Treatment of BCG failures with intravesical BCG/ Interferon: the University of Montreal experience

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Objective: *Bacillus Calmette-Guerin (BCG) has shown promise in large scale studies. We assessed recurrence-free survival in patients treated with intravesical BCG/ Interferon (IFN) for non-muscle invasive, BCG refractory, transitional cell carcinoma (TCC) of the urinary bladder at our local institution.*
Methods: *Cancer control data were gathered for patients enrolled in a BCG/Interferon protocol at the University of Montreal. The main inclusion criteria consisted of pathologically proven evidence of intravesical BCG failure, and of complete transurethral resection of latest post BCG recurrence. Induction consisted of eight intravesical BCG/Interferon instillations. Select patients were treated with BCG/Interferon maintenance therapy.*
Results: *Thirteen patients aged from 45 to 81 years (mean: 65) were included. Stages at TCC diagnosis were distributed as follows: 6 (46%) CIS, 3 (23%) Ta, and 4 (31%) T1. Induction BCG consisted of an average of 11 weekly instillations (range 3-24). Prior to BCG/ Interferon stage distribution was as follows: 9 (69%) CIS, and 4 (31%) T1. BCG/Interferon maintenance was administered to 5 (38%) patients. Follow-up ranged from 1.5 to 32 months (mean=15, median=12). Recurrence was diagnosed in 5 patients (38%). Recurrence free survival (RFS) at 24 months was 66%. When stratified according to T stage prior to BCG/IFN, patients with CIS fared worse than T1 patients (50% versus 100%). Maintenance had no effect on RFS (75% versus 69%).*
Conclusions: *Our results corroborate previous BCG/ IFN reports. In selected patients, intravesical BCG/IFN offers a valid alternative to definitive therapy.*

Key Words: bladder cancer, BCG failure, salvage therapy, BCG/Interferon

Introduction

Bacillus Calmette-Guerin (BCG) represents the most widely used intravesical treatment modality for non-muscle invasive transitional cell carcinoma (TCC).[1] After the first course of BCG 35%-45% of patients with papillary tumors and 20%-25% of patients with CIS can expect to have recurrent disease.[2] A second course is generally recommended and response rates of 30%-50% may be anticipated.[3] Intravesical treatment options for patients that recur after either their first or second BCG cycle include repeat BCG, intravesical chemotherapy (mitomycin C, valrubicin), interferon-α2B (IFN) monotherapy, or BCG/IFN combination therapy. BCG/ IFN combination therapy is associated with the highest response rate when administered to such patients. More than 50% of those patients may be expected to remain recurrence-free up to 2 years after initial BCG/IFN induction therapy.[4-6] We decided to explore the rate of non-recurrence after BCG/IFN combination therapy for BCG failures. Specifically, we hypothesized that BCG/ IFN can provide durable control in patients with recurrent TCC after initial BCG therapy.

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Materials and methods

Patients

Between October 2000 and November 2004, 13 patients with established failure BCG treatments were offered the option of intravesical BCG/IFN. Eligibility was

based on pathologically proven recurrent cancer on transurethral biopsy and on complete resection proven by post TUR cystoscopy and/or re-resection. Only patients with CIS, Ta, T1 or combination of these stages were included. The 1997 TNM staging system was used.

The BCG/IFN therapy protocol was based on previously published recommendations.[4] Briefly, all patients received induction therapy which consisted of eight 2 hour-intravesical instillations of one third dose of standard BCG combined with 50 million international units (MIU) of IFN (Präparatenname/ firma). These were delivered in 50 ml of pyrogen-free water. As of February, 2002, maintenance therapy was offered to patients without evidence of recurrent TCC after BCG/IFN induction therapy. It consisted of 3 weekly intravesical installations given every 6 months for 3 years, unless failure was documented prior to that time.

Response criteria

Patients were reassessed every 3 months with cystoscopy and cytology for the initial 24 months, and every 6 months thereafter. If either was suspicious, transurethral biopsies were performed. BCG/IFN recurrence was defined as either cytology demonstrating presence of transitional cell carcinoma or tissue proof of TCC.[7,8] As in the previous report, progression was defined as recurrence with higher pathological stage and/or grade, or the development of muscle-invasive disease or metastasis.[4-6] Tolerability of the treatment regimen was not examined in this study.

Statistical analysis

Actuarial recurrence-free survival after BCG/IFN instillation were based on life table analyses and were stratified according to mmaintenance therapy status, stage prior to BCG/IFN induction and number of BCG cycles prior to BCG/IFN induction. Two-sided statistical significance was set at $p < 0.05$. All tests were performed using S-PLUS software with the Design and Hmisc libraries (S-PLUS 2000 Professional, version 1, MathSoft Inc., Seattle, WA).

TABLE 1. **Descriptive characteristics of 13 patients receiving BCG/INF after failure of adjuvant BCG**

Variables	**Number**
Number of patients (n)	13
Gender (n, male)	10 (77%)
Age (years)	
Mean (median)	65 (65)
Range	45-81
Follow up (months)	
Mean (median)	15 (12)
Range	1.5-32
Stage at initial diagnosis	
CIS	6 (46%)
Ta	3 (23%)
T1	4 (31%)
Stage post ≥ 2 BCG failures	
CIS	9 (69%)
T1	4 (31%)
Risk factors	
Recurrence < 6 months	5 (38%)
CIS, T1, G3	9 (69%)
≥ 2 recurrences	9 (69%)
Disease > 4 years	4 (31%)

CIS: carcinoma in situ; BCG: Bacillus Calmette-Guerin; G3: grade 3

Results

Of the 13 patients included in the cohort the median age was 65 years (45-81 years) and their median follow-up since first BCG/IFN instillation was 12 months (1.5-32 months). At initial bladder cancer diagnosis, 6 (46%) had CIS, 3 (23%) had Ta, and 4 (31%) had T1 disease. After BCG failure, CIS was recorded in 9 (69%) and T1 disease in 4 (31%) patients, Table 1.

Of 13 patients treated with BCG/IFN induction therapy, 5 (38.5%) received between 1 and 4 cycles of

TABLE 2. **Recurrence rate according to stage prior to BCG/IFN induction**

Stage at BCG-failure	**Failure**				**No Failure**	**Total**
	Stage at BCG/IFN-α2B failure					
	CIS	**T1**	**T2**	**T4a**		
CIS exclusive	1	2	1	1	4	**9**
T1 with CIS	0	0	0	0	2	**2**
T1 without CIS	0	0	0	0	2	**2**
Total	**5**				**8**	**13**

maintenance therapy: 4 had CIS and 1 had T1 disease. Maintenance therapy was continued either until recurrence or up to 3 years after BCG/IFN induction therapy. No dose reduction or treatment interruptions were required.

Table 2 stratifies patients according to recurrence and non-recurrence after BCG/IFN therapy. Moreover, it provides tumor stage prior to BCG induction. Finally, it provides tumor stage at the time of recurrence after BCG/IFN therapy. Overall, recurrence was recorded in 5 (38.5%) of 13 patients. Of 9 patients with exclusive CIS prior to BCG/IFN, 3 (33%) recurred with the CIS or T1, 2 (22%) had progressive disease, and 4 (44%) did not recur. Of 2 patients that progressed, 1 progressed from CIS to T2, and 1 progressed from CIS to T4a disease. Of 4 patients with stage T1 prior to BCG/IFN, none recurred.

Figure1A shows the overall actuarial probability of non-recurrence after BCG/IFN, which was 66% at 2 years. Mean time to recurrence was 23 months (95% CI: 16-31 months).

Figure 1B shows the probability of non-recurrence according to BCG/IFN maintenance versus no maintenance therapy. At 24 months the probability

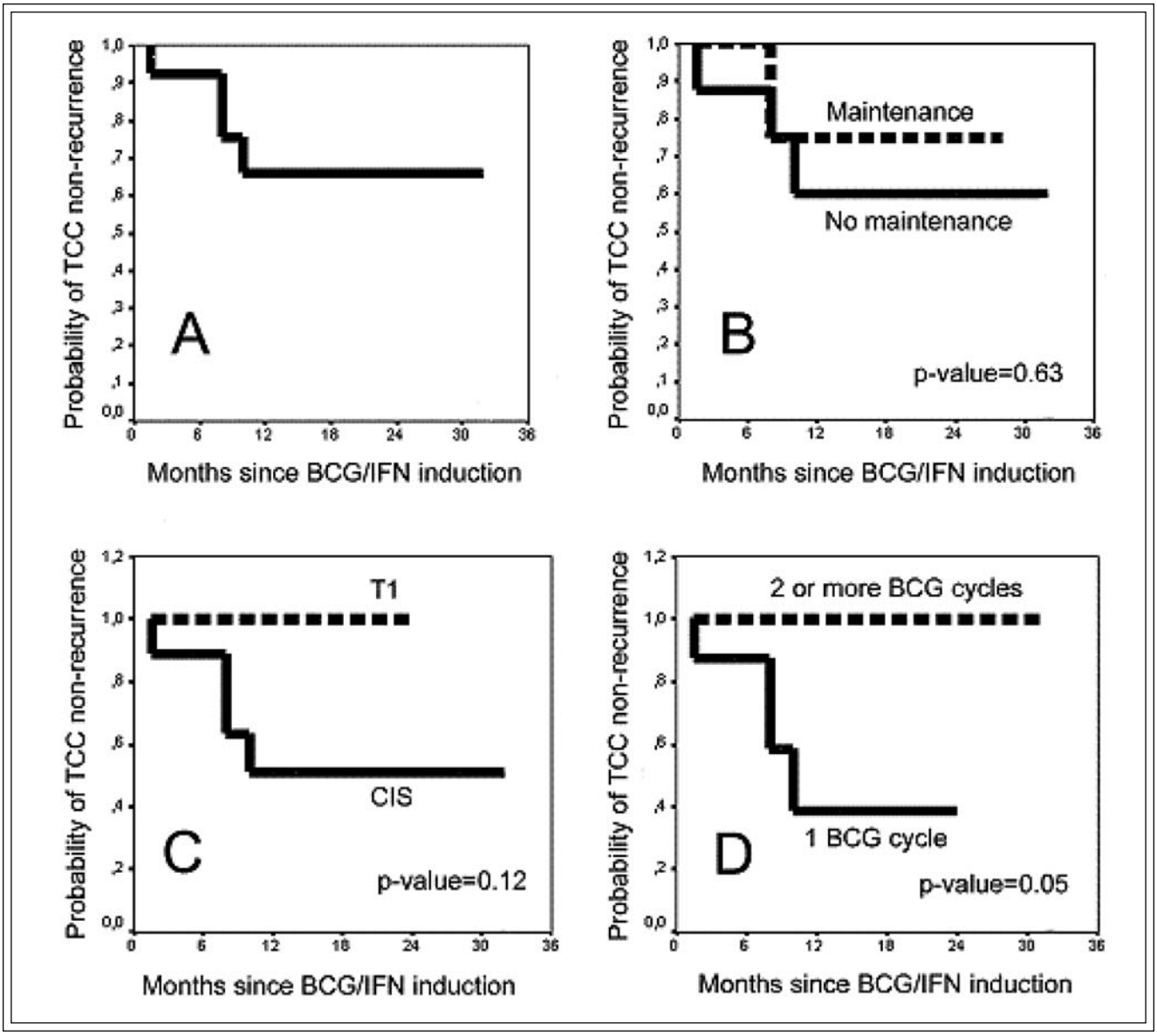

Figure 1. Actuarial recurrence-free survival after BCG/IFN-α2B.
A) Overall actuarial RFS, B) Maintenance versus non-maintenance, C) Stage prior to BCG/IFN induction, D) number of BCG cycles prior to BCG/IFN induction.

TABLE 3. **Actuarial recurrence-free probability at 24 months**

Variables	Recurrence-free probability	
All patients	0.66	
Eligible patients for maintenance treatment		
did not receive maintenance	0.69	p = 0.63
received maintenance	0.75	
Stage before BCG/IFN induction therapy		
CIS	0.50	p = 0.123
T1	1.00	
Number of BCG failures prior to BCG/IFN		
one	0.39	p = 0.051
2 or more	1.00	

of non-recurrence in the maintenance group was 75%, while the probability in the no- maintenance group was 61% (p=0.63).

Figure 1C shows the probability of non-recurrence according to stage prior to BCG/IFN induction therapy. At 24 months the probability of non-recurrence in those with T1 TCC was 100%, while the probability in those with CIS was 50% (p = 0.12).

Figure 1D shows the probability of non-recurrence according to the number of received BCG cycles prior to BCG/IFN induction therapy. At 24 months the probability of non-recurrence in those exposed to 2 or more BCG cycles was 100%, while the probability in those exposed to 1 BCG cycle was 39% (p = 0.05). Stratification of these patients according to tumor stage prior to BCG/IFN induction failed to reveal a statistically significant difference (p = 0.51). Overall, the recurrence-free probability with the combined regimen at 24 months was 66%, Table 3.

Discussion

BCG induction response rates range from 55%-65% for Ta and T1 TCC, and from 70%-75% for CIS.[2] However, over 60% of patients exposed to BCG will ultimately recur by 5 years.[9]

The definition of BCG failure is usually reserved to those who were exposed to two full 6-week cycles of induction therapy. The treatment of these BCG refractory patients is problematic. Radical cystectomy or chemo-radiation regimens represent treatment options. However, they are associated with morbidity, potential mortality and significant health-related quality of life detriments. Moreover, not all patients who fail BCG progress to muscle invasive disease, where definitive treatment modalities are indicated. For example, although 30%-40% of patients will initially recur after BCG treatment,[9] only 10% will recur with progressive disease. Therefore, at least a proportion of BCG failures represent suitable candidates for further transurethral resection (TUR) management with intravesical therapy.

Several treatment options are available after complete TUR. A second or third BCG cycle may provide a response in 20% of patients.[10] Intravesical chemotherapy, in the form of mitomycin C or valrubicine, represents another option with a similar 19%-21% response rate.[11,12]

Finally, interferons represent another alternative. They are known for their antiviral, antiproliferative and antitumor activities.[13] Interferon α2B has received most attention in non-muscle invasive bladder cancer and has been shown to potentiate T-helper cell type 1 immune response in humans, similar to the BCG-mediated response.[14] Moreover, a dose response effect was noted and response rates to intravesical instillations ranged from 5%-43%, when IFN was administered as a single agent.[15] After complete TUR of papillary non-muscle invasive TCC, prophylactic IFN instillations are associated with recurrence rates that may be as low as 20%.[16] These data demonstrate the efficacy of IFN as a main or adjuvant treatment modality for non-muscle invasive TCC. The efficacy of IFN has also been tested in the setting of BCG failure where 12% of patients may be expected to respond to IFN as monotherapy.[17]

Established response rates after BCG failure and similarity in the mechanism of action between IFN and BCG suggest a potential for synergy. Indeed, the combination of low dose BCG and IFN has demonstrated response rates in excess of 50% at 2.5 years.[4] A recent large scale multicenter phase II trial has confirmed these data, as 42% of BCG failures were free of recurrence at 24 months after BCG/IFN

induction.[18] Moreover, serious adverse events occurred in only 5% of patients. Taken together, these data indicate that IFN may be successfully and safely combined with BCG. However, novel regimens are often subject to many biases, which may exaggerate the true response rate. In consequence, despite encouraging results from centers of excellence, results seen in local patients may be less encouraging. Based on this premise we hypothesized that the combination of BCG/IFN will result in recurrence free status in a large proportion of patients that previously failed one or more BCG cycles.

To test this hypothesis, we implemented a protocol that consisted of BCG/IFN induction therapy with subsequent maintenance treatment for patients who did not recur after initial induction.[4] Recurrence-free survival (RFS) was 66% at 2 years. Our results are superior to those from a recently published phase II trial of BCG/IFN combination therapy where RFS of 42% at 2 years was reported.[18] At our institution the follow-up included fewer biopsies, which were performed exclusively based on cystoscopy or cytology findings. In consequence, we performed fewer biopsies than in previous studies. Therefore, it is possible that this might have affected our recurrence rate. On the other hand, this finding is in accordance with our hypothesis that durable RFS may be expected in patients treated with BCG/IFN in smaller trials, which reflect everyday practice.

Maintenance therapy was offered to those without evidence of recurrence after induction therapy. The introduction of maintenance therapy was based on publications of Southwest Oncology Group (SWOG) data indicating its effectiveness after BCG induction therapy.[19] Only 5 patients from this cohort received maintenance therapy. Seven additional patients were eligible for maintenance therapy, but did not receive it since they presented to our institution before the publication of these aforementioned data.

We hypothesized that BCG/IFN maintenance therapy may be associated with a similar benefit as noted in the SWOG study.[19] However, our actuarial analysis failed to show a statistically significant change in the probability of non-recurrence at 2 years between those who were and those who were not offered BCG/IFN maintenance therapy (75% versus 69%, $p = 0.6$). However it is possible that this absence of relation is confounded by the number of prior BCG cycles. Unfortunately because of the very limited number of patients, we could not perform multivariate analysis taking into account the number of prior BCG cycles. Although, our small series suggests no benefit for BCG/IFN maintenance therapy, this finding needs to be corroborated in larger studies. To date no study has compared recurrence free survival with respect to the addition of maintenance therapy in patients exposed to BCG/IFN induction therapy.

In order to identify ideal BCG/IFN responders, we stratified our data according to pathological stage prior to BCG/IFN induction. Patients with CIS fared substantially worse than patients with T1 disease, as evidenced by respective RFS of 50% and 100% at 2 years. Although this was not statistically significant ($p = 0.12$), this finding indicates that completely resected T1 disease responds to intravesical BCG/IFN better than CIS. Although only 15% of patients with completely resected T1 disease will harbor non-visible residual tumor,[20] virtually 100% of patients with CIS will have residual tumor after TUR since it is not amenable to surgical resection. Therefore, differences in RFS favoring patients with T1 TCC should be expected. Our findings mirror those of O'Donnell where BCG/IFN therapy resulted in RFS of 54% in T1 versus 40% in CIS patients.[4] However, similar to our data this difference was not statistically significant. These combined data suggest that alternative or further adjuvant therapies are needed in patients with CIS.

Lastly, we explored the effect associated with the extent of previous BCG exposure on RFS. We hypothesized that those patients who were exposed to one cycle of BCG prior to BCG/IFN induction therapy may enjoy better RFS than those exposed to two or more cycles prior to BCG/IFN induction therapy. Patients exposed to one BCG cycle had a RFS of 39% versus 100% for those exposed to two or more cycles. We explored whether this counter-intuitive difference may be accounted for by a difference in stage prior to BCG/IFN induction. However, our data failed to reveal a statistically significant difference in stage distribution ($p = 0.5$). Therefore, it may be postulated that other differences, such as initial stage at diagnosis, number of recurrences, recurrence-free intervals, and other unmeasured variables contributed to this difference.

These data corroborate previous findings and confirm the efficacy of BCG in our local patient population. However, there are several limitations to our study. First, patient tolerability was not examined. Second, we examined a very small patient population and thus study power is limited. Therefore the absence of effect of maintenance therapy and the possible response rate differences according to stage could be attributable to the lack of power. Larger size studies are crucial to further define the role of this combination therapy. Third, the patient population

was a heterogeneous mix of patients with either T1 or CIS disease, and thus it is difficult to draw conclusions from results and generalize them to either of the sub-stages of non-muscle invasive bladder cancer. Finally, pre-BCG/IFN TURs were performed by different surgeons. Thus, despite a negative cystoscopy prior to study inclusion, discrepancies may exist between the extent and aggressiveness of these resections, which can affect RFS.

Conclusion

We found that BCG/IFN therapy after BCG failure can reduce recurrence in patients with non-invasive bladder cancer. Our data are consistent with the results of larger trials in our local patient population. Furthermore, we observed that this treatment is more effective in patients with T1 disease than for patients with CIS. Despite the limitations of our study, our data show promise and encourage further use of BCG/IFN. Ideally, prospective studies should be performed to address unanswered questions such as the benefit of BCG/IFN maintenance and the response rate differences according to stage prior to BCG/IFN. □

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