RESEARCH

COMPARISON OF EFFICACY AND SAFETY OF INTRAVESICAL THERAPY FOR NON-MUSCLE INVASIVE BLADDER CANCER WITH INTRAVESICAL BACILLUS CALMETTE-GUERIN VS MITOMYCIN C: A PROSPECTICE RANDOMISED SYUDY

B. Santosh[1], Anand[2], Tushar[3], G. Mallikarjuna[4]

[1]Associate Professor, Department of Urology, Government Medical College, Sangareddy, Telangana, India.
[2]Assistant Professor, Department of Urology, Osmania Medical College, Koti, Hyderabad, Telangana, India.
[3]Post graduates/Resident, Department of Urology: Osmania Medical College, Koti, Hyderabad, Telangana, India.
[4]Associate professors &HOD, Department of Urology, Osmania Medical College, Koti, Hyderabad, Telangana, India.

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Corresponding Author:
Dr. G.Mallikarjuna,
Email. drgmallik@hotmail.com
ORCID: 0000-0002-8505-9663

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Abstract

Background: Bladder cancer is one of the most common types of urological cancer (BC). In the Western world, it is the fourth most common cancer in men and the ninth most common cancer in women. According to the Indian Disease Registry, BC is the ninth most frequent cancer and accounts for 3.9 percent of all cancer cases worldwide. This study looked at the efficacy and safety of intravenous immunotherapy using the Calmette-Guérin Bacillus against mitomycin C in patients with invasive non-muscle bladder cancer. **Materials and Methods:** This study is a prospective, randomised study conducted in a tertiary care hospital. In our study, 50 patients were enrolled who had histologically verified stage Ta, CIS, or T1 superficial transitional cell carcinoma and qualified for intrathoracic BCG instillation and intrathoracic mitomycin C instillation treatment. **Result:** The patients' ages ranged from 32 to 79, with a mean of 55. There were 50 patients in our study, 42 (84%) of them were males and 8 (16%) were women. The majority of patients (80%) had T1 cancer, with Ta (20%) coming in second. When the patients initially came, none of them had CIS. A total of 50 NMIBC patients were split into two groups of 25 and randomly allocated to either intravesicular BCG immunotherapy or intravesicular Mitomycin-C chemotherapy for 6 weeks. The P value for both the number and grade of tumours was 0.3772, which is statistically insignificant (P>0.05) when employing the Chi square test. In comparison to intravesical Mitomycin-C, intravesical BCG therapy caused much greater, but milder, adverse effects. Recurrence was more prevalent in high grade disease patients treated with mitomycin-C than in high grade disease patients treated with BCG. As a consequence, in severe sickness, BCG is more effective than mitomycin-C. **Conclusion:** This study discovered that BCG immunotherapy outperforms Mitomycin C treatment in terms of recurrence rate reduction. Because to organ retention, patients may live longer and of higher quality. Close, lifetime tumour surveillance is essential in these patients.

INTRODUCTION

Bladder cancer is one of the most common urological cancers (BC). It is the eighth most frequent cancer in women and the fourth most prevalent cancer in males in the Western world.[1] BC accounts for 3.9% of all cancer cases and is the tenth most common malignancy, according to the Indian Cancer Registry.[2] The most common histological form of BC is transitional cell carcinoma (TCC), which affects 90% of patients. Less common types include squamous cell carcinoma, adenocarcinoma, and small cell carcinoma. Sarcoma, pheochromocytoma, carcinoid, and small cell tumours are rare cancer types.[3]

Around 70% of these cancers are superficial, such as carcinoma in situ (Tis), Ta, and T1 carcinomas (show no signs of muscle invasion).[4] Carcinoma in situ (Tis), epithelial tumours (Ta), and tumours that enter the lamina propria (T1) are all types of superficial bladder cancer.[5,6] The bulk of these tumours are distinct types of histologically differentiated

transitional cell carcinomas (I-III). It has a diverse natural history and is a heterogeneous illness. On one end, there is low-grade Ta carcinoma, which has a low advancement rate, and on the other, there is high-grade T1, which has a high risk of disease progression and death. Ta lesions account for around 70% of superficial tumours, T1 lesions for 20%, and Tis lesions for 10% of the time. The biological activity of these tumours varies from a low level of recurrence and progression to a high level of recurrence and progression. Although transurethral resection of the bladder tumour (TURBT) is the preferred treatment approach, various additional treatments, including Bacillus Calmette-Guérin (BCG), mitomycin C, gemcitabine, and others, have been developed as adjunct therapies. This study looked at the efficacy and safety of intravenous immunotherapy using the Calmette-Guérin Bacillus against mitomycin C in patients with invasive non-muscle bladder cancer.

MATERIALS AND METHODS

This study is a 24-month, randomised, prospective study conducted in tertiary care centres between January 2019 and December 2021. The trial comprised all patients (50 in total) with a diagnosis of stage Ta, CIS, or T1 superficial transitional cell carcinoma who were eligible for intravesical BCG instillation and intravesical mitomycin C instillation treatment and supplied written informed consent. Patients with BCG hypersensitivity, compromised immune systems, short-term retention of BCG or mitomycin C, and refusal to participate in the experiment were all excluded. All patients with a preliminary diagnosis of bladder cancer had complete transurethral excision of the tumour (either in one or two sittings), establishing the tumor's size, histological type, grade, stage, and absence of muscle invasion. After stratified randomization to account for all baseline confounders across the two trial arms, patients were split evenly between the two treatment groups using simple randomization. First group of 25 patients had once-weekly intravesical BCG instillation for six weeks. A second group of 25 patients got weekly intravenous mitomycin C instillations for six weeks.

Innmunotherapy and Chemotherapy intravesical instillation

The intravesical immunotherapy consists of application of BCG of dose 80 mg reconstituted with 100 ml of normal saline for six consecutive weeks (induction). BCG strain used is Danish 1331 strain having 1-8 X 106 colony forming units. After transurethral resection and after each patient had histological confirmation of superficial bladder cancer, the administration of BCG was begun two to three weeks later. Instillation was performed after the bladder had been catheterized and completely emptied. We took cautious not to inject any air or cause trauma or bleeding during catheterization. Patients were instructed to remain still for two hours. For six weeks, Mitomycin-C 40 mg is dissolved in 50 mL of saline and delivered intravenously once a week.

Follow up

Every three months, a cytoscopical examination, urine cytology, and mucosal biopsies of any overt or worrisome bladder regions were performed as follow-up procedures. The follow-up was continued till the end of the study, the death of a patient, tumor recurrence (when this event was analyzed), or tumor progression (when this event was analyzed). Minimum follow up of each patient was 3 months duration.

RESULTS

This study included 50 patients.

Table 1: Demographics of the sudy populations

Age group (in years)	Number of patients	Percentage
Upto 20	0	0
21-30	0	0
31-40	3	6%
41-50	3	6%
51-60	18	36%
61-70	18	36%
71-80	8	16%
Sex	Number of patients	Percentage
Male	42	84%
Female	8	16%

The patients' ages, which varied from 32 to 79, were on average 55 years old. The bulk of the patients in the current research were older adults, with 36% of them in their sixth and seventh decades of life and 16% in their eighth. In our analysis, the male to female ratio is 5.2:1. [Table 1]

Table 2: Comorbidities and risk factors associated in patients.

Comorbidities	Number of patients n (%)	Group 1 N (%)	Group 2 N (%)
Hypertension	25 (50)		
Diabetes Mellitus	22 (44)		
CAD	2 (4)		
CVA	0		
Others	1(2)	2%	
Risk factor	Male?		
Smoker	34 (81%)	0 (0%)	
Sex (male)			

Most of the patients in our study had hypertension (50%) and diabetes mellitus (44%), at the time of presentation probably due to elderly age. Only 2 (4%) had coronary artery disease. 2% patients had hypothyroidism. In the present study 34 out of 42 male patients (81%) were smokers and none of the female patients were smokers. (Table 2) (Difference on both groups) (Table 1 and 2 can be combined)

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Table 3: Histopathology Staging and grading of study population (table 3 and 4 can be combined

Stage	Number of patients n (%)	Group 1 n (%)	Group 2 n (%)
Ta tumours (Low)	10 (20)		
T1	40(20)		
Carcinoma in situ (CIS)	0		

Majority of the patients were with T1 stage (80%) followed by Ta (20%). None of the patients presented with CIS.

Table 4: Patients characteristics, grade of tumours distribution in study groups and comparison of number of tumours in the two groups.

Patient Characteristics	Mitomycin C group (n, %)	BCG group (n, %)	Total
Male	21 (84%)	21 (84%)	42 (84%)
Female	4 (16%)	4 (16%)	8 (16%)
Grade	Mitomycin C group	BCG group	Total
Low	14 (56%)	18 (72%)	32 (64%)
High	11 (44%)	7 (28%)	18 (36%)
Number of tumours	Mitomycin C group	BCG group	P value
Single lesion	17 (68%)	16 (64%)	0.7544
Two lesions	5 (20%)	7 (28%)	
>2 lesions	3 (12%)	2 (8%)	

The histological staging, grading, and number of tumours in the two groups did not vary statistically. (P 0.754 Value) [Table 3 and Figure 1 &2].

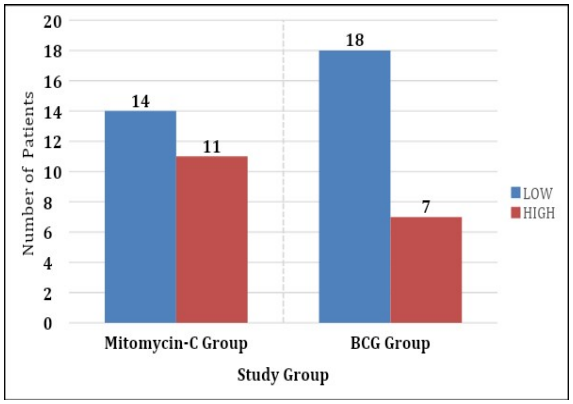

Figure 1: Grade of tumors in two groups

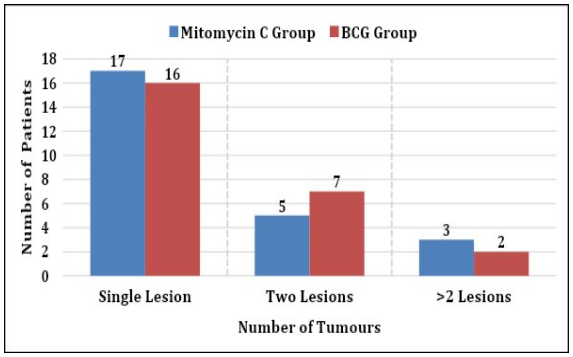

Figure 2: Number of tumours in two groups

Table 5: Comparison of side effects in the two groups

Side Effects	Mitomycin C group (n=25, %)	BCG group (n=25, %)	P value
Hematuria	3 (12%)	5 (20%)	0.4413
Dysuria	2 (8%)	8 (32%)	0.034
Fever	0 (0%)	6 (24%)	0.0091
Cystitis	8 (32%)	9 (36%)	0.7642

While comparing the safty progile in both the groups dysuria and fever was significantly higher in BCG group [Table 5].

Table 6: Recurrences in follow up at 3rd, 6th and 12th months

Recurrences	Mitomycin C group (n=25, %)	BCG group (n=25, %)	P value
At 3 mponths	0 (0%)	0 (0%)	>0.9999
At 6 months	3 (12%)	0 (0%)	0.2347
At 12 monthss	7 (28%)	1 (4%)	0.0488

Patients in each group were observed for no more than 12 months after completing the 6-week therapy of intravesical BCG and intravesical Mitomycin C to look for tumour formation and recurrence. Both groups had no recurrences at the end of the third month; however, the Mitomycin C group had three (12%) recurrences at the end of the sixth month, whereas the BCG group did not. After a year of follow-up, recurrence was found in 7 (28%) of the patients treated with mitomycin C, but just one (4%) of the patients treated with BCG. Because the grade of the tumour recurrence was the same as it was preoperatively, there was no disease progression in any of the patients. According to Fischer's exact test, the recurrence was only significant after 12 months of follow-up (P value 0.04), but not after 3 or 6 months. [Table 6 and Figure 3]

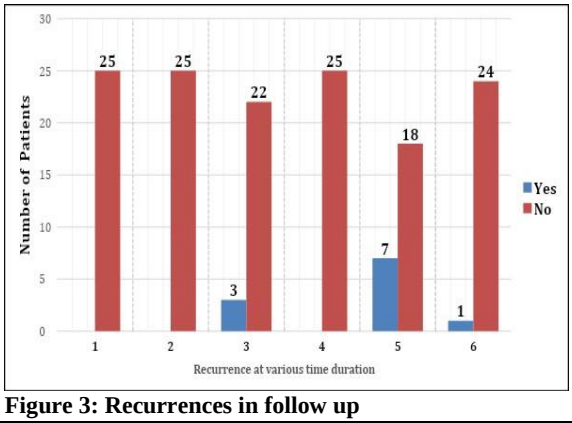

Figure 3: Recurrences in follow up

DISCUSSION

10% of superficial bladder tumours are urothelial carcinomas in stage pT1, grade 3. Recurrence rates after transurethral resection alone may reach 75%, and tumour growth due to muscle invasion has been seen in 30% to 50% of instances. Only 50% of people survive after five years. This demonstrates the need

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for effective adjuvant treatment. Depending on the severity of the illness, transurethral resection alone for stage pT1 urothelial carcinoma may result in a progression rate of 20% to 80%. The incidence of recurrence has been temporarily reduced by a number of regimens that use chemotherapeutic drugs infused into the bladder as adjuvant treatment. 50 patients were included in the current investigation, with a mean age at presentation of 55 years (range 32-79).

Bladder cancer reaches its peak in the eighth decade of life, according to Siegel R et al7. The average age of diagnosis for bladder cancer in our research was in the sixth decade. A ratio of 5.2:1 (out of 50 patients) showed that 42 were men and 8 were women.[7]

Similar to our research, Parkin DM et al.[8] found that men had a 3–4 times higher risk of developing bladder cancer than women. In our investigation, smoking was identified as a significant risk factor for bladder tumour. 34 of the 50 patients had a history of smoking.

According to a Brennan P et al,[9] study tobacco use, especially cigarette smoking, is the leading known cause of urothelial cancer formation and is responsible for 60% and 30%, respectively, of all urothelial cancers in men and women. The majority of patients in the current study (80%) had T1 stage cancer, followed by Ta stage (20%). No patient had CIS when they first arrived. In our study, 34 out of 50 patients (or 68% of the total) had low grade lesions, while 16 had high grade tumours (or 32% of the total).

In the current research, patients in the BCG study group (66% of the patients) had greater local side effects than those in the MitomycinC group (40% of the patients), which included cystitis, hematuria, dysuria, and fever.

Similar to our research, Mondal et al,[10] Friedrich et al,[11] Di stasi et al,[12] and Krege et al,[13] found that patients in the BCG study group had greater local side effects than those in the Mitomycin C group. The most common adverse impact in the present study is cystitis, which is consistent with studies by Mondal et al,[10] and Krege et al,[13] in which cystitis was also the most common adverse effect. In the current research, patients treated with BCG had higher side effects of fever and dysuria than patients treated with mitomycin-c ($p < 0.005$), which is statistically significant. The BCG group had more side effects than the Mitomycin-C group did, although they were minor and did not necessitate delaying or stopping treatment.

In the present study, we examined the efficacy of BCG and Mitomycin C in 50 patients and observed that after a mean follow-up of 12 months. 4% of individuals who received BCG have illness recurrence, compared to 28% of those who received mitomycin C. No patient treated with BCG or Mitomycin-C showed illness recurrence during a 3-month follow-up ($p>0.005$). While no patients in the BCG group had illness recurrences following a 6-month follow-up, 3 patients in the Mitomycin-C group did ($p>0.005$), which is statistically insignificant.

After a 12-month follow-up, 4% of patients treated with BCG had recurrence, but 28% of individuals treated with mitomycin C do. This difference is statistically significant ($p < 0.005$), and the 12-month follow-up is the same as in the current research. In order to comment more on the prevalence of illness recurrence, additional research is required. In trials evaluating non-muscle invasive superficial bladder cancer, the effects of intravesical BCG vs Mitomycin C treatment after TUR were compared.

De Bruyne et al,[14] examined the effectiveness of BCG VS Mitomycin C in a total of 308 patients and discovered that, after a mean follow-up of 24 months, 36% of patients treated with mitomycin C and 42% of patients treated with BCG, respectively, exhibited illness recurrences.

After a mean follow-up of 24 months, Rintala et al,[15] examined the effectiveness of BCG VS Mitomycin C in 91 patients, finding that 3% of patients treated with BCG exhibited recurrence whereas 21% of patients treated with mitomycin C showed illness recurrences.

After a mean follow-up of 36 months, Lundholm et al,[16] examined the effectiveness of BCG VS Mitomycin C in 261 individuals and discovered that 51% of patients treated with BCG exhibited recurrence whereas 66% of patients treated with mitomycin C showed disease recurrences.

After a mean follow-up of 60 months, Friedrich et al,[11] examined the effectiveness of BCG VS Mitomycin C in a total of 261 individuals. While 66% of individuals treated with mitomycin C had relapses, 53% of those treated with BCG did not.

After a mean follow-up of 6 months, Mondal et al,[10] examined the effectiveness of BCG VS Mitomycin C in a total of 40 patients and discovered that 0% of patients treated with BCG exhibited recurrence whereas 10% of patients treated with mitomycin C showed illness recurrences.

In the current trial, all recurrences in the BCG and Mitomycin-C arms occurred in individuals with high grade illness as opposed to low grade disease, and In high grade disease patients treated with mitomycin-C as opposed to high grade disease patients treated with BCG, recurrences were more common. Consequently, BCG is more effective than mitomycin-C in high grade illness.

CONCLUSION

According to this research, BCG immunotherapy is superior to Mitomycin C treatment in terms of lowering the recurrence rate. Organ retention enables patients to have higher quality of lives. In these individuals, careful, lifetime tumour monitoring is essential. Patients receiving BCG have more adverse effects than those receiving Mitomycin-C. Intravesical mitomycin-C therapy is therefore a potential option for persons with intermediate risk conditions.

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