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Adjuvant Intravesical Chemotherapy Versus Immunotherapy for All Risk Groups of Patients With Non-muscle Invasive Bladder Cancer

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ABSTRACT

Background: The treatment strategy for non-muscle invasive bladder cancer (NMIBC) has not changed significantly over the past 30 years. Chemotherapeutic agents (mitomycin-C, epirubicin, etc.) and BCG (Bacillus Calmette-Guerin) immunotherapy are used as adjuvant intravesical therapy. **Objective:** To compare the difference between adjuvant chemotherapy and adjuvant immunotherapy in their efficacy of reducing the number of tumor recurrences. **Methods:** In this prospective clinical study, which included 99 patients with NMIBC from March 2018.–March 2023., we publish the results for all risk groups of patients treated with intravesical chemotherapy Epirubicin or with BCG immunotherapy, after TURBT (Trans urethral resection of bladder tumor) within 1 year. Patients were stratified into 2 groups. The first group was treated with Epirubicin (1 dose within 24 hours of surgery, then 6 weekly instillations and 3 maintenance doses), and the second group was treated with BCG (2-3 weeks after TURBT 6 weekly instillations, and 3 maintenance doses). The monitoring period was 24 months. **Results:** In patients treated with intravesical chemotherapy, recurrence occurred in 9 patients (17.64%), and in patients treated with BCG, recurrence occurred in 7 patients (14.58%). A similar incidence of disease recurrence was observed in both groups (p=0.787). **Conclusion:** The results of our study show a similar therapeutic response by risk groups of patients treated with chemotherapy and immunotherapy. Since BCG production will cease in the future, the task of urologists is to introduce intravesical chemotherapy into wider use and to modernize it as a safe and effective method of adjuvant treatment for non-muscle-invasive bladder cancer.

Keywords: Non-muscle invasive bladder cancer; chemotherapy; immunotherapy; epirubicin; Bacillus Calmette-Guerin.

1. BACKGROUND

Bladder cancer (BC) is the seventh most commonly diagnosed cancer in the male population worldwide, and it is the tenth when both genders are considered. The worldwide age- standardised incidence rate (per 100,000 person/years) is 9.5 in men and 2.4 in women (1).

Bladder cancer incidence and mortality rates vary across countries due to differences in risk factors, detection and diagnostic practices, and variations in access to, and delivery of, healthcare

(2). The incidence and mortality of BC has decreased in some registries, possibly reflecting the decreased impact of causative factors (3). Approximately 75% of patients with BC present with a disease confined to the mucosa (stage Ta, CIS) or submucosa (stage T1); in younger patients (< 40 years of age) this percentage is even higher (4).

To date, no clinically relevant genetic alteration has been linked to BC. Genetic predisposition may lead to a higher susceptibility to other risk factors, and thereby explain the familiar clustering of BC in first- and second-degree relatives that has been confirmed more recently (5). Tobacco smoking is the most important risk factor for BC, accounting for approximately 50% of cases (6). Medical conditions may predispose individuals to bladder tumor genesis through direct causation or as a side effect of treatment. Examples of direct causative include chronic urinary retention and upper tract dilation increasing urothelial exposure to carcinogens and carcinogenesis associated with chronic inflammation or schistosomiasis (7).

Patients with TaT1 and CIS have a high disease prevalence due to long-term survival in many cases and lower risk of cancer-specific mortality compared to patients with T2-4 disease (2).

To be able to facilitate treatment recommendations, the Guidelines Panel recommends the stratification of patients into risk groups based on their probability of progression to muscle- invasive disease (8). To be able to predict both the short- and long-term risks of disease recurrence and progression in individual patients, the EORTC Genito-Urinary Cancer Group (GUCG) published a scoring system and risk tables, which was further developed in 2016 (9). The guidelines panel recommends stratification of patients into three risk groups that will facilitate treatment recommendations.

The treatment strategy for intravesical therapy of non-muscle invasive bladder cancer has not changed significantly in the last 30 years. In addition to standard chemotherapeutics (such as mitomycin-C (MMC), epirubicin, valrubicin, etc.) newer ones such as gemcitabine are being introduced. Even earlier, it was proven that BCG immunotherapy proved to be significantly better in the prevention of recurrence compared to chemotherapy, however, BCG causes significantly more side effects compared to chemotherapy (10). Despite numerous studies, the treatment strategy has not changed significantly.

The treatment of these patients requires high costs, and the reasons are that the disease is common, a large number of patients survive, more than half of the patients have a recurrence of the disease and require lifelong monitoring, and repeated surgical procedures (11). The goal is to reduce the number of recurrences and thus reduce treatment costs (12).

2. OBJECTIVE

The aim of the study was to determine the therapeutic response in all risk groups in patients with non-muscle invasive bladder cancer who were adjuvantly treated with epirubicin chemotherapy and BCG immunotherapy.

3. PATIENTS AND METHODS

This prospective clinical study was conducted from March 2018.–March 2023., which included 99 patients divided into 2 groups, of which 51 were treated with intravesical chemotherapy, and 48 were treated with intravesical BCG immunotherapy. Treated patients were followed for 2 years.

Patients

The study included 99 patients of both sexes, aged between 45-85 years with newly discovered NMIBC. Risk stratification of disease recurrence and progression was done using EORTC risk tables according WHO 2004/2016. classification system into 3 riskgroups: low, intermediate and high risk of progression. The scoring system is based on the following 4 significant clinical pathological factors: Number of tumours, tumour diameter, T category, WHO 2004/2016. grade and 3 additional clinical risk factors: age >70, multiple papillary tumours, tumour diameter >3cm. (8) In our study, we treated newly diagnosed tumors, without patients with CIS. All subjects were treated with TURBT surgery, and all pathohistological analyzes were performed using standard methods of pathohistology at our Pathology Clinic.

Inclusion criteria are: pathohistologically confirmed non-muscle invasive bladder cancer, performance status ≤2, patients without contraindications for instillation of chemotherapy or BCG immunotherapy, patients who signed consent to participate in the study.

Exclusion criteria are: pathohistological finding of CIS, development stage pT2 and higher, patients older than 85 years, according to WHO performance status 3 or 4, previous treatment with chemotherapy or immunotherapy, patients who did not give written consent to participate in the study, pathohistological findings of non-transitional cell carcinoma, urothelial carcinoma involving the urethra or upper urinary tract, previous partial cystectomy, bladder diverticulum greater than 1cm, residual urine greater than 100ml, bladder volume less than 150ml, urinary incontinence, urethral stricture impermeable to a 20 F catheter, persistent hematuria, active urinary infection, active tuberculosis, known allergy to epirubicin or BCG, known weakened immune response, positive HIV serology, recipients of systemic steroids or immunosuppressant, hematological disorders, suspected perforation of the urinary bladder during surgical treatment, number of leukocytes below 3,500, platelets below 100,000, kidney and liver function disorders, pregnant or lactating women.

Methods

Preoperatively, tumors were diagnosed by cystoscopy, using a Storz rigid cystoscope with 0°, 30° and 70° field of view angle and cold white light source. They were operated on under general or spinal anesthesia. In the case of smaller tumors, up to 1 cm, en-bloc resection was performed, and in the case of larger tumors, the classic method of resection was performed.

Pathohistological confirmation of the disease was performed ''ex tempore" or within 24 hours in the case of epirubicin instillation, and within 2 weeks in the case of BCG instillation. Patients were classified into 2 groups.

The first group was given epirubicin 50mg in 50ml of 0.9% NaCl within 24 hours of the operation, it remained in the bladder for one hour, and later once a week for 6 consecutive weeks with the start of instillation within 24 hours of the operation, and after that one instillation every 3 months (6, 9, 12) after a cystoscopic examination for a total period of one year.

The second group of patients was instilled with BCG, 14-21 days after TURBT, followed by a total of 6 weekly instillations, and one instillation every 3 months (6, 9, 12) for a total period of one year after the cystoscopic examination.

Patients were followed for 2 years from the start of treatment with regular three-monthly cystoscopic examinations. As part of follow-up at control examinations, an ultrasound of the urinary tract was performed with a Siemens Healthineers Acuson NX3 Elite US sys-

tem, and basic laboratory findings were done. In case of suspicion of disease progression, additional CT or MRI scans were performed (Siemens Somatom Definition Edge 128 slice MSCT and Siemens Avanto Magnetom 1.5T) as part of preoperative preparation.

The protocol was terminated at the occurrence of the first recurrence, at the progression to muscle invasive disease, at the diagnosis of CIS, at the occurrence of cancer of the prostatic urethra or upper urinary tract, or at the diagnosis of distant metastases. In cases of unwanted side effects of the therapy, the dose of the drug was not modified and the treatment was postponed or discontinued. For one patient treated with epirubicin, the protocol was interrupted due to elevation of liver function enzymes. The protocol was interrupted in 4 cases in patients treated with immucyst due to cystitis and dysuric complaints.

Each patient signed a consent form for the therapy "Intravesical instillation of BCG" or "Intravesical instillation of Epirubicin" before starting the therapy. In the form, the patients were explained what is the treatment they are receiving, its mode of action, the method of instillation and the instillation protocol, as well as possible side effects that they would have to report at follow-up in case of occurrence.

They agreed that after receiving the information they could refuse the specified procedure, that the diagnosis and prognosis of the disease, the goal and benefit of the specified therapy, were described to them, and they were also informed about possible changes in their condition after the therapy, about other possible methods of treatment (with a description of each of these methods) and their rights in deciding on the proposed measure. Patients were also informed about the organizational aspects of their therapy, the waiting list and waiting time, and scheduling appointments. Signed consent was used as inclusion criteria.

Statistical analysis

Processing, graphical presentation of data and testing of statistical hypotheses was done using the program for statistical data processing–"R". This program has the ability to display results graphically and by table, test hypotheses, analyze trends, predict and plan acceptance of assumptions. It can be used as a so-called Point-and-click interface, which means that the procedures are already in the program menu, and the user only needs to select them, which is why it is widely used. Also, "R" has the ability to write its own programs for statistical data processing. Basic tests of descriptive statistics were performed, and testing of the statistical significance of the difference in numerical variables was performed using the Mann-Whitney U test. The correlation between the frequency of occurrences and the applied treatment was tested using the $\chi 2$ (chi square) test. The log-rank test was used to assess the statistical significance of differences between groups in the context of recurrence and disease progression. A Kaplan-Meier analysis was performed to evaluate the function of recurrence or progression of the disease in different time intervals for groups of subjects. A univariate log-rank test (Cox's regression analysis) was performed in which two groups were compared in the context of disease recurrence or progression, taking into account only one independent variable, the risk factor, as well as a multivariate log-rank test that took into account several risk factors in order to assess their joint influence on the recurrence or progression of the disease. The p-value from the log-rank test provided an estimate of whether the differences between the groups in the time-to-event distributions were statistically significant. It was assumed that for $p<0.05$ there is a statistically significant difference between the groups in terms of recurrence and disease progression. The corresponding author has full access to all data in the study and had final responsibility to submit for publication. *Ethical statement:* The study was approved by the Ethical Committee of University Clinic center Tuzla (30.10.2018. No: 02-09/2-56/18).

4. RESULTS

A total of 99 patients with an average age of 66.85 years were included in the study. The male to female ratio was 82:17. Patients were divided into 2 groups according to the application of the therapeutic protocol, namely chemotherapy (n=51) and immunotherapy (n=48). (Table 1).

The log rank test showed a similar probability of disease recurrence in both groups (Chi2=0.014, p=0.905). (Figure 1.)

The monitoring period was 24 months. Disease recurrence occurred in 9/51 patients (17.64%%), in patients treated with intravesical chemotherapy, and in patients treated with BCG immunotherapy recurrence occurred in 7/48 (14.58%) patients. A similar incidence of disease recurrence was observed in both groups (p=0.787).

Multivariate Cox regression analysis showed that the number of tumors (p=0.006) and tumor size (p=0.028) had a significant prognostic impact on the recurrence of the disease in the group of patients who received immunotherapy.

In the group of patients who received chemotherapy, univariate Cox regression analysis revealed that only the number of tumors (p=0.062) had a significant prognostic impact. In the multivariate analysis, none of the risk factors had a significant prognostic impact.

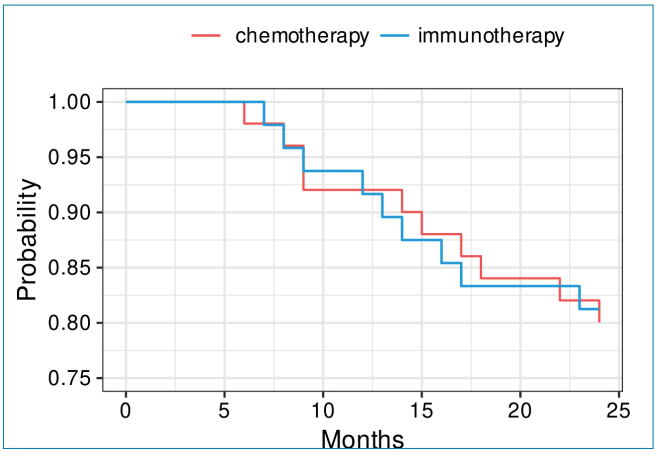

Figure 1. Kaplan-Meier curve for recurrence in both groups

Patient sample	**Total** (N=99)		**Male** (N=82)		**Female** (17)
	Chemotherapy		Imunotherapy		
	N	%	N	%	P-values
Age, yr, mean (SD)	68.6 (7.3)		65.1 (8.9)		0.542
Gender					
Female	9	17.6	8	16.7	1.00
Male	42	82.4	40	83.3	
Stage					
pT1	16	31.4	13	27.1	0.804
pTa	35	68.6	35	72.9	
Grade					
High	14	27.4	20	41.7	0.790
PUNLP	6	11.8	1	2.1	
Low	31	60.8	27	56.2	
Tumor size					
<3 cm	37	72.5	35	72.9	0.946
≥3 cm	14	27.5	13	27.1	
Number of tumors					
=1	25	49.0	28	58.3	0.594
>1	26	51.0	20	41.7	

Figure 1. Kaplan-Meier curve for recurrence in both groups

			Recurrence		Total
			Yes	No	
Risk of recurrence Chemotherapy group	Low risk	N	1	20	21
		%	4.8%	95.2%	100%
	Intermediate risk	N	4	11	15
		%	26.7%	73.3%	100%
	High risk	N	4	11	15
		%	26.7%	73.3%	100%

Table 2. EORTC risk of bladder cancer recurrence in the chemotherapy group

			Recurrence		Total
			Yes	No	
Risk of recurrence Immunotherapy group	Low risk	N	0	19	19
		%	0.0%	100%	100%
	Intermediate risk	N	3	10	13
		%	23.1%	76.9%	100%
	High risk	N	4	12	16
		%	25.0%	75.0%	100%

Table 3. EORTC risk of bladder cancer recurrence in the immunotherapy group

Tables 2 and Table 3 show the number of recurrences by EORTC risk groups. Recurrence in the first group occurred in 4.8% (1) of low-risk, 26.7% (4) of intermediate-risk and 26.7% (4) of high-risk patients. Recurrence in the second group occurred in no low-risk cases, 23.1% (3) of intermediate-risk, and 25% (4) with high-risk patients. There is no statistically significant difference in the risk of recurrence between the groups (for low risk p=0.888, medium risk p=0.973, high risk p=0.839).

In both groups of patients who received chemotherapy and immunotherapy, the EORTC score was a significant predictor of recurrence (patients who received chemotherapy: OR=2.7, %95 Cl=1.2-6.4, p=0.022; patients who received immunotherapy: OR= 2.7, %95 Cl=1.1-6.8, p=0.035). This meant that for every additional EORTC score point for relapse, the risk increased 2.7 times in both groups. In both groups, two patients had disease progression. All patients belonged to the high-risk group, and had HG and pT1 tumor.

5. DISCUSSION

The main characteristic of non-muscle invasive bladder cancer is recurrence. The TURBT alone is an insufficient treatment because recurrence is expected in over 60% of cases (13). Adjuvant chemo or immunotherapy is required to achieve the good prognosis in NMIBC and to prevent recurrence and progression of the disease (14).

With the natural history of NMIBC alone it is difficult to predict recurrence and progression of the disease due to the unpredictable biological behavior of the tumors. To predict the risks of recurrence and progression in individual patients of NMIBC, a scoring system and risk tables were developed by the European Organization for Research and Treatment of Cancer (EORTC) (15).

The need for adjuvant therapy is greater than ever. BCG immunotherapy has long been proven to be superior to chemotherapy. A meta-analysis compared Mitomycin C versus BCG. In the trials with BCG maintenance, they found 32% reduction in the risk of recurrence for BCG compared with MMC (16).

Although adjuvant intravesical chemotherapy has been widely promoted, the prognosis of patients with high-risk NMIBC is still unsatisfactory. Therefore, novel therapies that could effectively reduce the recurrence rate and alleviate the side effects of chemotherapy are being explored. Xing Li et al. have shown that intra-arterial chemotherapy in combination with intra- vesical chemotherapy in the treatment of patients with high-risk NMIBC is superior to intra- vesical chemotherapy alone (17).

In 2016, Arends et al. published a prospective randomized study in which they compared intravesical chemohyperthermia with MMC versus BCG immunotherapy as adjuvant treatment in patients with intermediate and high-risk non-muscle invasive bladder cancer. Chemohyperthermia with MMC has been shown to be superior in the 24-month recurrence free period in intermediate and high-risk patients compared to BCG-treated patients. Side effects were similar compared to earlier studies (18).

In our study, both groups of treated patients were similar in terms of age, gender, tumor stage, tumor grade, and the number and size of tumors. The time of recurrence was similar in both groups of patients (Chi2=0.014, p=0.905). For the group of patients treated with immunotherapy, the number and size of tumors had a significant prognostic impact, and for the group treated with chemotherapy, only the number of tumors had a significant prognostic impact. In both groups, two patients each had disease progression, belonged to the high-risk group, and had HG and pT1 tumor. After classifying patients according to EORTC risk groups, we found that there is no statistically significant difference in the risk of recurrence between chemotherapy and immunotherapy groups (for low risk p=0.888, medium risk p=0.973, high risk p=0.839), with the total thenumber of relapses in patients who received intravesical chemotherapy (9), higher than the total number of relapses of intravesical immunotherapy (7).

A limitation of the study is the relatively short period of monitoring and the small number of treated patients. One of the possible reasons for the low percentage of disease progression is the relatively short period of monitoring of 24 months.

In the last 10 years, the production of BCG has decreased and the complete suspension of production in the world has been announced, and there have already been periods of shortages on the market. Adjuvant intravesical chemotherapy is now the only alternative and should be considered for a wider usage. Side effects such as pain in the bladder area, dysuria, frequent urination, were more frequent in the group of patients treated with BCG therapy, which suggests that intravesical chemotherapy is safe for adjuvant treatment of patients.

6. CONCLUSSION

The results of our study show a similar therapeutic response by risk groups of patients treated with chemotherapy and immunotherapy. Chemotherapy treatment costs are significantly lower. Since BCG production will cease in the future, the task of urologists is to introduce intravesical chemotherapy into wider use and to modernize it as a safe and effective method of adjuvant treatment for non-muscle-invasive bladder cancer.

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