Intravesical Bacillus Calmette-Guérin (BCG) Immunotherapy for Patients with Non-Muscle Invasive Bladder Tumors

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Introduction: Intravesical instillations with bacillus Calmette-Guerin (BSG) is currently considered the most effective intravesical therapy for non-muscle invasive bladder tumors. The aim of this study is to present our experience with intravesical BCG immunotherapy instillations in patients with non-muscle invasive bladder tumors.
Material and method: Between September 30, 2005 and March 31, 2012 we performed intravesical instillation with BCG in 183 patients with non-muscle invasive bladder tumors, initiated at 6 weeks after transurethral resection of the tumor. The induction of BCG instillations was administrated according to the empirical 6-weekly induction schedule. Maintenance therapy was scheduled to 3 and 6 months following the instillation with BCG and at every 6 months afterwards for 3 years.
Results: Five patients did not finish the induction therapy protocol and were excluded from the study. The median clinical follow-up was 37 months. Endoscopic examination showed no reccurence in 126 patients. For 52 patients with bladder tumor reccurence, we performed tranurethral resection of the bladder. Histopathological examination demonstrated no progression in 30 cases. For this group of patients we continued the BCG tratment. The other 22 patients with progression of the tumor were excluded from the BCG treatment and received oncological or surgical treatment. The main complications were represented by tuberculization of the bladder, hematuria and fever, BCG treatment was stopped for these patients.
Conclusions: Our results show a low rate of tumor recurrence in patients with non-invasive tumors treated with BCG instillation. Complication rate is low, but the treatment required discontinuation in several patients.

Keywords: non-muscle invasive bladder tumor, intravesical instillations, bacillus Calmette-Guerin

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Introduction

Bladder cancer is the 4th most common neoplasia in men and it is the most common malignancy of the urinary tract. The lowest incidence is observed in Eastern European countries (14.7/100,000 males and 2.2/100,000 females) and the highest incidence has been reported in Western and Southern Europe, up to 27.1/100,000 patients [1]. In the last 20 years the mortality due to bladder cancer decreased by 12–14%, but there was an increase in mortality in Romania, Croatia, Poland and Denmark [2].

The treatment of bladder tumours in early stages has suffered a major shift after the introduction of transurethral techniques, leading to an improvement in the quality of life of patients, which has been affected deeply by palliative treatments used in advanced stages. During the last years, the focus has been on early diagnosis, genetic research and minimally invasive therapy of bladder cancer. Approximately 75–85% of patients with bladder cancer present with a disease that is confined to the mucosa (stage Ta, CIS) or submucosa (stage T1). These categories are grouped as non-muscle-invasive bladder tumours.

Currently most studies are trying to demonstrate the importance of intravesical treatment for tumor recurrence prevention. Intravesical instillations with bacillus Calmette-Guerin (BCG) is currently considered the most effective intravesical therapy for non-muscle invasive bladder tumors, especially for those at intermediate and high risk of relapse.

The mechanism of BCG action is not fully clarified, it was observed that it involves an immunological reaction, which is closely correlated with cell apoptosis. One of the main mechanisms of action is the effects on cytokine production. They occur in inflammation (IL-1, IL-8, IL-6, TNF-α), the immune response of T1 lymphocytes (interferon γ and IL-2) and Tk2 lymphocytes (IL-10 and IL-4) [3].

The aim of this study is to present our experience with intravesical BCG immunotherapy instillations in patients with non-muscle invasive bladder tumors.

Material and methods

Between September 30, 2005 and March 31, 2012 a number of 183 intravesical instillations with BCG were performed in patients with non-muscle invasive bladder tumors. Due to the major complications that can appear following the systemic absorbtion of the drug, intravesical administration of BCG was initiated 6 weeks after the transurethral resection of the bladder tumor in patients with confirmed non-muscle invasive bladder tumor. Also, no treatment was administrated in patients with macroscopic haematuria, urinary tract infection, or after traumatic catheterisation.

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Table I. The BCG intravesical instillation schedule

TUR-P	WEEKS AFTER TUR-P						CYSTOSCOPY	MONTHS AFTER TUR-P						
	INDUCTION THERAPY							MAINTENANCE THERAPY						
	6	7	8	9	10	11		3	6	12	18	24	30	36
	↓	↓	↓	↓	↓	↓		↓	↓	↓	↓	↓	↓	↓
	INSTILLATION							INSTILLATION + CYSTOSCOPY						

All patients underwent tuberculin test in local hospitals before the onset of treatment with BCG. Prophylactic antibiotic therapy was given to all patients.The induction of BCG instillations was administrated according to the empirical 6-weekly induction schedule introduced by Morales in 1976. Maintenance therapy was scheduled at 3 and 6 months with BCG instillation and at every 6 months afterwards for 3 years (Table I).

Cystoscopy was performed on the 7th week and after each stage of the BCG instillation treatment. BCG toxicity, recurrence and progresion of the tumor were followed.

Results

A total of 183 patients underwent intravesical treatment with BCG for non-muscle invasive bladder tumors in this period. Five patients did not finish the induction therapy protocol, with no cystoscopy control and were excluded from the study. In the end, 178 patients entered the study group. The mean age was 61.9 years. The gender ratio was 5.59/1 for male patients. The median clinical follow-up was 37 months. Endoscopic examination showed no reccurence in 126 patients (71%).

For the 52 patients with bladder tumor reccurence, we performed transurethral resection of the bladder (TUR-B). From the total of 52 patients with tumor recurrence, 32 patients already terminated the BCG treatment due to complications, the other 20 patients received the BCG according to the schedule. The histopathological examination of the material obtained from TUR-B demonstrated no progression in 30 cases (57.7%). We continued the BCG treatment of these patients according to the schedule. The other 22 patients with progression of the bladder tumor (invasive tumor) were excluded from the BCG treatment and received oncological or surgical treatment, according to the stage of the disease and patients' preference. Out of these 22 patients with progression of the tumor 19 patients were from the group who stopped BCG treatment because of complications, 3 patients were under BCG treatment. In the end a total of 54 patients (30.33%) were lost due to complications after BCG tratment or progression of the bladder tumor. The main complications were represented by tuberculization of the bladder, cystitis with macroscopic hematuria, fever over 38º (Figure 1). We considered it best to discontinue the BCG treatment for these patients. There was no need to initiate izoniazid treatment for these patients.

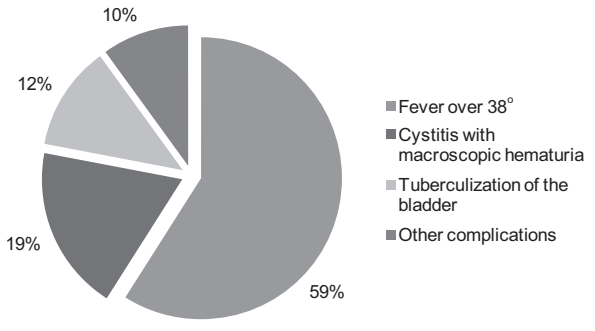

Fig. 1. Complications of BCG treatment in the studied group

Discussions

Currently there is still controversy about the optimal management scheme for BCG treatment and the type of patients with non-muscle invasive bladder who could benefit from this type of treatment to prevent recurrence and tumor progression [4,5]. According to the literature continued therapy with BCG after the induction period appears to reduce the risk of recurrence and tumor progression with 16–37% compared to patients who receive BCG therapy only during the 6 weeks induction period [6]. Assuming that maintenance therapy is necessary for optimal efficacy, the issue of BCG toxicity becomes more relevant. To reduce complications after intravesical instillation it is necessary that this treatment should not be administered if the patient has urinary infection, hematuria, after a traumatic urethral catheterization or in immunodefficient patients [7]. Another proposed method was dose reduction to 1/3 or 1/4 of the total dose, but it had negative effects on treatment efficacy [8]. BCG therapy is considered failed when the tumor exceeds the muscle layer, the number of relapses increases, the T factor worsens (invasion), or carcinoma in situ develops. The presence of bladder cancer at high risk of progression and relapse both at 3 months and 6 months after BCG immunotherapy is also considered failure [9].

The study published by Martínez-Piñeiro JA [9] performed on 500 patients showed tumor recurrence in 28% of patients and progression was seen in 11.5% of patients. The study of Decobert et al revealed recurrence-free survival in 89% of patients who received at least 3 maintenance BCG cycles [5].

Data published in our study are similar to those in the literature on tumor recurrence and progression and the complications of treatment with BCG.

Conclusions

1. Our preliminary results show a low rate of tumor recurrence in patients with non-invasive tumors treated with BCG instillation.
2. Complication rate is low, but the treatment required discontinuation in several patients.

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