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INTRAVESICAL CHEMOTHERAPY FOR NON-MUSCLE INVASIVE BLADDER CANCER

Summary. This review presents modern views on diagnostics, the role of repeated surgical interventions for non-muscle invasive bladder cancer. The results of treatment of patients with NMIBC who received intravesical chemotherapy and who were not instilled are also presented.

Key words : bladder cancer, transurethral resection, recurrence, chemotherapy.

Introduction

In the structure of cancer, bladder cancer ranks 7th among men and 11th overall [2]. The worldwide incidence of the disease is 9.0 per 100,000 population among men and 2.2 per 100,000 among women [2]. Indicators vary widely between countries, due to differences in risk factors, detection, diagnosis and treatment features. The variation is somewhat related to the different methodology and quality of data collection [3].

In Ukraine, as of 2018, it registers, with an average of 11.4 cases of MSM incidence and 4.4 cases of deaths per 100,000 population. Men in Ukraine get sick about 4 times more often than women. In 2018, according to the National Cancer Registry, 3895 cases were first diagnosed [4]. Mortality from this pathology continues to remain at a fairly high level - 4.4 per 100 thousand population [4]. It is known that according to statistics, up to 20.8% of patients die within the first year after the disease is detected [4].

About 75% of patients at diagnosis have stage T, T1 in people younger than 40, this figure is even greater [5]. High ability to relapse and progression characterize PCM as an aggressive disease. Relapses usually occur in 50%, most often in the first 2 years after surgery. Metastases are usually found in the pelvis 15-20%, in regional lions 10-15%, urethra 6-11%, in the upper urinary tract up to 5% [1,5,6, 7, 8].

Currently, the etiology of PCM has been studied in great detail. Among the main reasons that lead to the development of this pathology, in the first place highlight the influence of occupational factors (prolonged contact with petroleum products), smoking, nutrition and drinking, genetic determination, the presence of chronic inflammatory diseases of the genitourinary system and infections that lead to infections [1,5].

The modern standard for the diagnosis of bladder tumors in most cases is cystoscopy with biopsy and subsequent histological examination of the drug. The stratification of the risk of recurrence and progression of the disease is based on the clinical and histological characteristics of the tumor, and therefore, in the pathomorphological examination of surgical and biopsy material of urothelial bladder cancer, it is necessary to take into account, first of all, the forms of tumor growth (the presence of papillary structures, the presence of papillary structures,), the degree of differentiation of tumor cells (G1-G3). In the presence of an invasion, it is imperative to determine its depth, which is necessary to evaluate the stage of the tumor process by the TNM system [9]. Due to the unpredictability of the disease, it is necessary to look for factors that will allow you to predict the onset of the disease and to choose the optimal treatment regimen.

Conditional forecast factors can be divided into several groups:

Histological Tumor Variety. In 1998, the World Health Organization (WHO) and the International Society of Urological Pathology presented and

published in 2004 the classification of non-invasive urothelial tumors (WHO / ISUP classification 1998). [10,11]. The classification consists in the detailed determination of the various degrees of anaplasia on the basis of selected cytological and histological criteria.

The classification divides flat urothelium formation into: urothelial hyperplasia, reactive urothelial atypia, atypia of unknown malignant genesis, dysplasia and CIS [12,13].

Among the non-invasive urothelial neoplasms, the 2004 WHO classification distinguishes PUNLMP, a low- and high-grade urothelial cancer. PUNLMP is defined as an entity that has no cytologic signs of malignancy, but normal urothelial cells combine into papillary structures. These entities have a low risk of progression, are non-malignant, and tend to relapse (G2).

The degree of differentiation. Surface tumors are usually differentiated by the degree of anaplasia (G) [14,15]. Transient cell carcinoma is highly differentiated, characterized by a good cure rate of up to 80% .Recurrences of such cancer are due to molecular genetic disorders [16,17,18,19]. due to the prevalence of the tumor. [20,21].

The nature of tumor growth. The leading role in the pathohistological genesis of transitional cellular PCM belongs to the cambial elements of the transitional epithelium, which are malignant and capable of uncontrolled division. The risk of progression with the development of invasion is low, but with T1G3 tumor increases to 50%, which increases the progression [22,23].

Multifocal impression. During TURB, small tumors of the bladder are often invisible or missed. The incidence of recurrence in papillary cancer in these cases is 65-85%, progression to 20% [24, 25, 23]. Upon examination 1 to 1.5 months after the primary TOUR, 40-65% detect residual tumors. This explains to us that PCM is a disease of the entire mucous membrane. [21,5,26].

Prevalence of the tumor. Superficial cancer progresses to invasive form in 1 year only by 10-20% [27,20]. For low-risk tumors the probability of recurrence in the first year after treatment is 15%, after 5 years 30%. The probability of progression of tumors is less than 1%. recurrence and it occurs, as a rule, the tumor has the same stage and stage as the first formation and has little effect on the prognosis and quality of life of the patient [28, 29]. High risk of recurrence is noted in multiple and large tumors, as well as formations that relapse despite treatment. Such tumors require aggressive treatment and dynamic monitoring.

Treatment of NMIBC

The gold standard in the treatment of MNRSM is TURB. The resection plan depends on the size of the formation. Small tumors (less than 1 cm) can be removed with one block, where the removed area includes the entire tumor and part of the bladder wall. Large tumors should be removed with fragments that will include the exophytic part of the formation, a proper bladder wall with the muscular layer, and the borders of the removable area. coagulation in the process of resection [30].

Following the TURB formation of TA-T1 formulations, there is a high risk of residual tumor. There is also a risk of insufficient staging of the tumor during primary resection. survival [1,32,33]. There is no common decision on the performance of the second TOUR. It is recommended to perform the second operation 2-6 weeks after the first TURB [30, 31].

Intravesical chemotherapy

The use of therapeutic techniques that will reduce the rate of progression and recurrence, has been the basis of scientific research on muscular-non-invasive bladder cancer since the 1950s. Thus, the main indication for intramuscular chemotherapy was its use in adjuvant mode [1]. Chemotherapy was due to the following factors:

• A high concentration of drug substance is created locally.

• The systemic effect of the drug is limited due to the low absorption of the bladder wall

• Intra-bladder chemotherapy allows you to act on subclinical lesions.

• Due to the difference in the biological properties of the tumor, the effect of the chemotherapy agent is higher on the tumor tissue than on the unchanged, healthy mucous membrane.

• Repeated intra-bladder administration of chemotherapeutic agents is possible.

• In most cases, intra-bladder administration of the drug is convenient for the physician.

The objectives of intravesical chemotherapy are the following:

• Reduced recurrence rates and progression after surgical treatment.

• Destruction of subclinical tumor foci.

• Obtain a therapeutic effect with a minimum frequency of complications and side effects.

• Prevention of tumor cell implantation after TOUR.

The clinical and morphological features of the tumor are evaluated: stage, degree of differentiation, size and number of tumors, frequency of relapses, association with cancer in situ. Based on this, patients are traditionally divided into the following groups:

• Low risk group: pTa stage, G1 or G2 differentiation, single tumor, recurrence-free period of at least 3 months after transurethral resection. In this group, a single administration of chemotherapy after TOUR is sufficient [1].

• Intermediate risk group: pT1G2, multiple tumors of RT1, with multiple relapses, pT1G4, adjuvant BMXT is shown to all patients.

• High risk group: pT1, G3; multiple tumors; pT1 if recurrence occurs within 6 months after surgery; pTis, diffuse in nature. These patients are the most unfavorable prognosis. The distribution of patients according to the risk groups of progression and single direct introduction of chemotherapy is shown to all patients after transurethral resection. One-time administration is also shown to all patients after a TOUR biopsy of the bladder with suspected cancer. If

it is impossible to carry out chemotherapy immediately after transurethral resection, the administration of the chemotherapy should be carried out within the first 24 hours, otherwise the risk of recurrence is doubled [1,34,35]. There were no significant differences when using mitomycin C, epirubicin and doxorubicin. Basically, the prophylactic effect of intravesical therapy is realized immediately after its implementation. Currently, the use of intracellular chemotherapy reduces the incidence of relapse, but no effect on progression has been observed. The duration and intensity of intramolecular chemotherapy regimens have not been determined at this time due to data conflicts.

The absolute contraindication to carrying out intravesical chemotherapy is intra- and extraperitoneal perforation. Relative contraindications to carrying out chemotherapy - severe macrohematuria, severe dysuria. The chemical is diluted, as a rule, before being injected into the bladder with a suitable solvent. Catheterize the bladder in compliance with the rules of aseptic and antiseptic thin urethral catheter.The drug is injected intravenously, after which the urethral catheter is removed. The patient is advised not to urinate for the time necessary for exposure, and also to periodically change the position of the body in order to uniformly influence the chemical on all the walls of the bladder. To maintain the required concentration directly in the bladder, the patient is advised to limit fluid intake to several hours before the procedure. When developing treatment tactics in patients with non-invasive bladder cancer, accurate risk assessment is required to correctly stratify patients by prognosis groups. This will avoid the most common clinical errors in chemotherapy, patients with moderate and high risk groups are not adjuvant therapy, adjuvant chemotherapy is advisable in patients with good prognosis. It is important to keep the correct dose, concentration and exposure time of the drug, as well as the number of drug injections.

Today the most common drugs are:

Mitomycin is an antitumor antibiotic. Principle of action: when penetrating into the cell exhibits the properties of bi- and trifunctional alkylating agent, thereby selectively inhibiting the synthesis of deoxyribonucleic acid (DNA). In high concentrations it causes suppression of cellular ribonucleic acid (RNA) and protein synthesis, to a greater extent in phase G1 and S. Single dose of 40 mg. The drug is dissolved in 40 ml of isotonic sodium chloride solution. The first installation - on the day of completion of the TURB, then 1 time per week, intravesically 6-10 doses. Exposure is 1-2 hours [36,37,38].

Thiophosphamide is a trifunctional alkylating cyclospecific compound of the ethyleneimine group that disrupts nucleic acid metabolism, blocks mitosis, forming complex bonds with DNA. It is given 20-60 mg 1-2 times a week intravesically. Exposure - up to 2 hours, course dose - 200-220 mg. The disadvantage is good permeability through the wall of the CM, which causes systemic side effects (leukemia, thrombocytopenia) [43,44].

Doxorubicin is an antitumor antibiotic of the anthracycline series. The mechanism of action is based on the formation of free radicals when interacting with DNA, the direct effect on the cell membrane with suppression of nucleic acid synthesis, inhibition of topoisomerase II. Scheme of administration: 30-50 mg daily № 10, or 20-50 mg 2-3 times a week [39].

Epirubicin is also an antitumor antibiotic of the anthracycline series, due to intercalation between the major nucleotide pairs in DNA, leads to disruption of DNA, RNA and proteins. Exposure - 1-2 hours. Gemcitabine is an antimetabolite of a pyrimidine analogues group. Scheme of administration: 1000-3000 mg 1-2 times a week. Exposure - 1-2 hours. [40,41,42].

It is not yet possible to speak of any of the drugs as the "gold standard" because there is not enough clinical material to build such a bold conclusion. Moreover, the efficacy of chemotherapy was to determine the efficacy of Doxorubicin in intra-bladder instillations in patients with NMIBC (Ta-T1, G 1 -2).

Objective

Was to evaluate the results of treatment of patients with NMIBC who underwent TUR and patients with NMIBC who underwent TUR and subsequent intravesical instillations of Epirubicin.

Subjects and methods

An analysis of the results of treatment of 45 patients who underwent treatment and follow-up in the clinic of the Institute of Urology of the National Academy of Medical Sciences of Ukraine during 2012-2018. The youngest patient was 14 years old, the oldest 89 years old. The ratio of men to women was 4: 1.

The criterion for inclusion of patients in the study was the presence of urothelial bladder cancer stage Ta, T1; histologically G1-G2, total EORTC glass score up to 9 points.

The exclusion criteria were patients with T2 bladder invasion, histologically G3, patients who had previously received chemotherapy or BCG therapy, patients with bladder resection.

In the first group (n = 32) patients underwent only TUR of bladder tumors.

In the second group (n = 31) was combined treatment TUR and intravesical administration of Epirubicin 50 mg according to the scheme 1 / week - 4 weeks, 1 / month - 4 months.

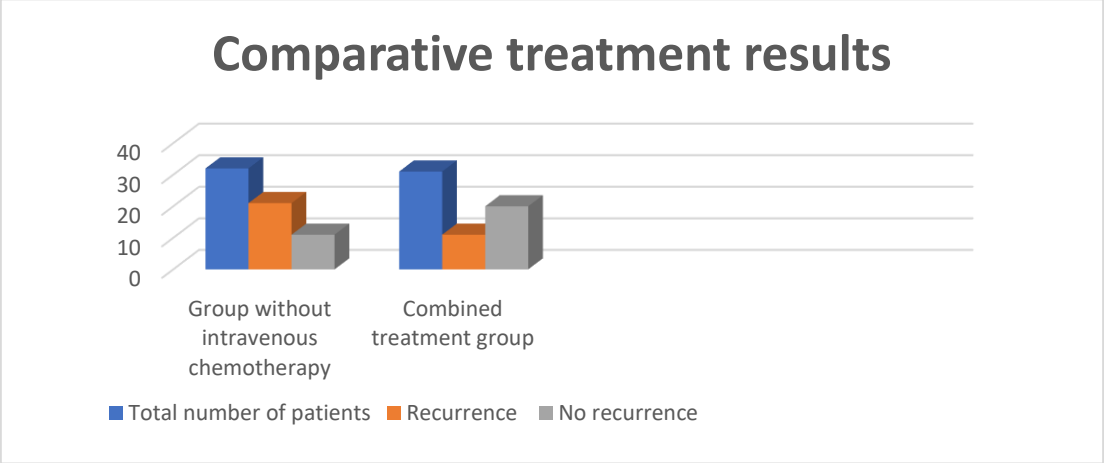
The reason for intravesical chemotherapy was the presence of risk factors in the patient such as: the formation of more than 2 cm, multifocal growth. Tumor growth was confirmed histologically in all patients.

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

Results

The duration of supervision was 2 years. Analysis of the results showed that when performing TUR without further intravesical chemotherapy, the recurrence was 65.6% (21 patients), with 11 patients showing progression of the disease.

In the group of patients who received combination therapy - TUR and the course of Epirubicin relapse is 35.5% (11 patients), in 6 patients there was progression of the disease.



Conclusions

Analyzing the dynamics of recurrence and progression of bladder cancer, we can conclude that the implementation of TUR followed by intravesical administration of Epirubicin makes it possible to reduce the recurrence rate, thereby increasing the recurrence-free period and reduce disease progression.

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