showed that the recurrence rate in patients receiving adjuvant BCG and epirubicin was better than transurethral resection (TUR) alone.[1–3] Furthermore, comparisons of response rates from different studies have also revealed that BCG was more effective than thiotepa, doxorubicin, or mitomycin.[4–6] We attempted to determine whether a combination of two effective agents, namely BCG and epirubicin, having different mechanisms of action could improve the prophylactic effect against high-risk superficial bladder tumors with acceptable morbidity.

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Methods

Between January 1994 and December 1995, 41 patients with superficial transitional-cell carcinoma of the bladder were prospectively enrolled to the randomized protocol at our institution, all with their informed consent. Patients with pT1 disease who had an addi-

Table 1 Patients' data

	BCG	BCG/epirubicin	*P*
Total no.cases	21	20	
Age (mean)	53	57	> 0.05
Females	1	1	> 0.05
Males	20	19	> 0.05
Grade I	3	2	> 0.05
Grade II	14	13	> 0.05
Grade III	4	5	> 0.05
Recurrent	7	9	> 0.05
Multiple	6	7	> 0.05
> 4 cm	6	5	> 0.05

BCG, Bacillus Calmette–Guérin.

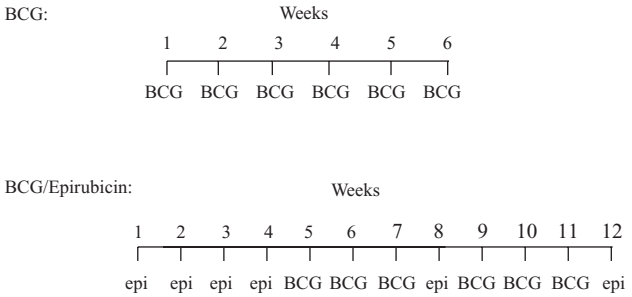

Fig. 1 Intravesical Bacillus Calmette–Guérin (BCG) and BCG/epirubicin installation protocol.

tional one of the four poor prognostic factors mentioned below were included in this study. These poor prognostic factors were: grade III tumors, multiple tumors, tumors greater than 40 mm and recurrent tumors. The distribution of the characteristics of the patients is summarized in Table 1. Patients older than 80 years, with Ta tumors and who were previously treated with any kind of intravesical therapy, radiotherapy, systemic chemotherapy, were excluded from this study. Patients with white blood cell and platelet counts lower than 3000 and 100 000, respectively, were also not included. Eligible patients were then randomized into BCG and sequential BCG and epirubicin treatments. Of 21 patients who were randomized into the BCG group, there was one woman and 20 men with an age range of 22–74 years (mean age 53 years). One female and 19 males aged from 42 to 73-years-old (mean age 57 years) were treated with sequential BCG and epirubicin. The statistical analysis revealed that both groups were similar in regard to demographic and histopathologic features.

Pretreatment studies included full blood count, renal and liver function tests, urine culture, abdominopelvic ultrasonography and intravenous pyelography. Complete blood counts were determined prior to each intravesical instillation. Treatment was commenced 10–15 days following complete TUR of the bladder tumors.

In the BCG group, patients were given 81 mg Connaught BCG intravesically weekly for 6 weeks. The sequential BCG and epirubicin protocol consists of weekly sequential intravesical administration of 81 mg BCG and 50 mg epirubicin according to the protocol in Fig. 1. In the case of urinary tract infection and gross hematuria, treatment was delayed. Both preparations were given at a volume of 50 mL and retention time was 2 h.

Patients were followed for 9–24 months (median 18 months) from the day of TUR of the tumor with 3-monthly cystoscopies for the first year and biannually thereafter. Any suspicious lesions were resected for histopathologic evaluation and random biopsies were performed in every patient during their first cystoscopy.

The primary endpoints used to determine the efficacy of the prophylaxis included median time to first recurrence and recurrence rates. Progression rate (stage progression to muscle invasive disease) was also analyzed in both groups. The complications in the two treatment regimens were compared.

Statistical analysis including Mann–Whitney *U*-test and chi-squared test for demographic data and recurrence rate comparison; log rank test for comparison of median times to first recurrence and Spearman correlation analysis were done using the SPSS program (SPSS Inc, Chicago, IL, USA).

Results

Three (15%) of the 20 patients who received sequential BCG and epirubicin therapy developed tumor recurrence when compared with four recurrences (19%) in the 21 patients who underwent intravesical BCG instillation. One of the relapsing patients (4.7%) in the BCG/epirubicin group and two (10%) in the BCG group developed tumor progression and underwent radical cystoprostatectomy. The difference of the progression rates in two groups was not statistically significant ($P > 0.05$).

The median follow up was 18 months (9–24 months). Eighty-five percent of patients in the sequential BCG/epirubicin protocol and 81% of patients in BCG group were recurrence-free during the follow-up period. Median time to first recurrence was 11 months for the BCG/epirubicin group and 16 months for the

Table 2 Adverse effects occurring in 16 patients according to the treatment group

Adverse effect	BCG (%)	BCG/epirubicin (%)
Hematuria	8 (38)	4 (20)
Irritative bladder symptoms	9 (43)	7 (35)
Fever	3 (14)	2 (10)
Malaise	1 (4.7)	1 (5)
Renal morbidity		1 (5)
Hepatitis		1 (5)
Skin rash		1 (5)
Contracted bladder		1 (5)

BCG, Bacillus Calmette–Guérin.

BCG group. The difference was not statistically significant ($P > 0.05$).

The biopsies at first control cystoscopy revealed chronic inflammation (100%) and in some specimens granuloma formation (17%). Three patients (15%) in the BCG/epirubicin group and four patients (19%) in the BCG group showed granuloma formation in their biopsies during the first control cystoscopies. Granuloma formation did not correlate with tumor recurrence rate or with complications.

There was no treatment-related death. Treatment with sequential BCG and epirubicin resulted in more adverse reactions than BCG treatment alone. Of 20 patients on the sequential BCG and epirubicin treatment, two (10%) developed hepatitis and dermatitis resulting in the termination of the treatment protocol and one (5%) patient had a contracted bladder. These patients received antituberculosis treatment (Table 2).

Discussion

Bacillus Calmette–Guérin immunotherapy has been successfully used in the management of superficial bladder cancer. Numerous randomized prospective studies of BCG immunotherapy and intravesical chemotherapy were performed to evaluate the relative efficacy of these treatments. Results of BCG treatment compare favorably with that of intravesical chemotherapy.[1–6] In our study, the relative efficacy and toxicity of BCG immunotherapy alone and in combination with an intravesical chemotherapy was evaluated. Epirubicin is a derivative of doxorubicin with an improved spectrum of antitumor activity and lower toxicity. Epirubicin may be as effective or even more effective than doxorubicin if used as adjuvant local chemotherapy for transitional cell carcinoma of the bladder. Intravesical trials have shown epirubicin to be effective and safe.[3,7,8]

It is clear from the studies performed to date that BCG is retained and internalized after intravesical instillation. The studies on a mouse tumor model suggests that BCG attachment to fibronectin is a requisite step for the development of an immunologic response.[9] Furthermore, studies have also shown that BCG only exerted its effect on mouse bladders damaged with electrocautery in contrast to normal bladders.[10] Fibronectin, which is preferentially distributed throughout the basement membrane of the normal uroepithelium, appears to mediate attachment of BCG to areas of disrupted mucosa. As anthracyclines are known to cause chemical cystitis, it may be postulated that initial treatment with epirubicin may cause disruption of the bladder mucosa and thus more fibronectin sites will be available for BCG to interact. The alternating treatment model of an initial cystitis provoking agent and then BCG was thought to enhance BCG efficacy.

The recurrence free rates in the BCG and sequential BCG/epirubicin groups are 81 and 85%, respectively, a difference which is not statistically significant ($P > 0.05$). This relatively high level of recurrence-free rates might be due to the short follow-up period.

Cystitis which on biopsy typically consists of chronic inflammation and in some of the specimens granuloma formations were also observed. These findings typically did not require treatment and did not affect the clinical outcome. Patients were generally symptomatic for a short time and relieved by symptomatic medication.

Serreta and Ferrari *et al*. have investigated the potential benefits of epirubicin and interferon-2-alpha and have reported better results in combination group, albeit the differences were not statistically significant and the follow-up period was not long enough to be conclusive.[11,12] They have also found that the immune response to interferon-2-alpha was augmented when combined with epirubicin. Rentala *et al*. have reported their experience on combination of BCG and mitomycin-C.[13] Although the recurrence rates were similar in both treatment protocols, side-effects were suprisingly less in the alternating protocol. However, we were not able to show any beneficial effect of an alternating regimen with BCG and epirubicin over BCG alone in regard to either recurrence rates or recurrence-free interval. Furthermore, serious side-effects of intravesical BCG were only observed in the alternating protocol. This high incidence of side-effects was probably due to the development of chemical cystitis by epirubicin, which in turn may augment systemic

absorption of BCG. Therefore we do not recommend combination therapy of BCG and epirubicin in high-risk patients with superficial bladder cancer as a combination of BCG with an agent that causes chemical cystitis will lead to more conspicuous systemic side-effects without any additional benefit.

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