IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 18, Issue 6 Ser. 2 (June. 2019), PP 28-31
www.iosrjournals.org

A Prospective Randomized Controlled Trial Of Adjuvant Intravesical Chemotherapy Versus Immunotherapy In Superficial Transitional Cell Carcinoma Of Urinary Bladder.

Suhail Khuroo, MBBS, DNB (Surg), DNB (GI), FMAS[1]; Ajaz Ahmad Wani, MBBS, MS[2]; Asim Rafiq Laharwal, MBBS, MS, FIAGES[3]; Arshad Rashid, MBBS, MS, FNB (MAS), FIAGES, MCLS[3].

[1]*Department of Surgery, Northern Railway Central Hospital, New Delhi – 110001*
&Consultant Surgeon, New City Hospital, Srinagar – 190011.
[2]*Surgeon Specialist, Health Services Kashmir, Srinagar – 190001*
& Consultant Surgeon, Ahmed's Hospital, Srinagar – 190011.
[3]*Lecturer, Department of Surgery, Government Medical College, Srinagar – 190010*
&Consultant Surgeon, New City Hospital, Srinagar – 190011.
Source of Funding: Nil
Conflicting Interest: None declared
Running Title: Intravesical chemotherapy versus immunotherapy.
Corresponding Author: DrAsim R Laharwal

Abstract: *This was a prospective randomized controlled study, in which the outcome of post operative intravesical chemotherapy with Mitomycin C [MMC] and immunotherapy with BCG was evaluated and compared in patients with superficial (Ta/T1) transitional cell carcinoma urinary bladder. From January 2008 to June 2017, 189 patients of superficial transitional cell carcinoma urinary bladder were evaluated. Patients were divided into two groups [BCG group (n=95) & MMC group (n=94)]. The baseline parameters were similar in both the groups. All patients underwent TURBT followed by intravesical instillation of weekly dose of either BCG or MMC starting from six weeks following TURBT depending on the group. The patients were followed up with 3 monthly urinary, radiological and cystoscopic investigations. The standard follow up was 1 year. In the present study, the recurrence rate was more in MMC group [9.57% versus 4.21%, p= 0.0044]. The side effects weresignificantly higher in the BCG group [38.95% versus 25.53%, p=0.0012], but the side effects were mild and did not require any delay or cessation of therapies.The results of the study show that though BCG has a higher efficacy with respect to recurrence at 1 year follow up, but side effects are more commonly seen in the BCG group.It was also observed that there was no progression in the grade of the recurrence observed after intravesical therapy.*

Key words: *Intravesical therapy; Immunotherapy; Superficial TCC; BCG; MMC.*

Date of Submission: 20-05-2019 Date of acceptance: 05-06-2019

I. Introduction

Bladder cancer is one of the most common diseases treated by urologists and is the second most common cancer of the genitourinary tract. Transitional cell carcinoma [TCC] of the bladder is the fourth most common carcinoma in men after prostate, lung and colorectal cancers; and the eighth most common cancer in females [1]. Superficial bladder cancer is a commonly encountered urological malignancy because of its high incidence with five year recurrence rates between 30 to 66%. Risk factors for recurrence being more than one tumour, large (>3cm), high grade, or superficially invasive (pT1) tumours [2].

There has been a considerable change in the treatment for superficial bladder cancer. From the early days of repeated electro-coagulation in the 1950's to intravesical chemotherapy using thiotepa in 1960's and intravesical immunotherapy using BCG in the 1970's and 80's, the treatment options have been revolutionised [3,4]. The need for intravesical treatment evolved in order to prevent tumour recurrence after successful local surgical resection. For years various intravesical chemotherapeutic agents such as thiotepa, doxorubicin and mitomycin have been the mainstay of therapy, but although they achieved short remissions, a net durable benefit was only apparent in 7 to 14% of patients [5,6]. The disappointing results with chemotherapy and also radiotherapy set the stage for the induction of more unconventional forms of therapy, such as immunotherapy.In the present study, we report on the outcomes of patients with superficial TCC of urinary bladder with regards to intravesical chemotherapy versus immunotherapy.

PATIENTS AND METHODS

Ours was a prospective randomized controlled study conducted between January 2008 and June 2017. During this period, we treated 281 patients of patients with TCC of urinary bladder at three centers [Northern Raliway Central Hospital, New Delhi; New City Hospital, Srinagar & Ahmed's Hospital, Srinagar]. Out of these, 207 were superficial, 33were invasive and rest had metastatic disease. All of these patients presented with complaints of painless hematuria and underwent routine laboratory investigations followed by some special investigations including urinary cytology for 3 consecutive days, Chest roentgenogram, ultrasound abdomen, contrast enhanced computed tomogram [CECT] of abdomen/pelvis and bone scan. Patients underwent cystoscopic biopsy and histopathological confirmation includingthe depth and grade of the disease.

Only the 207 patients with histopathological confirmation of superficial disease [Ta and T1 TCC]were included in the study. These patients were subjected to transurethral resection of bladder tumour [TURBT] followed by instillation of intravesical agents. All patients received intravesical Mitomycin C [MMC] 40mg in immediate postoperative period. Patients were randomly distributed into two arms by table of random numbers [Figure 1]. Patients received six weekly cycles of either intravesical BCG (120mg) or MMC (40mg) starting from six weeks after initial TURBT. Thereafter patients received further maintenance doses at 3 month intervals for the next year. The patients were followed for a minimum period of one year at three monthly intervals by CBC, routine urine examination, urine cytology for 3 days, ALP, USG abdomen and cystoscopy and chest radiograph and CECT abdomen/pelvis at six month interval. We lost 18 patients to follow up and they were not included in the study.

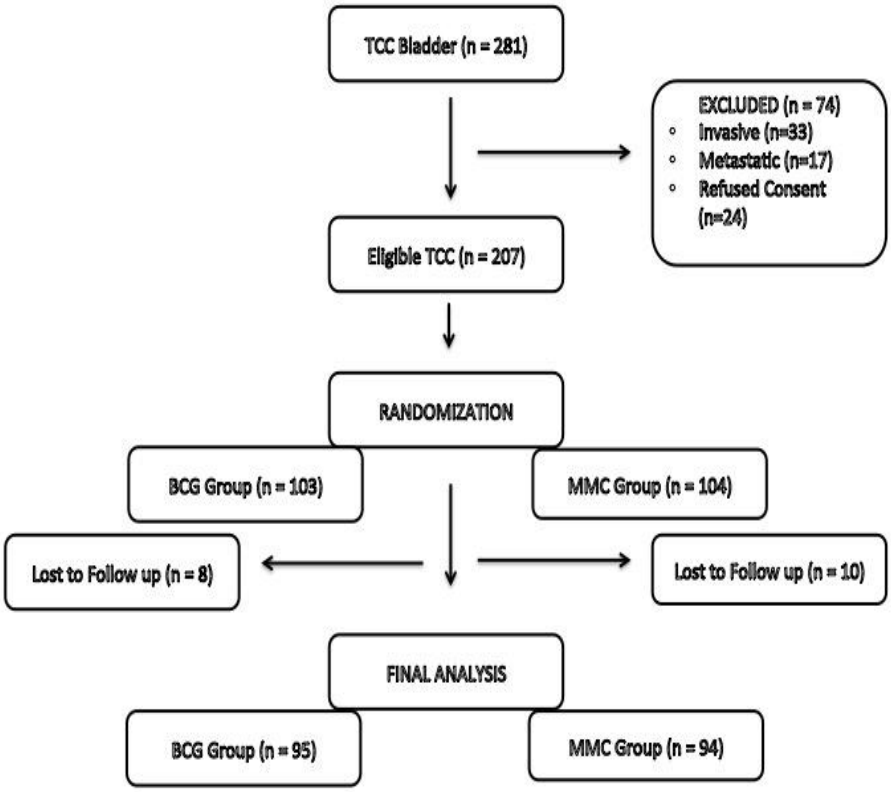

Figure 1 : Consort Diagram for the study.

An approval from the institutional ethical committee was obtained for the purpose of this study. A written and informed consent was taken from the patients for publication and analysis of their data after explaining to them the protocol of the study in their own language. The data thus collected was compiled and analyzed using SPSS version 21 for Mac (IBM Corporation, 2012). To calculate the P-value, Fisher's exact test and Pearson's chi-square test were applied to compare the frequencies for categorical parameters, and the unpaired t-test was used to compare the means (2-tailed) among continuous variables. The results were calculated on 95% confidence interval. A P-value < 0.05 was considered significant.

II. Results

The baseline parameters were similar in the two groups [Table 1]. Thirty seven (38.95%) patients in the BCG arm had side effects as compared to 24 (25.53%) in the MMC group (p = 0.0012). Cystitis was the most common complication in either group [23 (24.21%) in BCG vs 13 (13.82%) in MMC, p = 0.0035]. Symptoms observed were generally mild and cessation of the therapy was not required. Three(3.15%) patients in the BCG group developed severe cystitis requiring admission and anti tubercular therapy. None of the patients developed any allergic reaction in either of the group. A total of nine (9.47%) patients in the BCG group developed fever after instillations which was easily controlled by antipyretics. There was no mortality in either of the groups.

Six recurrences wereobserved at 3-month follow up and seven more recurrences were observed at the end of six months. Out of the 13 (6.87%) recurrences, nine(9.57%) were observed in MMC group and four (4.21%) in BCG group (p= 0.0044). Preoperatively, six of these tumours were grade II and seven were grade III and the recurrencesnoted were also of the same grade in all the cases and therefore no progression of disease was observed in the study.

Table 1: Baseline parameters of the two groups.

PARAMETER	BCG Group (n = 95)	MMC Group (n = 94)	P VALUE
Age (years)	66.13 ± 9.35	65.36 ± 8.61	0.5124
Sex (M: F)	68: 27	71: 23	0.6167
Rural: Urban	55:40	53:41	0.1736
Medical Comorbidities	41 (43.16%)	43 (45.74%)	0.2631
Multiple tumours	23 (24.21%)	21 (22.34%)	0.7883
Grade I:II:III	21:45:29	19:46:29	0.9228
Ta:T1	39:56	41:53	0.8184

III. Discussion

Superficial bladder cancer is notorious for a high recurrence rate. The intravesical therapy has evolved out of need to prevent tumour recurrence after successful surgical resection. Immunotherapeutic and chemotherapeutic agents can be instilled into bladder, thereby avoiding the morbidity of systemic administration. Adjuvant intravesical chemotherapy or immunotherapy is indicated in patients who are at high risk for tumor recurrence by virtue of having multiple tumors, recurrent tumors, high grade tumors associated with urothelial atypia or carcinoma in situ [7]. When instilled immediately following TURBT, it acts prophylactically to reduce implantation [8, 9].

Post TURBT intravesical chemotherapy using various agents like thiotepa, doxorubicin and mitomycin C has been the mainstay of treatment. These agents have achieved short remissions, a net durable benefit being apparently in only 7% to 14% of the patients [5-12]. Intravesical immunotherapy with agents such as BCG has become an important treatment modality, although there has been a difference of opinion with regards to its superiority over chemotherapeutic agents such as MMC [13-16].

Immunotherapy came up as a treatment modality for carcinoma bladder due to the disappointing results with chemotherapeutic agents. BCG is an attenuated strain of *Mycobacterium bovis* that has stimulatory effect on immune responses. The exact mechanism by which BCG exerts its antitumor effect is unknown, but it seems to be immunologically mediated. It appears to be the most efficacious intravesical agent for the management of CIS. Regardless of its actual target, intravesical BCG therapy clearly exercises some of its antitumor effects through immune mechanisms [15-18]. BCG induces a chronic granulomatous response in bladder of many patients [19-21]. Recurrence rates are reduced substantially in patients treated after TURBT (11-22%) versus a 70% recurrence after endoscopic resection alone [21].

In the present study BCG and MMC were compared with respect to efficacy of the therapy in prevention of recurrences following definitive TURBT in superficial bladder cancer and side effects to the therapy. In previously conducted studies, the disease free percentages at one year follow up period varied from 65% to 90% for BCG and 55% to 67% for MMC following TURBT in superficial bladder cancer [15-21]. The disease free percentage at 1 year follow up in our study was 95.79% for BCG therapy and 90.43% for MMC therapy. These values correlate with other studies that also shows comparable results between BCG and MMC at 1 year follow up [18-21].

Side effects of the therapy were divided into local, allergic and systemic. Local side effects were observed in both the study arms. In our study, patients in the BCG group had more local side effects (38.95%), which included cystitis, hematuria and acute retention of urine when compared to the MMC group. We believe that cystitis following BCG instillation occurs due to a marked immune response in the bladder wall. MMC generally produces a chemical cystitis but may produce a bacterial cystitis also due to secondary infection. In our study the patients were categorised as suffering from cystitis when they complained of burning micturition, dysuria and increased frequency of micturition. Fever was the only systemic side effect that was observed. Nine

(9.47%) patients in the BCG arm developed fever after almost every dose instillation. Fever was low grade accompanied with malaise. Patients were treated with antipyretics and responded well.

From our study it can be concluded that both BCG and MMC have comparable efficacies with respect to recurrence at 1 year follow up, while side effects are more commonly seen in the BCG group. The side effects are marginally higher in the BCG group but mild and did not require any delay or cessation of therapies. The strenghths of our study are that it was a randomized, multicentric trial adhering to a strict protocol and the population was non-homogenous and thus the results can be much widely extrapolated.

Acknowledgements

The authors would like to acknowledge the help of the theater staff of these hospitals.

Bibliography

[1]. Boring CC, Squires TS, Tong T, et al. Cancer statistics-1995. *Cancer J Clin* 1995;45:2-7.
[2]. Lang P, DeBruyne F, Fradet Y, Narayan P. Symposium: Treating superficial bladder cancer. *Contemp Urol* 1996;8:61-64.
[3]. Jone HC, Swinney J. Thiotepa in the treatment of tumours of the bladder. *Lancet* 1961;2:615-19.
[4]. Lamm DL, Thor DE, Harris SC, et al: BCG immunotherapy of superficial bladder cancer. *J Urol* 1980;124:38-41.
[5]. Pawinsky A, Sylvester R, Kurth KH, et al: A combined analysis of European Organisation for Research and Treatment of Cancer, and Medical Research Council: randomized trials for the prophylactic treatment of stage TaT1 bladder cancer. *J Urol* 1996;156:1934-39.
[6]. Lamm DL, Riggs DR, Traynelis CL, Nyeso UO. Apparent failure of current intravesical chemotherapy prophylaxis to influence the long term course of superficial transitional cell carcinoma of the bladder. *J Urol* 1995;153:1444-49.
[7]. Rubben H, Lutzeyer W, Fischer N, et al. Natural history and treatment of low and high risk superficial bladder tumors. *J Urol* 1988;139:283-287.
[8]. Jones HC, Swinney J. Thiotepa in the treatment of tumors of bladder. *Lancet* 1961;2:615-621.
[9]. Prout GR Jr, Griffin PP, Nocks BN, et al. Intravesical therapy of low stage bladder carcinoma with mitomycin C: Comparison of results in untreated and previously treated patients. *J Urol* 1982;127:1906-11.
[10]. Stricker PD, Grant AB, Hosken BM, et al. Topical mitomycin C therapy for carcinoma of the bladder. *J Urol* 1987;138:1164-67.
[11]. Issell BF, Prout GR Jr, Soloway MS, et al. Mitomycin C intravesical therapy in noninvasive bladder cancer after failure of thiotepa. *Cancer* 1984;53:1025-31.
[12]. Van Helsdingen PJ, Rikken CH, Sleeboom HP, et al. Mitomycin C resorption following repeated intravesical instillations using different instillation times. *Urol Int* 1988;43:42-46.
[13]. Kowalowski TS, Lamm DL. Intravesical chemotherapy of superficial bladder cancer. In: Resnick M (editor): *Current Trends in Urology*. Williams & Williams, Philadelphia, PA, 1988.
[14]. Herr HW, Laudone VP, Whitmore WF. An overview of intravesical therapy for superficial bladder tumors. *J Urol* 1987;138:1363-67.
[15]. Drago PC, Badalament RA, Lucas J, Drago JR. Bladder wall calcification after intravesical mitomycin C treatment of superficial bladder cancer. *J Urol* 1989;142:171-74.
[16]. Catalona WJ, Ratliff TL. Bacillus Calmette-Gue'rin and superficial bladder cancer: Clinical experience and mechanism of action. *Surg Ann* 1990;22:363-67.
[17]. Kavoussi LR, Brown EJ, Ritchey JK, et al. Fibronectin-mediated Calmette-Gue'rin bacillus attachment to murine bladder mucosa. *J Clin Invest* 1990;85:62-66.
[18]. Morales A, Eidinger D, Burse AW. Intracavitary Bacillus Calmette- Gue'rin in the treatment of superficial bladder tumors. *J Urol* 1976;116:180-85.
[19]. Lamm DL, Thor DE, Harris SC, et al. Bacillus Calmette -Gue'rin immunotherapy of superficial bladder cancer. *J Urol* 1980;124:38-42.
[20]. Schellhammer PF, Ladago LE, Fillion MB. Bacillus Calmette-Gue'rin (BCG) for superficial transitional cell carcinoma (TCC) of bladder. *J Urol* 1986;135:261-65.
[21]. Torrence RJ, Kavoussi LR, Catalona WJ, et al. Prognostic factors in patients treated with intravesical Bacillus Calmette-Gue'rin for superficial bladder cancer. *J Urol* 1988;139:941-45.

DrAsim R Laharwal. "A Prospective Randomized Controlled Trial Of Adjuvant Intravesical Chemotherapy Versus Immunotherapy In Superficial Transitional Cell Carcinoma Of Urinary Bladder." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 18, no. 6, 2019, pp 28-31.