The Place of Instilational Immunotherapy in the Treatment of Non-muscle Invasive Bladder tumors

A. Brad\textsuperscript{1,2}, Corina Mateescu\textsuperscript{1}, A.O. Vida\textsuperscript{1,2}, M. D. Vartolomei\textsuperscript{1,2}, D. Balan\textsuperscript{1,2}, C. Catarig\textsuperscript{1}, C. Chibelean\textsuperscript{1,2}, Orsolya Martha\textsuperscript{1,2}, D. Porav\textsuperscript{1,2}

\textsuperscript{1} Mureş County Clinical Hospital, Urology Clinic, Târgu Mureş, Romania
\textsuperscript{2} University of Medicine, Pharmacy, Sciences and Technology, Târgu Mureş, Romania

Abstract

**Introduction:** Bladder tumors are the most common tumors of the urinary tract, accounting for about 5.5\% of all cancers. In male it is on the 4th place, and in females it occupies the 7th place. TURBT is the gold standard for the initial treatment and diagnosis of bladder tumors. This intervention can be followed, in the case of non-muscle invasive tumors, by intravesical instillation, with a chemotherapeutic or with BCG.

The aim of this work was to follow the evolution of patients with non-muscle invasive bladder tumors who have been treated with BCG (Bacillus Calmette-Guérin) immunotherapy.

**Material and methods:** The study was a retrospective one, for a period of 5 years, between 2010 January 1 and 2014 December 31, including a number of 91 patients hospitalized in the Urology Clinic of Mureş County Clinical Hospital. Follow-up data at 24 months was present in 76 patients.

**Results:** Of the 76 patients, 80.26\% were male and 19.74\% were female. The distribution of patients according to the environment of origin highlights the prevalence of the urban environment in the percentage of 72.36\%, the rural area having a percentage of only 27.64\%. The average age was 61.43 years.

There was no statistically significant association between the gender of the patient and the rate of tumor recurrence. Of the 76 patients, 21 had tumor progression during the follow-up period. No patient was found to have progressed to invasive bladder tumor. Of the total number of 76 patients, at the end of the follow-up period, it was found that 8 discontinued treatment with BCG due to side effects such as: haematuria and tuberculous cystitis. In 3 patients, treatment with BCG failed and due to repeated recurrences required a total cystectomy.

**Conclusions:** Instillational treatment with BCG immunotherapy remains the best option as an adjuvant in patients with non-muscle invasive bladder tumors to prevent recurrence and progression, in well-selected cases and with clear indication.

**Keywords:** bladder tumor, TURBT, immunotherapy, BCG.

Correspondence to: Dr. Brad Alexandru
e-mail: brad.alexandru@yahoo.com
Introduction

Bladder tumors are the most common tumors of the urinary tract, accounting for about 5.5% of all cancers. In males, it is on the 4th place, and in females, it occupies the 7th place.

Regarding the ratio between the two genders, there is a predominance for males, the ratio being 4:1 in their favor. Bladder tumors have a higher frequency among the elderly, with the average age at diagnosis being 70 years.

It has been found that the incidence of bladder tumors would be higher in industrialized countries than in rural regions, due to the higher exposure to different pollutants.

About 75% of all these tumors are, at the time of diagnosis, limited to the mucosa or submucosa, 20% are found in T2-4 stages, the remaining 5% are found in metastatic stages \(^\text{[1,2]}\).

Different risk factors and carcinogens are involved in the development of bladder tumors. The latency time between exposure and development of bladder cancer is 10-40 years \(^\text{[3]}\).

The most important risk factors include: smoking, occupational exposure, medication, chronic cystitis and other infections, alcohol consumption, pelvic irradiation \(^\text{[3]}\).

Bladder cancer is a complex and aggressive disease. Although we have many technical resources at present, the only way to improve the prognosis of this type of tumor is early diagnosis, improvement of treatment and monitoring patient's evolution. It is also very important for the correct treatment: the tumor site, the clinical and pathological stage, the tumor grading \(^\text{[4]}\).

Transurethral resection of bladder tumors (TURBT) is the gold standard for the initial treatment and diagnosis of bladder tumors. This endoscopic intervention can be followed, in the case of non-muscle invasive tumors, by intravesical instillation, either with a chemotherapeutic or with BCG \(^\text{[5,6]}\).

The aim of this work was to follow the evolution of patients with non-muscle invasive bladder tumors who have been treated with BCG (Bacillus Calmette-Guérin) immunotherapy.

Material and methods

The study was a retrospective one, for a period of 5 years, between 2010 January 1 and 2014 December 31, including a number of 91 patients hospitalized in the Urology Clinic of Mureș County Clinical Hospital.

Follow-up data at 24 months was present for 76 patients.

The parameters followed were: sex, age, risk factors, symptomatology, tumor stage and grade, anatomical localization, immunotherapeutic treatment, evolution and post-TURBT complications.

Data were processed using Microsoft Excel and

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Age/gender groups distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Număr persoane</td>
</tr>
<tr>
<td>20-29 years</td>
<td>0 2 9 3 1 0</td>
</tr>
<tr>
<td>30-39 years</td>
<td>1 1 6 17 27 8 1</td>
</tr>
<tr>
<td>40-49 years</td>
<td></td>
</tr>
<tr>
<td>50-59 years</td>
<td></td>
</tr>
<tr>
<td>60-69 years</td>
<td></td>
</tr>
<tr>
<td>70-79 years</td>
<td></td>
</tr>
<tr>
<td>80-89 years</td>
<td></td>
</tr>
</tbody>
</table>

\[\square \text{Women} \quad \square \text{Men}\]
Results

Of the 76 patients, 80.26% were male and 19.74% were female.

The distribution of patients according to the environment of origin highlights the prevalence of the urban environment in the percentage of 72.36%, the rural area having a percentage of only 27.64%.

Patients included in the study range in age from 20 to 89 years, with an average of 61.43 years.

According to the results obtained in the studied group, the group most affected by non-muscle invasive bladder tumors is the one between 60-69 years (42%).

Of the total number of patients, 55.26% (n = 42) were exposed to toxics such as smoking and alcohol, and 44.74% (n = 34) were not exposed.

Regarding urinary tract infection, it was present in 27 patients (35.52%).

BMC was also followed in the studied patients. Thus, 32 patients were overweight and obese, and 44 had a BMC corresponding to normal values.

2 patients (2.63%) had pelvic irradiation as a risk factor.

In the studied group, it was observed that haematuria was present in 100% of cases. 61 patients (80.26%) had macroscopic haematuria and 15 patients (19.74%) had microscopic haematuria.

Regarding the anatomical location of non-muscle invasive bladder tumors: 23.68% (18 patients) were located on the right lateral wall; 30.26% (23 patients) were located on the left lateral wall; 13.15% (10 patients) were located on the anterior wall; 5.26% (4 patients) were located on the bladder neck; 13.15% (10 patients) were located on the posterior wall; and the remaining 14.15% (11 patients) had multiple locations.

In the studied group, the tumor grades and stages were: G1pTa in 18 patients, G1pT1 in 2, G2pTa in 36, G2pT1 in 5 cases, G3pTa in 11 patients and G3pT1 in 4 cases.

According to the results, 25% of the tumors were well differentiated, 55.26% moderately differentiated, and 19.74% weakly differentiated.

<table>
<thead>
<tr>
<th>Tumor grade</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage</td>
<td>25%</td>
<td>55.26%</td>
<td>19.74%</td>
</tr>
<tr>
<td>Nr. of patients</td>
<td>19</td>
<td>42</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 2-Tumors grading

Patients who received treatment between 24 and 36 months, as a percentage of 42.1% (32) could be included in the complete treatment group, and the remaining 57.9% (n = 38) did not completely follow the treatment maintenance with BCG.

According to the results, 24 of the patients who received treatment had local tumor recurrences at the periodic controls, and the rest did not have recurrences during the follow-up period.

There was no statistically significant association between the sex of the patient and the rate of tumor recurrence (p> 0.05).

The group of the patients between the ages of 60-69 are predisposed to relapse, with statistical correlations, p = 0.04.

Regarding patients with high body mass index, a statistically significant correlation between overweight and obesity with tumor recurrence was observed.

Of the 76 patients, 21 had tumor progression during the follow-up period. No patient was found to have progressed to invasive bladder tumor.

Of the total number of 76 patients, at the end of the follow-up period, it was found that 8 discontinued treatment with BCG due to adverse effects such as: hematuria and tuberculous cystitis.

In 3 patients, treatment with BCG failed and due to repeated recurrences required a total cystectomy.

Discussion

From the demographic analysis there is a clear predominance of males, the ratio being 5: 1 in favor of them. A similar prevalence was found in 2014 in the US in a study by the American Cancer Society [6].

Regarding the patients environment, it was found that 72.36% come from the urban area, similar data were obtained by the doctors from Cluj-Napoca in 2013 in a study that included 135 patients [7].

From the 76 patients, the average age was 61.43 years (between 20-89 years). The highest percentage (42%) was registered in the age group 60-69 years, obtaining similar data to those from the literature [8].

Regarding the risk factors, the most important is the smoking which was found in 55.26% of the patients included in the study. A statistically significant association between toxical exposure and tumor recurrence was obtained, resulting in the fact that smoking has a negative impact on the evolution of patients with bladder tumors. This was also pointed out by Freedman and his colleagues following a study that concluded that...
the incidence of bladder cancer was higher in current and former smokers than in people who have never smoked[9].

It was also observed in the present study that patients with overweight and obesity had an unfavorable evolution, with statistically significant links being found for both recurrence and progression. Similar data were obtained by Kluth and his collaborators in a study which included 892 patients. High BMI was correlated with an increased risk for tumor recurrence and progression[10].

The symptomatology of the patients was dominated by haematuria. 80.26% of cases presenting as main symptom macroscopic haematuria, the most common symptom in bladder tumours, being found in all studies in over 80% of cases[11]. In the studied group, 8 patients had to discontinue instillations due to the side effects. These data are close to those reported by Brausi M and his collaborators in a study conducted in 2014[14].

Regarding the anatomical location, the most frequent were on the lateral walls of the bladder, followed by the posterior and anterior walls.

During the follow-up period, 42.1% of the patients received complete immunotherapeutic treatment. The tumor recurrence was registered in 7 of these patients, and the progression in 4 patients, observing that the maintenance treatment with BCG has positive effects for the patient’s evolution. Also, following a meta-analysis by Han RF and Pan JG, it was found that maintenance treatment with BCG is effective for prophylaxis of tumoral recurrence and progression in non-muscle invasive bladder cancer. Also, in a meta-analysis conducted by EORTC, which evaluated 4863 patients with bladder tumors, it was observed that the combination of BCG immunotherapy reduces the risk of tumor progression[12, 13].

According to the statistical analysis it appears that the age group 60-69 years is more prone to tumor recurrence, being found a statistically significant associations.

In the studied group, 8 patients had to discontinue the instillations due to the side effects. These data are close to those reported by Brausi M and his collaborators in a study conducted in 2014[14].

According to the results, 3 patients underwent total cystectomy due to multiple local recurrences and lack of response to immunotherapeutic treatment.

Conclusions

Instillational treatment with BCG immunotherapy remains the best option as an adjuvant in patients with non-muscle invasive bladder tumors to prevent recurrence and progression, in well-selected cases and with clear indication.

In cases of low risk tumors or if we do not have BCG, instillation chemotherapy can be considered.

Also, in the case of BCG failure, total cystectomy is the option of choice.

References

5. Glück G., Tumorile vezicale, Tratat de urologie sub redacția I Sinescu,G Gluck, 2008;25:1947-2142
13. Sylvester R.J., van der Meijden A.P., Oosterlink W. et al., Predicting recurrence and progression in individual patients with stage TaT1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials, Eur Urol, 2006, 49(3):466-477