Management of bacillus Calmette-Guerin (BCG) refractory superficial bladder cancer: results with intravesical BCG and Interferon combination therapy

Sanoj P. Punnen, BSc, Joseph L. Chin, MD, Michael A. S. Jewett, MD

Divisions of Urology, University of Toronto and The University of Western Ontario, Department of Surgical Oncology, Princess Margaret Hospital, Toronto, Ontario, Canada

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Introduction and objective: *BCG is the most efficacious intravesical treatment for superficial bladder cancer. However, 30%-40% of tumors are refractory. BCG failure is an indication for cystectomy but several salvage intravesical (IVe) strategies have been proposed. Early results with reduced dose BCG in combination with IFN-α in patients are currently the most promising. We have adopted this approach and now report our preliminary results. This is the first report of this salvage therapy from Canada, the birthplace of IVe BCG therapy for superficial bladder cancer.*

Methods: *The "O'Donnell protocol" of reduced dose IVe BCG plus IFN-α was followed in 12 patients with BCG refractory superficial transitional cell carcinoma. A retrospective review of the efficacy and toxicity of the treatment was conducted.*

Results: *One year from induction therapy with salvage BCG/IFN-α, 6 of the 12 (50%) of patients were tumor free. Of the six recurrences, 3(50%) did not respond to the IVe therapy and had residual/recurrent tumor at the first follow-up visit. Risk factors for treatment failure were identified. The combination therapy was well tolerated with minimal toxicity compared to previous full dose BCG.*

Conclusion: *Our 12 month data with reduced dose IVe BCG plus IFN-α salvage therapy for BCG refractory superficial TCC confirm previous reports in >50% complete response rates. We need longer follow up in a larger patient population to determine the durability of this promising therapy in patients who would otherwise undergo radical cystectomy.*

Key Words: bladder cancer, superficial, immunotherapy, intravesical therapy

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Address correspondence to Dr. Michael A. S. Jewett, Division of Urology, University of Toronto, 610 University Avenue, 3-124, Toronto, Ontario M5G 2C4 Canada

Remembrance

Above all, we remember Ernie for his zest and clear expression of opinion. He lived energetically. That is why his premature death has left a palpable gap in our Canadian Urological community. I never worked directly with Ernie as a urologist but I knew him as a committed academic and leader in our country. His

enthusiasm and commitment was also recognized internationally which helped his adopted and relatively small community, Winnipeg, to be widely known in the global Urology village. He was a wonderful ambassador for all of us and we miss him. We expected to have his wise counsel for years to come.

His interest in bladder cancer began as a resident and like many of us in Canada, he was seduced by the many intriguing aspects of BCG use in superficial bladder cancer. His teacher and mentor, Dr. Andrew Bruce, was the senior author of the first report of its use. We therefore thought it fitting to report a very interesting development in the use of BCG in this report.

Michael Jewett

Introduction

Currently the most effective adjuvant therapy for superficial bladder cancer is intravesical (IVe) instillation of bacillus Calmette-Guerin (BCG) which was first described by Dr. Alvaro Morales of Queen's University, Canada.[1] However, in 30%- 40% of cases, this treatment fails to eradicate residual tumor, usually carcinoma in situ, after resection. Furthermore, many who initially respond, experience late recurrence and/or progression.[2] These scenarios constitute BCG failure and with failure, radical cystectomy is usually recommended. Alternative less invasive options for salvage therapy with further IVe instillations, external radiation and several experimental strategies have been reported.[3]

The antitumor effect of BCG is mediated by incompletely understood cellular and humoral immunological mechanisms.[4] BCG failure may therefore, be due to an inability to mount an appropriate immune response to the BCG vaccine.[5]

Among alternative intravesical immunotherapeutic agents, interferon-α2B (IFN-α) monotherapy has been found to be less effective than BCG in the management of superficial bladder cancer.[6] However, recent studies have suggested that IFN-α serves as a potent enhancer of the BCG elicited immune response. Zhang et al found that a combination of BCG and IFN-α had an additive effect on the production of cytokines from bladder cancer cells, which correlate with the cytotoxicity and growth inhibition induced by these agents.[7] In addition, the combination may produce response with a lower dose of BCG, thereby reducing the toxicity of BCG therapy.[5] The combination of reduced dose BCG and IFN-α has been tested clinically as a salvage therapy for patients who have failed IVe BCG with a reported 63% rate for durable response at one year.[5] This unprecedented effectiveness in the face of previous BCG failure plus the apparently better tolerated lower BCG dose stimulated us to test this approach at the Princess Margaret Hospital, University Health Network (UHN) and the University of Western Ontario.

Methods

Twelve patients with superficial transitional cell carcinoma (TCC) of the bladder who had failed one or more courses of BCG therapy, received BCG/IFN-α according to the O'Donnell protocol[5] (9 at the UHN, University of Toronto, and 3 at the London Health Sciences Center, University of Western Ontario). Of the 2 women and 10 men, 5 had BCG refractory disease less than 6 months from the last BCG induction course of 6 weekly instillations and 8 had stage CIS or T1 TCC or high grade (G3) tumor; 10 had 2 or more recurrences prior to BCG/ IFN-α treatment; 4 had a disease duration greater than 4 years before treatment with BCG/IFN-α; and 3 had failed BCG therapy on 2 or more occasions Table 1.

The O'Donnell protocol induction treatment of 6 weekly instillations of 1/3 dose BCG combined with 50 million units of interferon-α2B (Schering IntronA®) mixed in 50 cc buffered saline was followed by maintenance therapy (see later). A further dose reduction to 1/10 dose BCG was recommended if significant BCG side effects occurred.[5] The timing and dosage of instillations were selected in an attempt to optimize the immunotherapeutic effects based on animal and in vitro observations by O'Donnell and others.[5]

Patients who achieved a complete response at 3 months, received maintenance therapy of 3 weekly combination instillations at approximately 3, 5, 11 and 17 months from the start of induction. Each 3 dose maintenance course consisted of a 1/3 dose BCG with 50 million units of interferon-α2B for the first dose followed by 1/10 dose BCG with 50 million units of interferon-α2B for the second and third doses. Further

TABLE 1. **Risk factors in BCG refractory patients**

	No.	**(%)**
BCG refractory with recurrence less then 6 months	5	(42)
Aggressive histology (CIS, T1, G3)	8	(67)
Greater or equal to 2 recurrences	10	(83)
Disease greater than 4 years	4	(33)
Two or more BCG failures	3	(25)

reductions in BCG dosage and delays in treatment were permitted for intolerable BCG/IFN-α toxicity. Written consent was obtained from the patients and the review of their records received Research Ethics Board approval.

Results

Treatment efficacy

Overall, the combination of low-dose BCG/IFN-α produced a 75% (9 of 12 patients) complete response rate at the 3 month follow-up cystoscopy after starting induction. Six patients have been followed for one or more years and four or 50% had a durable complete response. No patient was given a second induction cycle of BCG/IFN-α. Of those that failed, 3/6 (50%) had recurrent disease at the first follow up cystoscopy. Of those that had at least one maintenance dose of reduced dose BCG with IFN-α, only one has had a recurrence. There has been no progression of disease to muscle invasion or metastases to date.

Table 2 shows the disease free status after BCG/IFN-α combination therapy by tumor characteristics. There is a trend for patients with two or more previous failures to BCG therapy to be more likely to have a recurrence than patients who had only failed once. Patients who presented with an "aggressive" histology, defined by CIS, T1, or G3 tumor, were more likely to recur then patients with a less aggressive histology. Furthermore, patients who have had two or more previous recurrences prior to BCG/IFN-α therapy were more likely to recur than patients with less than two previous recurrences. Patients who had a relapse within 6 months of BCG therapy were more likely to recur then patients who had a late relapse (> 6 months) to previous BCG therapy. Finally, patients who have had disease for greater then 4 years prior to BCG/IFN-α therapy were more likely to have a recurrence than patients who had bladder cancer for less then 4 years prior to therapy. There appeared to be a lower response rate for those patients who had the risk factors identified in Table 1.

Table 3 displays the disease free status after BCG/IFN-α therapy based by the pathology of the tumor. Although numbers are small, there did not appear to be any obvious difference in response to BCG/IFN-α therapy based on stage, grade, or the presence of CIS.

Toxicity to treatment

There was no apparent difference in toxicity with low dose BCG/IFN-α combinative therapy compared to that of BCG alone Table 4. Side effects typically consisted of irritative symptoms, flu–like symptoms and mild gross hematuria. Only one patient had to reduce the dose of BCG and he was advised to cancel the last two instillations of induction due to severe local symptoms.

Discussion

Bacillus Calmette-Guerin (BCG) has become first line IVe treatment for superficial carcinoma of the bladder

TABLE 2. **Disease free status based on tumor characteristics**

Subgroup	No.	3 months (%)	6 months (%)	12 months (%)	24 months (%)
Overall	12	9/12 (75)	7/10 (70)	3/6 (50)	0/2 (0)
Previous BCG courses					
1	9	8/9 (89)	6/8 (75)	3/3 (100)	0/1 (0)
2 or more	3	1/3 (33)	1/2 (50)	0/1 (0)	0/1 (0)
"Aggressive" histology					
No	4	4/4 (100)	3/4 (75)	2/3 (67)	0/2 (0)
Yes	8	5/8 (63)	4/6 (67)	1/3 (33)	
Recurrence					
2	2	2/2 (100)	1/1 (100)		
>2	12	7/10 (70)	6/9 (67)	3/6 (50)	0/2 (0)
Relapse					
Late >6 months	7	6/7 (86)	4/6 (67)	2/4 (50)	
Early <6 months	5	3/5 (60)	3/4 (75)	1/2 (50)	0/2 (0)
Disease duration					
<4 years	8	6/8 (75)	5/6 (83)	3/3 (100)	0/1 (0)
>4 years	4	3/4 (75)	2/4 (50)	0/3 (0)	0/1 (0)

TABLE 3. **Disease free status based on pathology of tumor**

Stage	No.	3 months (%)	6 months (%)	12 months (%)	24 months (%)
Ta	6	5/6 (83)	3/5 (60)	1/2 (50)	0/2 (0)
w/CIS	1	1/1 (100)			
no CIS	5	4/5 (80)	3/5 (60)	1/2 (50)	0/2 (0)
T1	2	1/2 (50)	1/2 (50)		
w/CIS	2	1/2 (50)	1/2 (50)		
no CIS	0				
Isolated CIS	3	2/3 (67)	2/3 (67)	1/3 (33)	
w/papillary TCC	2	1/2 (50)	1/1 (100)		
any CIS	5	3/5 (60)	3/4 (75)	1/3 (33)	

since the first report of its use published in 1976 by Morales et al. Intravesical BCG therapy produces a complete response rate of 70% or greater and a significant long term decrease in the rate of recurrence.[1] Recently, a meta-analysis of clinical trials comparing BCG with other intravesical therapies has been reported demonstrating a reduction in the risk of progression after maintenance therapy as well.[8] However, in 30%- 40% of patients, intravesical therapy with BCG fails.[2] After first line BCG therapy failure, the patient is left with limited treatment options.

Current alternatives include intravesical chemotherapy including combined immunotherapy and radical cystectomy.[9] Further instillations of BCG in the management of BCG refractory patients failed to show promising results, especially in patients who had failed more then two courses of BCG therapy.[10] A study by the Valrubicin Study Group of 90 BCG refractory patients found a complete response after 6 months in only 19 (21%) of the patients treated with Valrubicin.[11] Mitomycin C and adriamycin have been used with limited response rates in comparison with immunotherapy.[12] Radical cystectomy remains the standard of care for BCG failure.

Although the exact effector mechanism of BCG therapy has not yet been determined, it appears to function through a cellular and humoral immune response.[4] Zlotta et al showed that the ability of BCG to enhance cytotoxicity against bladder tumor cells was related to its ability to provide positive stimuli for T helper 1(th-1) release.[13] Other studies have shown BCG to mediate its effects through the

TABLE 4. **BCG/IFN toxicity by patient**

Patient	Toxicity to BCG	Toxicity to BCG/IFN
1		right epidiidymitis
2	irritative symptoms, freq. dysuria, chills	severe arthritis, mandible, back, leg pain
4	mild gross hematuria, dysuria, freq. (24h)	
7	developed Reiters Syndrome related to BCG	severe local symptoms
8		back pain
9		fever, malaise + irritative symptoms
10		polymyalgia/polyarthritis
12		irritation + debility

increased release of interleukin- 2(IL-2). Saint et al demonstrated that when urinary IL-2 levels were less then 27 pg./ micromole creatinine, patients were significantly more likely to have recurrences than those patients with higher values.[14] A drop in circulating IL-2 has been reported to be consistently associated with tumor relapse.[15] These findings suggest that BCG failure may be due to a deficiency in the appropriate immune response.[5]

Recent studies have demonstrated that the addition of interferon alpha-2B can be used to enhance the immune mediated anti-tumor effects of native BCG. Luo Y et al showed that IFN-α acts as a potent enhancer of the BCG immune response by promoting th1 expression.[16] IFN-α also enhances the BCG response by increasing the levels of circulating IL-2.[17] This ability of IFN-α to enhance the immune mediated anti-tumor effects of BCG is the immunological basis for rational use of IFN-α in conjunction with BCG in combination therapy. Gan et al reported that 14/15 BCG/IFN-α treated mice compared to 8/16 BCG only treated mice became tumor free. They also found that combination of BCG and IFN-α had superior and earlier anti-tumor activity than BCG alone.[18]

Combination therapy with BCG and IFN-α for the treatment of superficial carcinoma of the bladder refractory to BCG has been reported by Dr. O'Donnell. The single centre study showed that 63% of 40 patients were disease free after one year.[5] Similar results are expected from a multicentre study with more than 100 patients followed for up to 3 years.[19] The key aspects of this protocol, first tested in BCG refractory patients but potentially of use in BCG naïve patients as well, is the ability of reduced dose BCG to decrease toxicity and potentially increase the effectiveness of BCG with the addition of the cytokine. [5]

Our results with the O'Donnell protocol have supported his initial findings with a 57% disease free status at 1 year post induction. We also found that 50% of the patients that recurred had a recurrence by their first cystoscopy evaluation at 3 months. This is important because an early failure of this protocol allows the patient to be placed on more aggressive therapy earlier on in their management. Our results also showed that patients who presented with any of the risk factors for recurrence outlined in Table 1 (relapse within 6 months, failure to 2 or more BCG courses, more then 2 recurrences, aggressive histology, or greater then 4 years of disease) were more likely to have a recurrence than those patients without these risk factors. The results did not show any difference in the response rate to combination therapy based on the tumor stage, grade or presence of CIS.

The second objective of our review was to investigate the toxicity of low dose BCG/IFN-α compared to our experience with BCG alone. BCG therapy has been reported to produce systemic symptoms with flu- like illness characterized by fever and malaise as well as local cystitis and transient hematuria.[5] Brown et al found that in contrast to BCG, intravesical interferon alone is associated with minimal side effects and a very low dropout rate of patients on treatment.[20] These findings support the rational behind this protocol suggesting that the addition of interferon alpha enhances the anti-tumor effects of BCG thereby allowing the use of a lower dose of BCG and therefore having less toxic effects of the treatment.[5] Stricker et al found that the combination of BCG/IFN-α was well tolerated, with adverse affects being mild to moderate and resolves at the end of treatment.[17] This coincided with our own results. We found that the combination of BCG/IFN-α was well tolerated by our patients with minimal dropout rates that subsided after treatment cessation.

Although a larger population size and more extensive follow up is required to help further define the appropriate criteria for the use of this combination therapy in the clinic, this study validates the encouraging results for the use of this treatment as a salvage therapy for BCG refractory disease. The combination of BCG and interferon alpha is both an efficacious and well tolerated treatment for patients that have failed prior BCG therapy. □

References

1. Morales A, Eidenger D, Bruce AW. Intravesicular Bacillus Calmette-Guerin therapy for *in situ* transitional cell carcinoma. *J Urol* 1976;116:180.
2. Lamm DL, Blumenstein BA, Crawford ED et al. A randomized trial of intravesical doxorubicin and immunotherapy with bacille Calmette-Guerin for transitional –cell carcinoma of the bladder. *N Engl J Med* 1991;325:1205.
3. Lopez BA. Bladder treatment. Immunotherapy and Chemotherapy. *Urol Clin North Am* 1999; 26(3):535-545.
4. Mikkelsen DJ. Mechanism of action of intravesical bacillus Calmette-Guerin for bladder cancer. *Cancer Treat Res* 1989;46:195-211.
5. O'Donnell MA, Krohn J, DeWolf WC. Salvage intravesical therapy with interferon-a2B plus low dose bacillus Calmette-Guerin is effective in patients with superficial bladder cancer in whom bacillus Calmette-Guerin alone previously failed. *J Urol* 2001;166:1300-1305.
6. Glashan RW. A randomized controlled study of intravesical alpha-2B-interferon in carcinoma in situ of the bladder. *J Urol* 1990;144:658.
7. Zhang Y. Effects of bacillus Calmette-Guerin & # X00E8; rin and interferon alpha-2B on cytokine production in human bladder cancer cell lines. *J Urol* 1999;161(3):977-983.

8. Sylvester RJ, Van der Meijden APM, Lamm DL. Intravesical Bacillus Calmette-Guerin reduces the risk of progression in superficial bladder cancer: A meta-analysis of published results of randomized clinical trials. *J Urol* 2002;168:1964-1970.
9. Kim JC. The limits of bacillus Calmette-Guerin for carcinoma in situ of the bladder. *J Urol* 2001;165(3):745-756.
10. Catalona WJ. Risks and benefits of repeated courses of intravesical bacillus Calmette-Guerin therapy for superficial bladder cancer. *J Urol* 1987;137(2):220-224.
11. Steinberg G. Efficacy and safety of valrubicin for the treatment of bacillus Calmette-Guerin refractory carcinoma in situ of the bladder. *J Urol* 2000;163(3):761-767.
12. Morales A, Salvatori VA, Filion MC, Phillips NC. Mycobacterium cell wall (MCC) in the treatment of refractory CIS of the bladder. *BJU International* 2002;90(Suppl.2):1-4.
13. Zlotta AR. What are the immunologically active components of bacille Calmette-Guerin in therapy of superficial bladder cancer. *Int J Cancer* 2000;87(6):844-852.
14. Saint F. Prognostic value of a T helper 1 urinary cytokine response after intravesical bacillus Calmette-Guerin treatment for superficial bladder cancer. *J Urol* 2002;167(1):364-367.
15. Magno C. The anti-tumor activity of bacillus Calmette-Geurin in bladder cancer is associated with an increase in the circulating level of interleukin-2. *Immunol Lett* 2002;81(3):235-238.
16. Luo Y. IFN-a 2B enhances Th1 cytokine response in bladder cancer patients receiving Mycobacterium bovis bacillus Calmette-Guerin immunotherapy. *J Immunol* 1999;162(4):2399-2405.
17. Stricker P, Pryor K, Nicholson T et al. Bacillus Calmette-Guerin plus intravesical interferon apha-2B in patients with superficial bladder cancer. *Urology* 1996;48:957.
18. Gan YH. Antitumor immunity of bacillus Calmette-Guerin and interferon alpha in murine bladder cancer. *Eur J Cancer* 1999;35(7):1123-1129.
19. O'Donnell MA: personal communication.
20. Brown DH. Interferons and bladder cancer. *Urol Clin North Am* 2000;27(1):171-178,xi.