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Efficacy, Safety and Tolerability of Intravesical 80mg BCG in Intermediate and High Risk Superficial Transitional Cell Carcinoma of Urinary Bladder

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ABSTRACT

Objectives: To determine the efficacy, safety and tolerability of intravesical 80 mg BCG (6 induction and 9 maintenance doses) in intermediate and High Risk superficial Transitional Cell Carcinoma of Urinary Bladder.

Methods : A total of 51 cases of intermediate and high risk superficial transitional cell carcinoma of urinary bladder received 80 mg BCG intravesically induction followed by 9 doses of maintenance phase. The endpoints were disease free interval (dates of 1st and 2nd recurrence), efficacy end points (success, failure and indeterminate) and adverse event profile followed up for a minimum of 18 months.

Results: Recurrence occurred in 12 (23.52%) cases and out of these disease progressed in 3(5.88%) patient at a mean follow up of 18 months. Adverse event profile was favourable with 2 (3.92) cases forced to withdraw due to intolerance to the therapy and mild fever and dysuria being the most common adverse effects- 45.09% and 47.05% respectively.

Conclusion: The results of our study have shown that low dose BCG with limited maintenance therapy is equally efficacious with considerably lower incidence of adverse effects but long term follow up is required.

I. INTRODUCTION

Intravesical bacillus calmette Guerin immunotherapy has become the treatment of choice and prophylaxis for superficial bladder cancer. The bacillus Calmette-Guerin (BCG) is regarded as the most successful immunotherapy against superficial bladder carcinoma recurrences to date.The mechanism of action has been intensively investigated. The initial step appears to be direct binding to fibronectin within the bladder wall, subsequently leading to direct stimulation of cell-based immunologic response. The observed pattern of cytokine induction with preferential upregulation of interferon-γ and IL-2 reflects induction of a Th1response. This immunologic response activates cell mediated cytotoxic mechanisms that are believed to underlie the efficacy of BCG in the prevention of recurrence and progression[1].

BCG is an attenuated mycobacterium developed as a vaccine for tuberculosis that has demonstrated antitumor activity in several different cancers, including urothelial cancer[2] . BCG is stored in refrigeration and reconstituted from a lyophilized powder. The vaccine is reconstituted with 50 mL of saline and should be administered through a urethral catheter under gravity drainage soon thereafter because aggregation occurs[3].

Morales observed that a dose reduction of BCG results in diminished toxicity withoutchanging its efficacy[4] . Two prospective, randomized studies in patients with superficial bladder tumors also showed that low-dose BCG was more effective than transurethral resection alone or mitomycin C and had lower toxicity[5,6] .

II. PATIENTS AND METHODS

A prospective study was conducted to compare the efficacy and toxicity of lowdose (80 mg) BCG. A total of 51 patients of intermediate and high risk superficial bladder cancer were included in this study. The inclusion criteria were resectable, superficial biopsy proven TCC of the bladder – intermediate risk (all other tumours between the low and high-risk group namely Ta-1, GI-G2, multifocal, >3 cm in diameter) and high risk (TIG3, multifocal or highly recurrent (3 in 24 months) tumours and CIS. The exclusion criteria included previous or concurrent secondary tumour other than BCC of skin, uncontrollable UTI, active tuberculosis, previous BCG therapy, cystostatic agents in past 3 months, renal or liver function values of > 2x upper limit of normal, pregnant or lactating, previous concurrent leukemia or lymphoma, transplant recipient or HIV positive, solitary tumour other than T1G3, WBC count of < 3,000/ml or platelet count <100,000/ml.

Written and explained informed consent was obtained in all patients of good performance status. After complete transurethral resection, the bladder tumors were staged according to the 1997 TNM classification. The total dose of BCG was

reconstituted in 50 ml of normal saline. The drug was instilled into the bladder through an in-dwelling soft urethral catheter after lubrication of urethra with 2% lidocaine jelly.The vaccine was held in the bladder for approximately 2 hours after each instillation. All patients were prescribed 3 day course of nitrofurantoin postinstillation. Demographic data, personal history, medical history and disease profile was noted in each case. All patients received a weekly instillation of the 80 mg dose for 6 weeks, followed by a maintenance schedule of 3 weekly doses at 3, 6 and 9 months (total 15 doses). After treatment patients were evaluated for a mean follow-up period of 18 months (range 14 to 30 months). Adverse events were recorded and patient compliance was ensured accordingly.

Study evaluation consisted of routine blood investigations, CXR, urine cytology at baseline then at 3, 6, 9 and 12 months; USG abdomen, CT abdomen, NMP-22 was performed pre and posttreatment and cystoscopy at 3, 6, 9, and 12 month and 6 monthly afterwards.

III. RESULTS

A total of 51 patients with superficial transitional cell bladder carcinoma were included in the study, but 3 patients dropped out. The age of the patients ranged from 29 to 79 years, 43 were men and 8 were women. In our study 33% of all patients were in their sixth decade. 56 % patients had high grade tumour. All patients were observed at 3 months intervals by urinary cytology and follow-up cystoscopy. At 3 months , 2 patients dropped out but none of the patients developed disease recurrence and all available patients completed induction phase. At 6 months of follow up disease recurred in 3 patients including one patients who has disease progression and was subjected to radical cystectomy. At 1 year, disease recurrence occurred in 8 (15.62%) patients including disease progression (T2 disease) in 3 (5.88%). Disease progression leading to radical cystectomy occurred in all patients with T1G3 histopathology. Finally disease recurrence and progression at 18 months were 23.52% and 5.88 % respectively.

During the follow-up patients were evaluated for both local and systemic side effects of BCG. Among local side effects dysuria was the most common symptom, found in 24 patients (47.05%), followed by frequency in 20 patients (39.21%). Hematuria was seen in 6 patients (11.76%) . Among the systemic side effects fever less than 38.5 was seen in 23 (45.09%), fever greater than this was seen in 3 (5.88%) patients including 1 (1.96%) patient having it more than 48 hours. Therapy in the same dosage was started again after symptomatic treatment for these side effects. Migratory polyarthritis occurred in one female patient where maintenance phase has to be stopped and she recovered with steroid therapy. Pulmonary or hepatic symptoms did not develop in any of the patients, and there was no mortality. None of the patients required antitubercular therapy.

IV. DISCUSSION

Intravesical BCG significantly reduces the risk of progression after transurethral resection in patients with superficial bladder cancer who receive maintenance treatment[7]. Treatment for superficial bladder cancer has to take into account a high recurrence rate. The emphasis on prevention of recurrence has shifted from intravesical chemotherapy using thioteapa in the 1960s to immunotherapy using BCG in the 1980s [8,9.] In a study by paganoet al no significant change was observed in the results for recurrence and progression upon reducing the dose to half the standard dose (BCG Pasteur strain, 75 mg versus 150 mg)[5]. Results of our study are consistent with these findings. In the present study, the tumor recurrence rate of 23.52% was observed which confirms the observation of efficacy of BCG in reducing tumor recurrence effectively in superficial bladder carcinoma. Bohle et al suggested superiority of BCG over mitomycin C for prevention oftumor recurrences, particularly in the BCG maintenance treatment subgroup, irrespective of the actual (intermediate or high) tumor risk status[10] . In the study by Pagano et al reducing the dose of BCG to half (75 mg) resulted in decreased toxicity (cystitis in 27%, hematuria in 3% and fever in 19 %) compared with standard- dose BCG (cystitis 91%, hematuria 43% fever 28%)[11] . The incidence of dysuria was 47.05 % in our study and none of the patients dropped out due to this particular side effect. Frequency was the second most common local symptom (39.21%). Martinez – Pinerio et al in their study have reported hematuria in 12 % of the patients, and ali-el-dein et al reported hematuria in 7%[12,13] . The incidence of hematuria in our study was only 11.76%. Pagano et al reported fever in 28% of the patients in the BCG group using a standard dose of BCG (120 mg). Martinez-Pinerio et al reported fever in only 2% of the cases with use of lower-dose BCG therapy. Mild fever was reported in 45.09 % of our patients but that may be due to small sample size. Very few cases of pulmonary and hepatic side effects of BCG have been reported in the literature, and in our

study none were observed. Migratory polyarthritis led to drop out of one female patient in our study. BCG was withdrawn in this patient because of toxicity , and instillations were delayed in none of the patients. In our study , quality of life was better as none of the patients dropped out due to bothersome lower urinary tract symptoms. Another approach to dose reduction includes Mike O' Donnell's work on reduction of BCG dose with concurrent use of interferon in superficial bladder carcinoma[14] . Concurrent antibiotic administration with BCG therapy has also been used for reducing toxicity[15] . However, the effect of antibiotics is highly variable and depends on patients compliance. It is both safer and more economical to reduce the dose of BCG. The results of the present study suggest that the toxicity of BCG intravesical therapy could be reduced by reducing the dose without affecting the efficacy of therapy. However, in patients with superficial bladder cancer with high risk of recurrence and progression, caution may be advisable in selecting the dose until further studies are performed on this subject with long term follow up.

Study by Madhu S. Aggarwal et al used a full maintenance schedule of BCG, thus they could not extrapolate results to a situation in which only a 6-week induction and 9 doses maintenance schedule is used like ours[16].

The results of the present study suggest that the toxicity of BCG intravesical therapy could be reduced by reducing the dose without affecting the efficacy of therapy.

V. CONCLUSION

The results of our study have shown that low dose BCG with limited maintenance therapy is equally efficacious with considerably lower incidence of adverse effects but long term follow up is required.

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Table 1

80 mg BCG STUDY RESULTS

At 3 months follow up	
Drop outs	2
Patients available	49
Muscle invasive tumour	-
Non- muscle invasive tumour	-
No recurrence	49
Patients on Follow up	49

Total Patients = 51

At 6 months follow up	
Drop outs	1
Patients available	48
Muscle invasive tumour	1
Non- muscle invasive tumour	2
No recurrence	45
Patients on Follow up	47

At 9 months follow up	
Drop outs	-
Patients available	47
Muscle invasive tumour	1
Non- muscle invasive tumour	2
No recurrence	44
Patients on Follow up	46

At 12 months follow up	
Drop outs	-
Patients available	46
Muscle invasive tumour	1
Non- muscle invasive tumour	1
No recurrence	44
Patients on Follow up	45

At 15 months follow up	
Drop outs	-
Patients available	45
Muscle invasive tumour	-
Non- muscle invasive tumour	2
No recurrence	43
Patients on Follow up	45

At 18 months follow up	
Drop outs	-
Patients available	45
Muscle invasive tumour	-
Non- muscle invasive tumour	2
No recurrence	43

Patients on Follow up	45

Efficacy at 18 months	
Out of total enrolled including drop outs	86%
Out of final evaluable sample size	95.5%
Safety assessment	Dysuria (47.05%), Frequency (39.21), Hematuria (11.76%), Mild Fever (45.09%)