Safety and Efficacy of Intravesical Bacillus Calmette-Guerin Instillations in Steroid Treated and Immunocompromised Patients

Ofer Yossepowitch, Scott E. Eggerner, Bernard H. Bochner, S. Machele Donat, Harry W. Herr and Guido Dalbagni*

From the Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, New York

Purpose: We assessed the safety and efficacy of intravesical bacillus Calmette-Guerin instillations in steroid treated and immunocompromised patients.

Materials and Methods: We retrospectively reviewed the charts of 697 patients treated with bacillus Calmette-Guerin instillations at our institution from 1991 to 2004. In 24 patients (3.5%) an underlying comorbidity directly affecting the immune system was diagnosed before bacillus Calmette-Guerin administration or steroids were administered at least 6 weeks before and at the time of bacillus Calmette-Guerin instillations. The immunosuppressive effect of steroids was assessed by the percent of lymphocytes. End points were the bacillus Calmette-Guerin response at 6 months, defined as normal cystoscopy, cytology and biopsy when available, and treatment related toxicity.

Results: Four patients (17%) had active lymphoma or chronic lymphocytic leukemia during bacillus Calmette-Guerin administration and 21 (88%) had a concurrent condition for which oral steroids (11), inhaled steroids (14) or oral and inhaled steroids (4) were administered. Patients treated with oral steroids had a lower percent of lymphocytes than patients treated with inhaled steroids and 15 age matched patients with high risk superficial bladder cancer and no steroid treatment (12.3% vs 17.5% and 18.6%, respectively). The overall bacillus Calmette-Guerin response rate at 6 months was 58%. Ten of the 24 patients had disease recurrence and 3 had disease progression at a median followup of 63.5 months (IQR 19.5, 89). One patient treated with oral steroids had self-limited febrile disease and worsening of myalgia 48 hours after his third bacillus Calmette-Guerin cycle. No other systemic adverse event following bacillus Calmette-Guerin therapy was recorded and all patients completed scheduled treatments.

Conclusions: Intravesical bacillus Calmette-Guerin is a viable therapeutic option in patients with high risk superficial bladder cancer and concomitant lymphoma or chronic lymphocytic leukemia, treatment with low dose oral steroids or treatment with inhaled steroids. The bacillus Calmette-Guerin response rate at 6 months and the side effects profile associated with bacillus Calmette-Guerin therapy in these patients were comparable to those in patients with no evidence of immunosuppression. Further studies are warranted to assess the safety and efficacy of bacillus Calmette-Guerin instillations in critically immunocompromised patients.

Key Words: bladder, Mycobacterium bovis, carcinoma in situ, immunocompromised host, steroids

The high recurrence rate and unpredictable nature of superficial bladder cancer has led to the widespread use of intravesical therapy as an adjunct to transurethral resection. Intravesical immunotherapy with BCG, a live attenuated strain of the cow tuberculosis bacillus Mycobacterium bovis, remains the standard of care in patients with high risk superficial bladder cancer. Several studies have shown that BCG effectively eradicates existing carcinoma in situ, decreases the likelihood of tumor recurrence and possibly lowers the risk of disease progression. Intravesical BCG may have local and systemic toxicity. Local BCG toxicity manifests as persistent irritative symptoms, which if intense may render succeeding treatments intolerable to the patient. However, it is the rare sequel of systemic BCG toxicity (BCGitis) that exposes patients to a life threatening situation requiring hospitalization and prolonged antituberculosis drug administration. As such, a critical adverse event related to intravesical BCG should be deemed an absolute contraindication to further therapy. Patients with bladder cancer and a significant smoking history often have concomitant chronic lung disease. These patients are frequently treated with inhaled or enteral steroids capable of suppressing the immune response. Steroid treated patients as well as patients who are immunocompromised because of an underlying medical condition are at increased risk for systemic infections. Therefore, it is generally assumed that intravesical BCG should be avoided in the setting of immunosuppression. However, to our knowledge no robust data support an increased risk of BCGitis following intravesical BCG therapy in patients with decreased immunity. Whether impairment of the immune system interferes with the local intravesical immunomodulating effect of BCG and alters its therapeutic efficacy also remains unknown.

During the last 2 decades we have treated patients with high risk superficial bladder cancer with intravesical BCG

Submitted for publication October 17, 2005.
Study received Institutional Review Board approval.
* Correspondence: Department of Urology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, New York 10021 (telephone: 646-422-4394; FAX: 212-988-0760; e-mail: dalbagni@mskcc.org).

DOI:10.1016/j.juro.2006.03.066
on an ablative basis for carcinoma in situ or on a prophylactic basis following complete tumor removal. When BCG therapy was deemed mandatory, patients were generally treated irrespective of underlying conditions or medical therapies that might be associated with immunosuppression. Recently Palou et al suggested that intravesical BCG is a valid option in renal transplant cases with no added morbidity. We analyzed our experience with intravesical BCG treatment in immunocompromised patients to address its tolerability and efficacy in this setting.

**MATERIALS AND METHODS**

Following Institutional Review Board approval a retrospective review of the Memorial Sloan-Kettering Cancer Center bladder cancer database was performed to identify patients treated at our institution with intravesical BCG between January 1991 and July 2004. Patient charts were specifically reviewed for underlying comorbidities and medications likely to alter the immune response. Of the 697 patients treated with BCG we identified 24 (3.5%) in whom an underlying comorbidity known to directly affect the immune system was diagnosed before BCG administration, or in whom steroids or other established immunosuppressive agents were administered at least 6 weeks before and at the time of BCG instillations.

Patient age, sex, medical history and medications (drugs and doses), the indication for BCG treatment (bladder cancer clinical stage according to the 2002 American Joint Committee on Cancer classification) and disease status at last followup were recorded. Also recorded were the number of BCG cycles and characterization of any adverse event following BCG treatments. All patients received weekly BCG therapy for 6 consecutive weeks. BCG was administered as 81 mg in 50 ml saline retained for 2 hours starting 2 to 3 weeks after the resection of grossly visible tumors. Initial patients received the BCG Pasteur strain (Institute Armand Frappier, Montreal, Quebec, Canada) and subsequent patients received the BCG Pasteur strain (Institute Armand Frappier, Montreal, Quebec, Canada). The end point for efficacy analysis was the BCG response, defined as normal cystoscopy, cytology and biopsy when available at the evaluation 6 months after the first BCG treatment. We did not perform actuarial analysis of disease-free recurrence or disease-free progression due to the relatively small cohort and low number of events.

Since the lymphocyte count may serve as an index for the immunosuppressive effect induced by steroids, we studied the pretreatment white blood count, total lymphocyte count and lymphocyte percent in our patients treated with inhaled or enteral steroids. For purposes of analyzing blood count variables an additional 15 randomly selected patients with high risk superficial bladder cancer and no steroid treatment or evidence of immunosuppression served as the control group. One-way ANOVA was used to test the difference in the mean of blood count variables, followed by pairwise comparisons between subgroups done as post hoc analyses assuming equal variance (Bonferroni). Statistical analyses were performed using SPSS®, version 8.0 statistical software and p < 0.05 was considered significant.

**RESULTS**

Table 1 shows clinical stage and immunosuppressive conditions in 24 patients at intravesical BCG treatment. A total of 12 patients (50%) were diagnosed with primary or secondary carcinoma in situ of the bladder and in these patients BCG was considered the only therapeutic option. Four patients (17%) had active lymphoma or chronic lymphocytic leukemia during intravesical BCG administration, 13 (54%) had concomitant chronic lung disease, that is COPD, emphysema or asthma, and 8 (33%) had another indication for steroid therapy. Of the patients 11 were on oral steroids and 14 were on inhaled steroids, of whom 4 received a combination thereof (table 2). In general patients were treated with low to intermediate dose steroids (3 to 10 mg prednisone daily) except 1 given 30 mg prednisone daily at the time of BCG instillations.

The total leukocyte count was increased and the lymphocyte percent was decreased in patients treated with oral steroids compared to those in patients treated with inhaled steroids or patients with no steroid treatment (table 3). Although the absolute lymphocyte count was slightly decreased in patients treated with oral steroids, the difference in subgroups did not attain statistical significance.

The BCG response rate at 6 months was 58% overall and 66% in patients with primary or secondary carcinoma in situ. Of the 14 patients who had a complete response to BCG at 6 months 11 (78%) remained free of disease at a median followup of 58 months. Overall 10 of the 24 patients had disease recurrence and 3 had disease progression at the last followup (median 63.5 months, IQR 19.5, 89). Five patients received a second 6-week induction course of BCG for recurrent disease after an initial complete response.
patients in this study received maintenance intravesical therapy. One patient treated with methylprednisolone for polymyalgia rheumatica had self-limited febrile disease up to 39.3°C and worsening myalgia 48 hours after his third BCG cycle. None of the other patients experienced any systemic adverse event following BCG therapy and all completed the scheduled treatments.

**DISCUSSION**

Two dilemmas are encountered when deciding whether to offer intravesical BCG to immunocompromised patients. 1) Is there truly an increased risk of systemic BCG toxicity in these patients? Fatal complications related to BCG in the setting of immunosuppression have been described, mostly in patients with malignant melanoma treated with BCG injections or in patients with various neoplasms given BCG vaccinations. BCGitis after intravesical BCG is believed to develop from haematogenous spread often following traumatic catheterization and from an immunological reaction. Thus, immunocompromised patients may not be at higher risk for BCGitis after intravesical instillation. 2) To achieve an optimal anticancer effect BCG must evoke a local inflammatory immune response. Although to our knowledge there is no evidence that systemic immunity to bladder cancer has a role in patients treated with BCG, immunodeficiency may theoretically decrease the local response induced by the drug and, hence, its biological activity.

The current study suggests that intravesical BCG can be safely administered without expecting a higher incidence of adverse events or compromise in outcome in patients with several potential causes of immunodeficiency, including active lymphoma or chronic lymphocytic leukemia, treatment with low dose oral steroids or treatment with inhaled steroids. The BCG response rate at 6 months and the side effects profile associated with BCG therapy in these patients are comparable to those in previously published reports.

BCG therapy also appears to be safe in patients with a renal transplant but to our knowledge its safety in other critically immunocompromised hosts has yet to be studied. It should also be emphasized that our current study is limited by its inability to account for any immunodeficient patients in whom intravesical BCG was avoided at the discretion of the involved attending physician.

Most patients in this study were deemed immunocompromised as a consequence of chronic steroid therapy. Steroids prevent interleukin-1 and interleukin-6 production by macrophages, alter T-cell differentiation and inhibit all stages of T-cell activation. Nevertheless, the degree of immunosuppression in our patients could not be accurately determined. The lymphocyte percent was decreased in patients treated with oral steroids, suggesting an immunosuppressive effect, but this may be attributable in part to relative leukocytosis. Although no prior studies have addressed the implications of intravesical BCG in patients treated with steroids, there has been some concern regarding corticosteroid use in patients with latent tuberculosis or a positive tuberculin skin test. The American Thoracic Society recommends that all patients with a positive tuberculin skin test expected to receive 15 mg prednisone or more daily or the equivalent for longer than 2 weeks should receive a prophylactic course of isoniazid. However, the native strain of Mycobacterium tuberculosis associated with primary tuberculosis is clearly more virulent than the live attenuated strain of Mycobacterium bovis used during intravesical instillations and an intact urothelium likely provides a barrier against haematogenous spread compared to quiescent pulmonary tuberculosis foci or direct injection into the skin. Thus, to our knowledge it remains to be studied whether intravesical BCG administration in steroid treated patients warrants preventive therapy with isoniazid. Paradoxically despite their negative influence on immune protection steroids serve to restrict the tissue damaging inflammatory reactions accompanying the antituberculous immune response. Accordingly high dose steroid treatment should be started promptly in patients with deteriorating BCGitis complicated by multi-organ failure.

Unlike oral steroid treatment, inhaled steroid treatment was not associated with relative lymphocytopenia in our patients. Inhaled steroids are absorbed into the systemic

<table>
<thead>
<tr>
<th>Steroids Mean ± SEM (range)</th>
<th>Control Mean ± SEM (range)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Age</td>
<td>69 ± 3 (48–80)</td>
<td>64 ± 6 (41–81)</td>
</tr>
<tr>
<td>White blood count (10^3 cells/mm³)</td>
<td>10.3 ± 1.0 (6.2–17.6)</td>
<td>7.9 ± 0.5 (5.3–11.9)</td>
</tr>
<tr>
<td>No. lymphocytes (10^3 cells/mm³)</td>
<td>1.2 ± 0.17 (0.5–2)</td>
<td>1.4 ± 0.08 (1–2.3)</td>
</tr>
<tr>
<td>% Lymphocytes</td>
<td>2.3 ± 1.1 (1.5–51)</td>
<td>17.5 ± 1.6 (8.4–24)</td>
</tr>
</tbody>
</table>

* Including 4 patients treated with combined enteral and inhaled steroids.
† In enteral vs inhaled steroid and control groups post hoc tests showed borderline significance.

### TABLE 2. Steroid schedule at intravesical BCG in patients with high grade superficial bladder cancer

<table>
<thead>
<tr>
<th>Steroid (dose)</th>
<th>No. Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>21</td>
</tr>
<tr>
<td>Enteral (mg/day):</td>
<td>11*</td>
</tr>
<tr>
<td>Prednisone (3, 5,† 10, 30)</td>
<td>2, 3, 2, 1</td>
</tr>
<tr>
<td>Hydrocortisone (30)</td>
<td>1</td>
</tr>
<tr>
<td>Methylprednisolone (3)</td>
<td>1</td>
</tr>
<tr>
<td>Inhaled (mcg‡)</td>
<td>14</td>
</tr>
<tr>
<td>Beclomethasone (100)</td>
<td>1</td>
</tr>
<tr>
<td>Flunisolide (500)</td>
<td>1</td>
</tr>
<tr>
<td>Fluticasone propionate (250)†</td>
<td>10</td>
</tr>
<tr>
<td>Triamcinolone acetonide (600)‡</td>
<td>2</td>
</tr>
</tbody>
</table>

Four patients were treated with a regimen combining oral and inhaled steroids for chronic obstructive pulmonary disease. * Accurate prednisone dose could not be retrieved from the chart in 1 patient. † A patient with underlying rheumatoid arthritis and COPD was treated with inhaled steroids, oral steroids and 25 mg methotrexate weekly. ‡ Average of 3.3 puffs daily (range 2 to 6).
circulation from gastrointestinal absorption of the swallowed fraction of the drug as well as from an additional fraction deposited in the lung tissue. Any systemic side effects are related to the amount of drug entering the circulation. However, different drugs may achieve different circulating levels due to variable first pass hepatic metabolism. Inhaled steroids should probably not affect the decision of whether to use BCG instillations.

CONCLUSIONS

Intravesical BCG should be considered a viable therapeutic option in patients with high risk superficial bladder cancer and concomitant lymphoma or chronic lymphocytic leukemia, treatment with low dose oral steroids or treatment with inhaled steroids. Further studies are needed to assess the safety and efficacy of BCG instillations in critically immunocompromised hosts.

Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>bacillus Calmette-Guerin</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
<td></td>
</tr>
</tbody>
</table>

REFERENCES