ABSTRACT

Background and Objectives: BCG has been used for more than 30 years and is currently the most effective agent for non-muscle invasive bladder cancer therapy after transurethral resection. The high-grade T1 lesion treated by transurethral resection alone is reported to progress to muscle invasion in 30% to 50% of the patients. Until now, optimal treatment schedule and optimal dose have not been defined as the toxicity related to BCG therapy is significant. In this study we tried to evaluate the efficacy and toxicity of 60mg intravesical BCG (Pasteur strain) therapy in patients with T1 transitional cell carcinoma of the bladder.

Patients and Methods: From January 2000 till December 2007, 74 patients with single T1 transitional cell carcinoma (TCC) of the urinary bladder (grade 3 in 24 patients and grade 2 in 50 patients) were treated by complete transurethral resection followed by a 6-weeks course of 60mg BCG intravesically. Follow-up ranged from 26-96 months with median of 61 months.

Results: Nine patients (12.1%) exhibited recurrence with muscle invasion after 6-18 months (5 with grade 3 tumors and 4 with grade 2), all were subjected to radical cystectomy and urine diversion. Whereas 19 patients (29.2%) showed recurrent T1 tumor after 16-45 months (7 with grade 3 tumors and 12 with grade 2) and were treated by TUR-T followed by a second 6-weeks course of 60mg BCG intravesically. Recurrence index was 0.82/100 patients/month and the median tumor free period was 20 months. Regarding toxicity; irritative symptoms occurred in 24% of patients, fever in 9%, microscopic hematuria in 14%; which appeared to be significantly low when compared with the rates reported for higher doses of BCG.

Conclusion: Intravesical therapy of 60mg BCG is effective in prophylaxis against recurrence and progression of T1 TCC of the bladder. Decreasing the dose resulted in reducing the side effects significantly without delay or cessation of therapy.

Key Words: Bladder cancer – T1 – Low dose BCG.

INTRODUCTION

Bacillus of Calmette-Guerin (BCG) immunotherapy has been demonstrated in randomized clinical trials and meta-analyses to provide superior protection from tumor recurrence and, unlike chemotherapy, even reduce disease progression in non-muscle invasive transitional cell carcinoma (TCC) of the bladder. Optimal treatment varies according to multiple host and tumor factors. Host factors include age, general immune status and previous exposure to BCG. Tumor factors include number, stage, grade, antigenicity, and doubling time [1].

A T1 TCC of the bladder is a tumor invading the lamina propria. The biological behavior of such tumors is unpredictable due to its high tendency for recurrence (40-70%) and progression (30-50%) after transurethral resection (TUR-T) alone [2]. Many trials have demonstrated that BCG reduced significantly the incidence of stage progression and recurrence in T1 TCC of the bladder utilizing a standard dose (150mg) of BCG intravesically after TUR-T [3]. However reviewing the side effects have shown that in addition to minor side effects occurring in 35-71% of patients, significant morbidity occurred in 5-23% of patients due to systemic sepsis. These major side effects often caused delay of installations and consequently reducing the efficacy of treatment [4].

Treatment strategies aiming at reducing the side effects of intravesical BCG while maintain-
ing efficacy were studied by several authors, suggesting three approaches: (i) reducing the dose of BCG per installation (low dose regimen; 75, 60, 45 or 30mg) (ii) administration of oral anti-tuberculous drugs, and (iii) delaying the interval of installations (slow rate regimen) [4–7].

The aim of this work is to evaluate the efficacy and toxicity of 60mg intravesical BCG therapy (Pasteur strain) in treatment of patients with T1 grade II and III TCC of the bladder after TUR-T.

PATIENTS AND METHODS

This study was conducted in the Urology department, Theodor Bilharz research institute (TBRI, GIZA, EGYPT) starting from January 2000 till December 2007. It included 74 male patients with a less than 3cm, single, primary pT1 TCC of the urinary bladder (grade III in 24 patients and grade II in 50 patients). Five patients (6.7%) had associated carcinoma in situ (CIS). Thirty one patients (41.8%) gave a history of receiving anti-bilharzial treatment. Pathological examination of tumors from 12 of these patients revealed bilharzial ova in the lamina propria. All patients were treated by complete TUR-T. Two weeks later, a 6 weeks course of 60mg BCG (Pasteur strain) diluted in 50ml isotonic saline was instilled in the bladder and kept for 2 hours.

Recurrence was defined as the appearance of a new tumor either of lower tumor stage and grade (pTaG1, G2), or of the same pT1 pattern. Progression in tumor stage was defined by depth of bladder muscle invasion or by regional or distant metastasis. Recurrence index was calculated by the equation proposed by Pagano et al., 1991 [5]:

\[
\text{Recurrence index} = \frac{\text{Number of positive cystoscopy} \times 100}{\text{Total period of follow-up in months}}
\]

Tumor free period was calculated from the time of TUR-T till the appearance of first tumor recurrence. BCG treatment-related side effects were classified as minor (persistence of local symptoms and/or low-grade fever for less than 48 hours) or major (severe or persistent local symptoms and/or higher-grade fever for more than 48 hours).

The follow-up schedule was urethro–cystoscopy with bladder wash cytology every 3 months for 2 years and every 6 months thereafter. An intravenous urography was performed every 2 years. When recurrence occurred re-TUR-T was performed and the same BCG protocol was applied. Follow-up ranged from 26-96 months with median of 61 months. Ethics Committee of TBRI approved the study. All patients gave written informed consent before participation.

RESULTS

Nine patients (12.1%) exhibited recurrence with muscle invasion (progression) after 6-18 months [median 13 months] (5 with grade 3 tumors and 4 with grade 2), all were subjected to radical cystectomy and urine diversion. Three of these 9 patients had bilharzial ova in the specimen. Whereas 19 patients (29.2%) showed recurrent pT1 tumor after 16-45 months [median 20 months] (7 with grade 3 tumors and 12 with grade 2) and were treated by TUR-T followed by a second 6-weeks course of 60mg BCG intravesically. Five of these 19 patients had bilharzial ova in the lamina propria of the tumor. Recurrence index was 0.82/100 patients/month and the median tumor free period was 20 months (range 16-45 months).

All patients completed the study and there was no treatment withdrawal. Regarding toxicity (Table 1), no major or severe side effects were encountered and there were no delayed instillations or cessation of therapy. Local adverse effects occurred in 39 patients (52.7%), while systemic effects, in the form of fever, occurred in 7 patients (9%). All adverse effects were minor, self-limiting and responded to symptomatic treatment in the form Ibubrufen and anti-cholinergics within 48 hours after intravesical instillations.

Table (1): Side Effects of low dose BCG therapy in patients with T1 TCC of the bladder.

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Number of patients (n=74)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Fever:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* ≤38°C</td>
<td>6</td>
<td>9%</td>
</tr>
<tr>
<td>* 39°C</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2-Bladder irritability: (Frequency &amp; Urgency)</td>
<td>18</td>
<td>24%</td>
</tr>
<tr>
<td>3-Dysurea</td>
<td>7</td>
<td>9%</td>
</tr>
<tr>
<td>4- Hematuria (microscopic)</td>
<td>14</td>
<td>19%</td>
</tr>
</tbody>
</table>
DISCUSSION

The development of BCG immunotherapy has greatly improved the prognosis of non-muscle invasive bladder cancer particularly T1 tumors [1]. However concerns were expressed regarding the toxicity related to the treatment, which introduced the "therapeutic index" of BCG. This index is the optimal ratio between therapeutic response and adverse effects [4-6]. From this point the aim of this study was to evaluate the therapeutic index of low dose (60mg Pasteur strain) BCG in treatment of patients with pT1 (grade 2&3) TCC of the bladder.

Van der Meijden et al., 1998 [6], classified pT1 tumors into 2 main risk groups: An intermediate risk group comprising single primary grade II tumors, whereas the high risk group comprising recurrent grade II tumors and grade III tumors whether single or multiple, primary or recurrent, with or without concomitant CIS. Intermediate and high-risk non-muscle invasive bladder cancer is the major indication for BCG to avoid the recurrence and/or progression.

BCG efficacy and toxicity are dose-dependent; the problem lies in finding a low BCG dose that is effective and has low toxicity. In 1991 the results of a randomized study [5] to evaluate the effectiveness and toxicity of a 75mg dose of Pasteur strain BCG (half standard dose) in the treatment of superficial bladder cancer were reported. The conclusions were that half of the standard BCG dose is effective as adjuvant treatment against recurrent superficial papillary tumors. Complete response rates were similar to those achieved using standard dose. Furthermore, treatment-related toxicity appeared to be significantly lower in patients with low dose regimen than the standard dose. In 1995 a phase 2 study [7] evaluated the feasibility, response, and toxicity of 27mg BCG(one third standard dose of Connaught strain) in patients with high-risk superficial TCC of the bladder. The results of the study suggested that this low dose could be successfully used as adjuvant therapy for high-risk tumors with comparable results to the standard dose. Toxicity included local reactions as irritative bladder symptoms and hematuria and were significantly lower than other reports with the standard dose. In 2005, the Spanish oncology group (CUETO) [8] published the results of a randomized study comparing a standard dose of 81mg of BCG Connaught strain with a low dose of 27mg as adjuvant treatment in high risk superficial bladder tumors. The results suggested that a third of the dose of intravesical BCG was as effective as the standard dose against recurrence and progression in patients with high risk tumors but with significantly less toxicity.

In the present study the intermediate risk group was 67% (50/74 patients) presenting as pT1 GII tumors while the high risk group was 33% (24/74 patients) presenting as pT1 GIII tumors with associated CIS in 5 cases. The end points in this study were; recurrence index, incidence of recurrence, tumor progression, tumor free period and toxicity. Progression occurred in 12.1% of patients and were subjected to cystectomy whereas recurrence occurred in

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Recurrence %</th>
<th>Progression %</th>
<th>Mean follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pagano et al., 1991 [5]*</td>
<td>126</td>
<td>26</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Mack &amp; Frick 1995 [7]*</td>
<td>32</td>
<td>34</td>
<td>25</td>
<td>57</td>
</tr>
<tr>
<td>Spanish oncology gp (CUETO 2005) [8]*</td>
<td>155</td>
<td>45</td>
<td>26</td>
<td>61</td>
</tr>
<tr>
<td>Wishahi et al., 1994 [10]**</td>
<td>13</td>
<td>16</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>Pansadoro et al., 1995 [11]**</td>
<td>50</td>
<td>28</td>
<td>12</td>
<td>42</td>
</tr>
<tr>
<td>Hurle et al., 1999 [12]**</td>
<td>51</td>
<td>45</td>
<td>17</td>
<td>85</td>
</tr>
<tr>
<td>Kamel et al., 2009*</td>
<td>74</td>
<td>29</td>
<td>12</td>
<td>64</td>
</tr>
</tbody>
</table>

* Low dose BCG. ** Standard dose BCG.

Table (2): Role of BCG therapy in prophylaxis against recurrence and progression in patients with pT1 TCC of the bladder.
29.2% of patients who were subjected to re-TUR-T and a 2nd 6-weeks course of 60mg BCG. Recurrence index was 0.82/100 patients/month and the median tumor free period was 20 months.

In November 2007, the Spanish oncology group (CUETO) [9] published the results of a randomized study comparing three intravesical adjuvant therapies for intermediate risk superficial bladder cancer: Low dose BCG (27mg Connaught strain) versus very low dose BCG (13.5mg) versus Mitomycin C. They reported the incidence of recurrence to be 26.8%, 36% and 38.9% respectively. The recurrence index was 0.57, 0.74 and 0.95/100 patients/month respectively. Whereas progression occurred in 9.9%, 12.9% and 9.4% respectively. They concluded that one third of the standard dose is the minimum effective dose as adjuvant therapy for intermediate risk non-muscle invasive bladder cancer.

Table (2) presents the role of BCG intravesical therapy in prophylaxis against recurrence and progression of pT1 TCC as shown in different western and Egyptian studies [5,7,8,10-12] utilizing either standard or low dose BCG therapy. These studies were mostly comparable to both regimens regarding tumor recurrence and progression. However, Lamm 2006 [1] reported that decreasing the dose of BCG will not significantly alter the disease free survival in patients with T1 TCC of the intermediate risk group whereas patients in the high risk group will not benefit from dose reduction as this low dose regimen will decrease the efficacy of therapy especially progression to muscle invasion.

Regarding toxicity, Pagano et al., 1991 [8], reported that the side effects were significantly reduced with low dose BCG in the form of bladder irritative symptoms in 27% and fever in 17% of patients. The Spanish oncology group (CUETO), 2007 [9], reported minor local toxicity in 56% in the BCG 27mg group and 51% in the BCG 13.5mg group. Fever was reported in 7% in the BCG 27mg group and 6% in the BCG 13.5mg group.

In the present study, local adverse effects occurred in 52.7% of patients, while systemic effects, in the form of fever, occurred in 9% of patients. All adverse effects were minor, self-limiting and responded to symptomatic treatment for less than 2 days. Comparing these results with two Egyptian studies utilizing the standard dose BCG regimen, Ismail et al., 1996 [13] and Sarhan et al., 2001 [14]. They reported bladder irritability to occur in 90% and 52% of patients respectively, severe enough in at least one third of patients to discontinue therapy for 2-3 weeks with administration of symptomatic treatment. They also reported systemic sepsis to occur in 15% and 17% of patients respectively in the form of high grade fever (≥39c), prostatic abscess, urinary T.B. and epididymo-orchitis. With these severe and major adverse effects they administered anti-tuberculous treatment with permanent cessation of BCG therapy. Ismail et al., 1996 [13] reported bladder contracture to occur in 3% of patients.

Conclusion:
This study demonstrated that low dose (60mg) BCG intravesical therapy is an effective adjuvant treatment in T1 TCC of the bladder. This low dose did not affect the response rate in terms of tumor free period and tumor progression, together with a significant decrease in frequency and severity of side effects.

REFERENCES
6- Van der Meijden AP, Brausi M, Zambon V, Kirkels W, de Balincourt C, Sylvester R. (Members of EORTC Genito-Urinary group): Phase III study of intravesical instillation of Epirubicin, BCG-tice and BCG plus isoniazid in intermediate and high risk pTa and pT1


