

Intravesical immunotherapy for superficial bladder cancer

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ABSTRACT

Objective: To compare and evaluate the efficacy and tolerance of intravesical instillation of Bacillus Calmette-Guerin (BCG) and interferon alpha-2b immunotherapy for superficial transitional cell carcinoma (TCC) of the urinary bladder.

Methods: Thirty-five patients with superficial TCC of the urinary bladder, primary and recurrent tumors, stage Ta, T1, and grade 1 and 2, were prospectively enrolled for intravesical immunotherapy at the Armed Forces Hospital, Riyadh, Kingdom of Saudi Arabia between January 1992 and December 2000. The treatment regimes used were either 120 mg of BCG weekly for 6 weeks followed by a 2nd 6 week course given only on first tumor recurrence, or 50 million i.u. of interferon alpha-2b weekly for 3 months, bi-weekly for the next 3 months and monthly for 6 months. Twenty-two patients received BCG and 13 received interferon alpha-2b. Adequate blood counts, renal and hepatic function profiles, and informed consent were required. Cystoscopy was repeated every 3 months for the

first 2 years, then 6 monthly for another 2 years and then yearly.

Results: The follow-up period ranged from 9-96 months (median 31.33 months). Twenty patients attended the follow-up and were evaluable in the BCG group and 13 in the interferon alpha-2b group. In the BCG versus interferon alpha-2b group, the rates of complete response were 80% and 41.6%, partial response were 5% and 33.3%, and progression were 15% and 8.3%. Mild side effects occurred in 5 patients and all of them completed their treatments. There was only one cancer related death in each group after 6 and 7 years of starting the treatment.

Conclusions: Bacillus Calmette-Guerin was confirmed as a more effective intravesical immunotherapy for superficial TCC of the urinary bladder as compared to interferon alpha-2b. Both agents' treatments are well tolerated.

Saudi Med J 2002; Vol. 23 (12): 1458-1461

Bladder cancer in the western literature forms the 2nd most common urologic malignancy with over 90% being transitional cell carcinoma (TCC) and 75-88% of them present as superficial tumors.^{1,2} In contrast to this, the National Cancer Registry (NCR) data in the Kingdom of Saudi Arabia (KSA) confirming the bladder cancer being the most common urologic malignancy of which TCC formed 75% and only 30-40% of them were superficial tumors.³ Superficial TCC is defined as TCC that is confined to the mucosa (stages Ta or carcinoma in situ) or that has involved the lamina propria (stage T1).⁴ Endoscopic evaluation and transurethral

resection (TUR) are the most important steps in the management of patients with bladder cancer.⁵ There is, however, a recurrence rate of up to 70% in 5-years, 90% in 15-years and a progression rate of 20% to muscle invasion and 40% to increase in tumor stage and grade in 10 years.² The incidence of recurrence and progression depend on several factors, such as tumor stage, grade, multiplicity, size, and so forth.⁶ Local instillation of different chemotherapeutic agents have shown ranging degrees of efficacy in preventing recurrence, but not progression.⁷ Intravesical Bacillus Calmette-Guerin (BCG) immunotherapy has been proven to be the

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Received 18th June 2002. Accepted for publication in final form 31st July 2002.

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most effective in providing long term protection from tumor recurrence and reduces disease progression.⁷ The use of BCG is associated with significant morbidity.^{7,8} It has been shown that Interferon (IFN) has a definite activity in the treatment and prevention of superficial TCC with minimal toxicity. However, controlled comparisons of immunotherapy suggest that BCG is superior to IFN.^{7,8} We report our experience with intravesical immunotherapy for superficial TCC comparing BCG and IFN.

Methods. Patient selection. An open uncontrolled study of intravesical immunotherapy using either BCG or IFN in superficial TCC of the urinary bladder was conducted at the Armed Forces Hospital, Riyadh, Kingdom of Saudi Arabia, over an 8-year period, between January 1992 and December 2000. The criteria of eligibility included patients with single or multiple, primary or recurrent, stage Ta or T1, grade 1-3 histologically proven TCC of the urinary bladder, and they were required to have adequate white cell count, platelet count, serum creatinine, liver function and coagulation profile. Exclusion criteria were patients with other associated tumors, severe systemic disease, pregnancy, leucopenia, active urinary tract infection and previous treatment with intravesical or systemic chemotherapy or immunotherapy and radiation therapy within the previous 3-months.

Patient initial evaluation. Patient initial evaluation included complete history, physical examination and base line investigations as complete blood count with differential, coagulation profile, renal and hepatic biochemical profile, urine analysis, culture and cytology and chest x-ray. All patients had cystoscopy, complete resection or fulguration of the tumor or tumors and random cold cup biopsies from normal looking mucosa as well as suspicious areas in the bladder.

Treatment regimes. Treatment plan involved intravesical instillation of either 50,000,000 i.u. of interferon alpha-2b (IFN α -2b) (Intron A, Schering-Plough, United States of America) in 100 mls of normal saline (NS) weekly for the first 3 months, bi-weekly for the next 3-months and monthly for 6-months, or 120 mg (BCG culture Statens Serum Institut, Danish strain) in 50 ml of NS weekly for 6 weeks and a 2nd 6 weeks course is repeated at any time of tumor recurrence. Treatment started 2 weeks after TUR. After emptying the bladder via a urethral catheter, the therapeutic agent was instilled, then catheter was removed and the patient was instructed to empty the bladder 2 hours later. Prior to each intravesical instillation, temperature was checked, urine analysis was carried out and side effects were documented including frequency, dysuria, hematuria, fever and other constitutional symptoms. Severe toxicity and patient's request would result in discontinuation of treatment. Treatment would only

be interrupted if urinary infection occurs until it is treated and subsided. No prophylactic anti-tuberculosis treatment was used.

Follow-up and evaluation of therapy. Basic investigations of complete blood count, urea and electrolytes, liver function test, and chest x-ray were repeated at the end of treatment. Cystoscopy and urine cytology were repeated 3 monthly during the first 2-years, 6-monthly for the next 2-years and yearly thereafter if there is no disease recurrence. If recurrence after IFN treatment, BCG was given and if recurrence after first BCG course, a 2nd 6 weeks course of BCG was given. Progression to muscle invasion disease T2 or greater, progression to grade 3 (G3) or appearance of metastasis was an indication for further other suitable treatment.

Criteria of evaluation. Response to treatment was considered complete response (CR) if there was no recurrence during follow-up, partial response (PR) if there was 50% reduction in the number of recurrences plus 100% increase in disease free interval, no change if the tumor status remains the same as before treatment and progression of the tumor if there was increase in stage especially to muscle invasion or development of metastasis.

Results. A total of 35 patients were eligible and enrolled in this study with male:female ratio of 11:1. The median age was 60.17 years (range 26-82 years). There were 13 patients who received IFN α -2b and 22 patients received BCG treatment. At the time of starting treatment, the tumor characteristics are shown in **Table 1** as all were stage Ta and T1, grade 1 (G1) and grade 2 (G2). There were no carcinoma in situ (CIS) and all the random biopsies did not show any malignancy. Urine cytology results did not affect treatment protocol. Twelve patients were evaluable in the IFN group and 20 in the BCG group, as they attended the follow-up period ranging from 9-96 months (median 31.33 months).

Side effects. Side effects occurred in one patient in the IFN group who developed fever, whereas in the BCG group 2 patients developed transient macroscopic hematuria and 2 others developed frequency or dysuria without proven bacterial cystitis. All were settled with non-specific treatments and without the need for antibiotics. The treatments were well tolerated and there were no occurrence of systemic side effects in the BCG group.

Efficacy. The evaluation criteria and definitions of responses illustrated in the methods section and the treatment responses were shown in **Table 2**. Bacillus Calmette-Guerin was clearly more efficacious than IFN in producing complete response to treatment. Those who showed partial or no response at 16-36 months follow up from IFN group were given BCG. Six patients in the BCG group had a 2nd 6-weeks course of BCG at first time recurrence at 9-30 months follow-up.

Table 1 - Tumor characteristics.

Stage and grade	IFN α -2b n=13	BCG n=22
Solitary / multiple	5/8	10/12
Size <3cm / 3cm	12/1	19/3
Ta G1	1	2
Ta G2	1	-
T1 G1	5	7
T1 G2	6	13

IFN α 2b - interferon alpha-2b, BCG - Bacillus Calmette-Guerin
n - number, Ta - stage a, T1 - stage one, G1 - grade one, G2 - grade 2

Table 2 - Response to treatments.

Response	IFN α -2b n=12 (%)	BCG n=20 (%)
Complete response	5 (41.6)	16 (80)
Partial response	4 (33.3)	1 (5)
No change	2 (16.6)	0 (0)
Progression	1 (8.3)	3 (15)

Three patients failed to follow-up.
IFN α 2b - interferon alpha-2b, BCG - Bacillus Calmette-Guerin,
n - number

Progression and mortality. In the IFN group, one case (T1G2) developed metastasis and in the BCG group 3 cases showed progression in stage and grade (one T1G1 to T2G3, 2 T1G2 to one T2G2 and another to T3G3). Two of these had radical cystoprostatectomy and Kock's orthotopic neobladder and they are alive and well. There was one death of metastasis in each group, 7 and 6-years after the inception of treatments both were T1G2 prior to progression.

Discussion. The most important risk of superficial TCC of the urinary bladder is tumor recurrence and progression to invasive and metastatic disease.⁶ Although TUR is the standard treatment of choice of superficial tumors, the high rate of recurrence and occasional multiplicity often makes resection alone insufficient.⁹ Intravesical chemotherapy has produced a short term reduction in tumor recurrence but on long term studies it showed no reduction in either tumor recurrence or progression.^{7,10} Intravesical immunotherapy has been applied now for more than 20-years as a treatment for multi-focal carcinoma in situ and an adjuvant for Ta T1 papillary bladder cancer after transurethral resection.¹¹ Intravesical immunotherapy using BCG has been proven to be the most effective agent in decreasing the incidence of recurrences and progression of superficial TCC of the urinary bladder compared to several chemotherapeutic agents.^{7,12,13} Reduction in mortality rate from 32% in patients treated with resection alone to 14% in those receiving additional BCG.¹⁴ Complete responses as high as 87% has been reported with long term disease free duration in over 80% of patients.¹³ The mechanism of action of BCG is not well understood, but it is believed to cause local inflammatory reaction in the bladder, which initiates a tumor specific immune response with release of several cytokines with anti-oncogenic activity.¹⁵ Bacillus Calmette-Guerin

instillation causes more side effects than intravesical chemotherapy. Most of these side effects are related to chemical cystitis causing significant dysuria, hematuria, occasional fever and constitutional symptoms, but fortunately, these are self limiting.¹⁵ More serious side effects from disseminated BCG infection occur rarely, but can be treated effectively.^{16,17} Interferons are cytokines that mediate immune responses including anti-viral, anti-proliferative and immunoregulatory activities.^{17,18} Complete responses of superficial TCC using alpha interferon intravesically was 32%.¹⁹

The results of our study support several other reports confirming the effectiveness of BCG instillation compared to IFN in producing complete responses. Both BCG and IFN were well tolerated by patients. Four of the 22 patients who received BCG developed local side effects, which were mild and self-limiting and none developed serious systemic BCG infections. It seems the regime of BCG treatment we used is satisfactory since the standard course of BCG comprises weekly intravesical instillations for 6 weeks and the long term results may be improved by an additional 6 weeks course²⁰ or maintenance therapy.¹⁶ As regards to the IFN, the dose of 50 million i.u. has worked quite well according to our pre-treatment protocol, although others use 100,000,000 i.u. but for a shorter period. Because we have noticed the accumulating evidence of the superiority of BCG over IFN and considering the significant cost of IFN we stopped using it since 1995. Although all the tumors were Ta, T1, G1 or G2 and absent CIS or G3, there was one case (T1G2) of IFN group who developed metastasis and 3 (one T1G1 and 2 T1G2) in the BCG group who showed progression into invasive disease (T2G2 and T3G3). Two deaths occurred, one in each group 6 and 7 years of starting treatment. We cannot find a specific factor contributing to this progression except that

invasion can occur in 10% of patients of TCC overtime in spite of whatever treatment given.²

The results of our study confirm the superiority of BCG intravesical immunotherapy effectiveness in the treatment of superficial TCC of the urinary bladder over interferon alpha-2b. Both treatments were well tolerated. Considering the modest response of IFN and its high cost compared to BCG, we do not recommend IFN use as first line of treatment as BCG for superficial TCC of the bladder after transurethral resection.

Acknowledgment. We would like to thank Corazon Domingo for secretarial services. We are also grateful to all members of the Department and colleagues who helped in the management of these patients.

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