The adjuvant instillational treatment with chemotherapic drugs in non-muscle invasive bladder cancer

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Abstract

Objective: The purpose of this paper is to evaluate the efficiency of the adjuvant instillational treatment with chemotherapic drugs in non-muscle invasive bladder cancer.

Materials and Methods: This study includes 50 patients diagnosed with non-muscle invasive bladder cancer in the Clinic of Urology in Brașov between 2006 and 2010. The patients have been divided in two groups: one group benefited from an adjuvant instillational treatment with chemotherapic drugs (27 patients) and a witness group was treated only by transurethral resection (23 patients).

Results: Analysing the resulting data, of the two groups of patients, we observed: Tumor relapses were significantly reduced from the statistical point of view (p<0,05) by the adjuvant instillational treatment with chemotherapic drugs. After 2 years Odds Ratio was 0,1401 with CI 95% (0,0321-0,5203), and after 5 years Odds Ratio was 0,1980 with CI 95% (0,0515-0,6792); Tumor progression in the group of patients treated only with TURBT is close to 40%, being reduced by epirubicin treatment to 18,51%, the result being statistically insignificant (p>0,05) Odds Ratio was 0,3612 with CI 95% (0,092-1,3064); Metastasis rate was more reduced in the group treated with epirubicin, but statistically insignificant (p>0,05), and the specific mortality rate (caused by bladder cancer) was little influenced by the chemotherapic drugs treatment and statistically insignificant.

Discussion: We analysed 50 patients with non-muscle invasive bladder cancer, divided in two groups: one group received intravesical adjuvant treatment with epirubicin and the witness group was only treated with TURBT. We discovered reduction of the tumor relapse rate from 56,52% after 2 years in the witness group to 14,81% in the epirubicin group, the result being statistically significant (p>0,05). Tumor progression was reduced by the treatment with chemotherapic drugs, from 39,13% in the witness group, to 18,51% in the epirubicin group, but the result is not statistically significant.

The metastasation rate and the specific mortality rate have been slightly influenced by the chemotherapic drugs.

Conclusions: The adjuvant instillational treatment with chemotherapic drugs has proved to be very valuable in reducing the relapse risk for non-muscle invasive bladder cancer.

Key words: adjuvant chemotherapy, epirubicin, non-muscle invasive bladder cancer

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**Introduction**

Bladder cancer represents approximately 6.6% of the total number of neoplasias in men and approximately 2.4% in women [1]. Moreover, these neoplasias of the urinary bladder are the most frequent within the oncological pathology of the urinary tract. In approximately 75-85% of cases, patients show non-muscle invasive cancer, limited to the bladder mucous (Ta, Tis) or submucous membrane (T1), the rest of the tumours being muscle invasive when presented in musculara propria, the adjacent structures of the bladder or lymphatic ganglion. The natural evolution of non-muscle invasive (superficial) bladder cancer is defined by two different factors, which are in a close interdependence relation: tumor relapse and progression towards infiltration or metastasation. The two possibilities of negative evolution depend on numerous factors, among which the most important are the tumor stage and degree [2].

The transurethral resection of bladder tumours (TURBT) is the gold standard for the diagnosis and the initial treatment of bladder cancer, but, as single treatment, is inefficient on a long term. This finding has led to the application of the adjuvant instillational treatment. The role of the instillation drugs is therapeutic (the destruction of the remaining cancer cells), adjuvant (prevention of the implantation of cancer cells after resection) and prophylactic (prevention of relapse and cancer progression). [3],[4] The low absorption capacity of the urinary bladder, as well as the relatively easy access to the endovesical cavity, made instillational therapy a fundamental component in the treatment of non-muscle invasive cancer. The need for an adjuvant instillational treatment is personalised for each patient (according to the prognosis). It is considered that, for patients with low-risk bladder cancer, the immediate administration post TURBT of chemotherapic drugs should be applied. The studies made by EORTC (European Organisation for Research and Treatment of Cancer) have shown that the monthly instillations made for one year have not been more efficient in reducing relapses as compared to their monthly administration for 6 months. Other studies have shown that the instillational treatment made during the first 3-4 months after the resection is as efficient as the one made during a longer period, the authors recommending regimens longer than one year only when the patient could not benefit from an immediate postoperative instillation [13], [3], [14], [4], [5], [7], [9], [15].

**Purpose**

The purpose of the study was to evaluate the efficiency of the adjuvant instillational treatment with chemotherapic drugs in non-muscle invasive bladder cancer.

**Material and method**

The study was conducted between 2006 and 2010 in the Clinic of Urology in Brașov and involved a number of 50 patients diagnosed with non-muscle invasive bladder cancer, with ages between 42 and 74. The patients have been divided in two groups: one group benefited from an adjuvant instillational treatment with chemotherapic drugs (27 patients) and a witness group was treated only by transurethral resection (23 patients). The patients from the witness group were present to every periodical check-up, but they could not benefit from any type of adjuvant instillational treatment for various reasons (the great distance...
between their homes and the hospital, the impossibility to obtain the chemotherapeutic drugs). Although recommended by all the urology associations, we could not apply postoperative instillations with chemotherapeutic drugs on all patients for objective reasons (the impossibility to obtain the chemotherapeutic drugs before the anatomopathological result).

For the adjuvant instillational treatment 50 mg epirubicin hydrochloride was used, with the commercial name of Farmorubicin. Epirubicin is an anthracycline type antibiotic with antiblastic action, which has a high capacity of cell penetration. The epirubicin hydrochloride is available in lyophilised form and is reconstituted by dissolution in 50 ml sterile saline solution. After reconstitution, the obtained solution was injected on 10 or 12 Ch urethrovessical catheter, after having previously emptied the urinary bladder. The asepsis conditions were strictly observed. The patients were recommended a low consumption of liquids 8-12 hours before the instillation. From the moment of the instillation, the patient was advised to retain the solution in the bladder for 2 hours, in order to insure a prolonged contact of the solution with the bladder walls.

The instillational treatment with chemotherapeutic drugs started 14-21 days postoperative (post TURBT), after obtaining the histopathological result. The therapeutic protocol consisted of 4 weekly instillations with epirubicin (attack dose) and one monthly instillation for 12 months.

The trial protocol of the patients involved in this study was applied as follows: once every three months during the first year, once every 6 months during the second and third year and once a year afterwards. During every appointment, kidneys and bladder ultrasound, urethrocystoscopy and additional tests were made on the patients, according to the situation.

The distribution of the patients from the witness group, according to the tumor grading was the following:

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-muscle invasive cancer G1</td>
<td>5</td>
</tr>
<tr>
<td>Non-muscle invasive cancer G2</td>
<td>8</td>
</tr>
<tr>
<td>Non-muscle invasive cancer G3</td>
<td>9</td>
</tr>
<tr>
<td>Carcinoma in situ</td>
<td>1</td>
</tr>
</tbody>
</table>

The distribution of the patients from the group who benefited from adjuvant treatment with epirubicin, according to the tumor grading was the following:

In this context, we want to mention that we have tried, as much as possible, to observe the present recommendations of the urology guides. Nevertheless, there were situations where we could not do this. Therefore, the 6 patients with G3 cancer, considered as high-risk, although they should have received instillational treatment with BCG, have benefited from intravesical chemotherapy because they could not obtain the immunotherapeutic drug for financial reasons (they being available only through the personal efforts of the patients).

**Results**

As a result of the data analysis, the characteristics of the two groups of patients according to the main issues aimed at have been:

<table>
<thead>
<tr>
<th></th>
<th>TURBT</th>
<th>TURBT + chemotherapeutic drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>relapse rate after 2 years</td>
<td>56.52%</td>
<td>14.81%</td>
</tr>
<tr>
<td>p&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>relapse rate after 5 years</td>
<td>78.26%</td>
<td>40.74%</td>
</tr>
<tr>
<td>p&lt;0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>the average relapse time</td>
<td>24 months</td>
<td>38.18 months</td>
</tr>
<tr>
<td>local progression rate (at least in T2)</td>
<td>39.13%</td>
<td>18.51%</td>
</tr>
<tr>
<td>metastasation rate</td>
<td>13.04%</td>
<td>7.40%</td>
</tr>
<tr>
<td>general mortality rate</td>
<td>13.04%</td>
<td>3.70%</td>
</tr>
<tr>
<td>cancer mortality rate (specific mortality)</td>
<td>8.69%</td>
<td>3.70%</td>
</tr>
</tbody>
</table>

According to the tumor grading, the relapse evolution of the patients from the two groups was the following:

<table>
<thead>
<tr>
<th>Relapse after 2 years</th>
<th>Relapse after 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>TURBT</td>
<td>TURBT + epirubicin</td>
</tr>
<tr>
<td>G1 Tumor</td>
<td>40%</td>
</tr>
<tr>
<td>G2 Tumor</td>
<td>50%</td>
</tr>
<tr>
<td>G3 Tumor</td>
<td>66.66%</td>
</tr>
</tbody>
</table>

In the group of patients to whom the adjuvant instillational treatment with epirubicin was applied, the following minor side effects were noticed:
In our group we noticed a reduction of the tumor relapse rate from 56,52% after 2 years in the witness group to 14,81% in the epirubicin group, the result being statistically significant (p>0,05). The favourable evolution of the group with adjuvant treatment is also maintained after 5 years, with a reduction from 78,26% in the witness group, to 40,74% in the epirubicin group, this result being also statistically significant (p>0,05).

The favourable effects of the epirubicin instillations were clear especially in the first trial period, but the results showed that, in time, they tend to decrease.

Tumor progression was reduced by the treatment with chemotherapic drugs, from 39,13% in the witness group, to 18,51% in the epirubicin group, but the result is not statistically significant. The metastasation rate and the specific mortality rate have been slightly influenced by the chemotherapic drugs. If the correct instillation conditions are observed, the side effects are at a minimum.

All international urology associations recommend the postoperative instillational treatment with chemotherapic drugs, and, as an adjuvant treatment, in superficial tumors with intermediate risk. Although there is no agreement as to the duration of the treatment, it is recommended to have monthly instillations for 6 to 12 months [3], [4], [7], [11].

Conclusions
The adjuvant instillational treatment with chemotherapic drugs has proved to be very valuable in reducing the relapse risk for non-muscle invasive bladder cancer. The results are conclusive especially for intermediate risk tumors, in agreement with the recommendations of the international urology guides. Intravesical chemotherapy proves to be very valuable also in reducing the cancer progression risk, but statistically insignificant in our group.

Bibliography
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