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COMPARATIVE CHARACTERISTICS OF ADJUVANT INTERNAL BLADDER CHEMOTHERAPY IN PATIENTS WITH MUSCLE-NON-INVASIVE BLADDER CANCER

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Abstract

Aim: to analyze and compare the results of treatment of patients with MNRSM who underwent only TUR of the bladder and TUR of the bladder with subsequent intravesical instillation of chemotherapeutics.

Adjuvant intravesical chemotherapy plays an important role in the treatment of non-invasive bladder cancer. Preference for a particular drug in this therapy depends directly on the attending physician. The aim of the study was to compare the results of treatment of patients who underwent transurethral resection (TUR) of the bladder and patients who underwent TUR with instillation of Epirubicin and patients who underwent TUR with instillation of Doxorubicin.

Methods and materials. A retrospective and prospective analysis of 102 patients treated at the Institute of Urology of the National Academy of Medical Sciences of Ukraine in the period from 2013 to 2019 was performed. Patients with PCM stage Ta, T1, histologically G1-G2 were analyzed. All patients were divided into three groups. The first group underwent only TUR, the second group performed TUR with subsequent instillations of Epirubicin, the third group after TUR performed instillation of Doxorubicin. The median follow-up was 36 months.

Results. The study showed that patients who underwent IBCT had better recurrence-free survival than patients who underwent only TUR of the bladder. The results of this study did not show the advantages of Epirubicin over Doxorubicin, which allows us to claim the same positive effect of both drugs.

All human studies were conducted in compliance with the rules of the Helsinki Declaration of the World Medical Association "Ethical principles of medical research with human participation as an object of study". Informed consent was obtained from all participants.

Keywords: muscle-noninvasive bladder cancer, intravesical chemotherapy, relapse, progression, recurrence-free survival

Introduction

Among cancers of the urinary system, bladder cancer (BC) ranks 1st. Unfortunately, the trend towards an increase in the number of patients with bladder cancer is growing from year to year [1 According to the US National Registry, bladder cancer is more common in Americans of Caucasian descent and people over the age of 65 [2]. In European countries, BC is most common in Belgium, while the lowest incidence is in Finland. In the world as a whole, men suffer from bladder cancer 4 times more often than women [3].

Of the total incidence of bladder cancer, the musculo-noninvasive form accounts for about 75% [4, 5]. About 25% of patients with MNBC tend to progress to the muscular-invasive form with a high risk of metastasis [6]. The American Urological Association (AUA) claims that the frequency of stage Ta has increased significantly over the last decade, and stages Tis and T1 have decreased [7].

Transurethral resection (TUR) is a traditional approach to the treatment of musculo-non-invasive bladder cancer (MNIBC). A feature of the non-invasive form is the multicentric lesion of the entire urothelium, potentially ready for a new tumor generation. Another important point is that after the primary TUR there is a significant risk of residual tumor, according to the literature after resection of T1 tumors residual tumor was present in 33-53% of patients [8 - 12]. It is proved that the implementation of repeated TUR in the first 4-6 weeks increases the recurrence-free survival [13, 14].

In order to improve the results of treatment, it is customary to perform intravesical chemotherapy (IVCT) or Bacillus Calmette-Guerin (BCG) immunotherapy in the postoperative period [15, 16]. In patients at low risk (highly differentiated, single tumor, up to 3 cm in diameter) is recommended single postoperative chemotherapy [17]. In patients with poorly differentiated, multiple tumors and tumors larger than 3 cm, the use of a course of intravesical instillations is recommended [18, 19]. Table 1 presents the treatment regimens of patients in relation to the risk group, which is recommended to us by the European Association of Urologists.

Objective to analyze and compare the results of treatment of patients with MNRSM who underwent only TUR of the bladder and TUR of the bladder with subsequent intravesical instillation of chemotherapeutics.

Methods

The retrospective comparative study included 102 patients who underwent examination, treatment and follow-up at the clinic of the Institute of Urology of the National Academy of Medical Sciences of Ukraine in the period from 2013 to 2019. The inclusion criterion in the study was the presence of the formation of Ta, T1, histologically G1-G2, the overall score on the scale EORTC to 9, the absence of a history of previous intravesical instillation. Criteria for exclusion from the study were the presence of patients with primary tumor stage T2, the presence of histological gradation G3, previous intravesical instillation of chemotherapy or BCG, the presence of metastases or tumors of the upper urinary tract, as well as an overall EORTC score greater than 9. All patients were divided into 3 groups. The first stage of treatment was to perform transurethral resection of the bladder according to conventional methods with the removal of all visible formations, this stage is presented in Figures 1, 2, 3.

The next stage of treatment was intravesical administration of a chemotherapeutic drug. According to the recommendations, the standard method of preparation of the solution for instillation is to dilute the chemotherapy with sterile water or a solution of 0.9% NaCl [21, 22]. The dilution method and instillation schemes according to the groups were as follows: In the first group (n = 35) patients underwent intravesical instillation of Doxorubicin according to the following scheme: once a week for 4 weeks, then once a month for 4 months. A single dose of chemotherapeutic drug per 1 instillation was 50 mg. 25 ml. Doxorubicin diluted in 30 ml NaCl 0.9%. The second group (n = 33) received in the postoperative period of instillation with the drug Epirubicin. The schedule was the same as the first group: once a week for 4 weeks, then once a month for 4 months. A single dose of chemotherapeutic drug per 1 instillation was 50 mg. 25 ml. Epirubicin diluted in 30 ml of NaCl 0.9%.

The second group (n = 33) received in the postoperative period of instillation with the drug Epirubicin. The schedule was the same as in the first group: once a week for 4 weeks, then once a month for 4 months. A single dose of chemotherapeutic

drug per 1 instillation was 50 mg. 25 ml. Epirubicin diluted in 30 ml of NaCl 0.9%.

The third group (n = 34) was a control group. The patients in this group did not receive any intravesical adjuvant chemotherapy. Patients in this group underwent only TUR of the bladder. The reason for non-adjuvant intravesical chemotherapy was the presence of hematuria in the postoperative period, suspicion of perforation of the bladder, the patient's refusal to instillation, drug deficiency.

It should be noted that the exposure to chemotherapy in the first and second groups of patients was 2 hours, during which patients were advised to change body position for better distribution of the drug in the bladder.

Further observation of patients after treatment was as follows: control cystoscopy in the first year was performed once every 3 months; the next two years cystoscopic examinations were performed once every 6 months. If a patient relapses, the degree of invasion (T) and histological differentiation (G) must be determined if the disease is progressing. In patients who had a recurrence without invasion, subsequent cystoscopy was performed after 3 months.

Statistical processing of the results was performed using Microsoft Word, Exel. The $\chi 2$ criterion was used to determine the differences between qualitative variables. The reliability of the differences is set at $p \leq 0.05$.

Results

The duration of observation was 36 months. The average age of patients was 63.12 ± 1.48 years. The youngest patient was 37 years, the oldest was 86 years old. The overall ratio of men and women was 3.96: 1.

The recurrence rate, progression and non-recurrent survival are shown in table 3. The recurrence rate for the first year of follow-up in the group with Epirubicin was 36.39% (12 patients), in the group with Doxorubicin 36.9% (13 patients), in the group where only TUR was performed - 67.5% (23 patients). The rate of progression during follow-up in the group with Epirubicin was 6.06% (2 patients), in the group with Doxorubicin 8.55% (3 patients), in the group where only TUR 35.3% (12 patients). Three-year recurrence-free survival rates were 39,3% (14 patients) in the Epirubicin group; 42,7 % (15 patients) in the group with Doxorubicin and 11.7% (4 patients) in the group where intravesical chemotherapy was not performed.

The literature suggests that patients at low risk need only one intravesical instillation in the first 24 hours after surgery with Methomycin C (MMC), for other chemotherapeutics such as Doxorubicin, Epirubicin, TioTef, Gemcitabine no data available. There are also no clear results on the schemes of intravesical chemotherapy. Our decision was to perform instillation in such patients according to the scheme - once a week for 4 weeks, then once a month for 4 months [23 - 25]. The reason for this decision was the inability of all patients to perform instillation in the first 24 hours due to contraindications such as hematuria, suspected perforation, drug deficiency.

Discussion

The results of treatment and follow-up of patients who received adjuvant intravesical chemotherapy showed high efficacy compared to patients who underwent only bladder TUR. Comparing the effectiveness of two chemotherapeutic agents for intravesical instillation - Epirubicin and Doxorubicin, it can be argued that the advantage of Epirubicin over Doxorubicin is insignificant. This in turn gives us reason to understand that these preparations are the same in their result.

Conflict of interest

The authors declsre that there are no conflicts of interest.

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Table 1. Guidelines of the European Association of Urology on adjuvant therapy in patients with non-muscle-invasive bladder cancer depending on the riskgroup

Riskgroup	Definition	Treatmentguidelines
Low	Primarytumor Solitarytumor TaG1 <3 cm	One-timeimmediateinstillationof a chemotherapydrug
Intermediate	Multifocaltumors TaG1–2 (Lowgrade)	One-timeimmediateinstillationof a chemotherapydrug + IVCT course: 6 weeks + maintenancetherapyupto 1 year or Intravesical BCG therapycourse: 6-week induction + maintenance therapyupto 1 year
High	T1G1–3or TaG3 or G2 (Highgrade) carcinomainsituor TaG1–2, multifocalandrecurrenttumors, >3 cm	Intravesical BCG therapycourse: 6-week induction + maintenance therapyupto 3 years or Radicalcystectomy

Figure 1. Cystoscopy (bladder tumor)

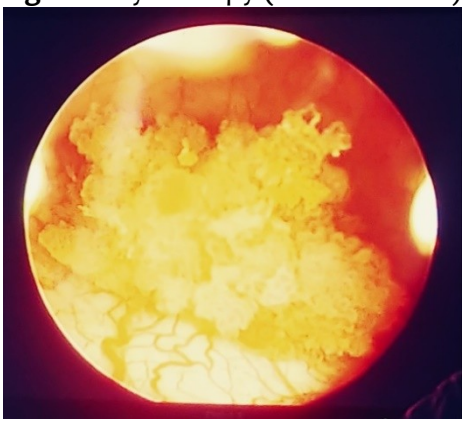

Figure 2. TUR bladder tumor

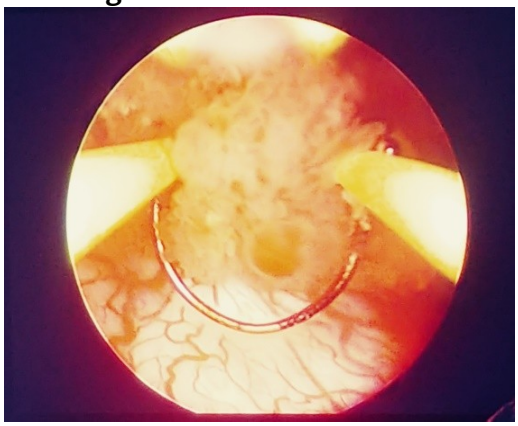

Figure 3. Place of resection of the bladder tumor

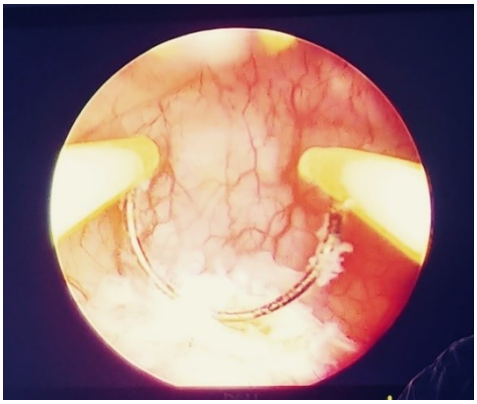

Table 2. Characteristics of patients by groups

Charaecteristic	Group with Epirubicin (n=33)	Group with Doxorubicin (n=35)	Group TUR (n=34)
Median follow-up time, months	36	36	36
Primary tumor, n	18	13	15
Relapse, n	15	22	19
Tumor invasion, n			
Ta	22	18	18
T1	11	17	17
Diferentiation grade, n			
G1	18	22	20
G2	15	13	14
Number of tumors , n			
single	24	22	21
multifical	9	13	13
Tumor size, n			
≤ 3 cm	21	22	19
≥ 3 cm	12	13	15

Table 3. Indicators of relapse and progression in groups

Charaecteristic	Group with Epirubicin (n=33)	Group with Doxorubicin (n=35)	Group TUR (n=34)	*p*
Relapse rate, %				
3 month	12,2 %	8,5 %	35,2 %	≤ 0,05
6 month	15,1 %	19,9 %	14,7 %	≥ 0,05
1 year	9,09 %	8,5 %	17,6 %	≥ 0,05
Rate of disease progression, with Ta,T1 in T2 %	6,06 %	8,55 %	35,3 %	≤ 0,05
2-year relapse-free survival rate, %	63,6 %	62,7 %	32,3 %	≤ 0,05
3- year relapse-free survival rate, %	39,3 %	42,7 %	11,7 %	≤ 0,05

Figure 4. Diagram of relapse and progression in groups