DOI: https://doi.org/10.30841/2786-7323.2.2024.310011
УДК: 616.62/.63-006.36.04-072.2:615.277.3Мітоміцин_С](043.3)

Ways to increase the effectiveness of intravesical chemotherapy with Mitomycin-C in patients with high-risk of non-muscle-invasive bladder cancer

F. I. Kostyev, R. S. Chystiakov, V. V. Lysenko, O. V. Bondar, V. O. Varbanets
Odessa National Medical University

The objective: **to analyze the experience of using hyperthermic intravesical chemotherapy (HIVEC) with Mitomycin-C (MMC) and the addition of dimethyl sulfoxide (DMSO) in high-risk of non-muscle-invasive bladder cancer (HR NMIBC) patients and to compare oncological results with BCG therapy.**
Materials and methods**. From March 2018 to January 2021, 53 patients with high-risk of NMIBC underwent a HIVEC adjuvant regimen at the University Clinic of Odessa National Medical University. The results were compared with a group of patients who received adjuvant intravesical BCG therapy from 2015 to 2019. In the HIVEC group, 16 (30.2%) patients with reduced bladder capacity underwent a session of the HIVEC therapy with prior injection of DMSO solution into the bladder. The primary endpoint was recurrence-free survival (RFS). Secondary endpoints were time to recurrence, progression-free survival (PFS), cancer-specific survival and overall survival at 36 months.**
Results**. The incidence of the disease recurrence (42.6% vs 22.6%; p=0.028) and progression (20.4% vs 7.5%; p=0.50) were different between the BCG and HIVEC, respectively. The mean time to recurrence in patients who received HIVEC MMC was significantly higher than in patients of the BCG group: 31.5 months (95% CI: 29.1–34.0) versus 26.0 months (95% CI: 22.7–29.3), respectively (p=0.034). Cox regression analysis showed that the hazard ratio for HIVEC vs BCG for the RFS at 36 months was 0.48 (95% CI: 0.24–0.96; p=0.04). The RFS and the PFS indicators during the 36-month follow-up period in patients who received additional intravesical DMSO administration were not significantly different from other patients in the HIVEC therapy group.**
Conclusions**. Hyperthermic intravesical chemotherapy with the addition of DMSO is a safe treatment option for patients with high-risk of noninvasive bladder cancer with efficacy comparable to BCG therapy.**
Keywords: *non-muscle-invasive bladder cancer, hyperthermic intravesical chemotherapy, dimethyl sulfoxide.*

Шляхи підвищення ефективності внутрішньоміхурової хіміотерапії мітоміцином у пацієнтів з м'язово-неінвазивним раком сечового міхура високого ризику

Ф. І. Костєв, Р. С. Чистяков, В. В. Лисенко, О. В. Бондар, В. О. Варбанець

Мета дослідження: аналіз досвіду застосування гіпертермічної внутрішньоміхурової хіміотерапії (HIVEC) з мітоміцином та додаванням диметилсульфоксиду (ДМСО) у пацієнтів з м'язово-неінвазивним раком сечового міхура (МНІРСМ) групи високого ризику та порівняння онкологічних результатів з БЦЖ терапією.
Матеріали та методи. З березня 2018 р. по січень 2021 р. в Університетській клініці Одеського національного медичного університету 53 пацієнти з МНІРСМ групи високого ризику отримали в ад'ювантному режимі курс HIVEC. Результати порівнювали з групою пацієнтів, які отримували ад'ювантну внутрішньоміхурову терапію вакциною БЦЖ протягом 2015–2019 рр. У 16 (30,2%) пацієнтів зі зниженою ємністю сечового міхура проводили сеанс HIVEC з попереднім уведенням розчину ДМСО до сечового міхура. Первинною кінцевою точкою було безрецидивне виживання (БРВ). Вторинними кінцевими точками були час до рецидиву, виживаність без прогресування (БПВ), канцер-специфічна виживаність та загальна виживаність через 36 міс.
Результати. Частота рецидивів захворювання (42,6% проти 22,6%; p=0,028) та прогресування (20,4% проти 7,5%; p=0,50) відрізнялися між групами БЦЖ та HIVEC відповідно. Середній час до рецидиву у пацієнтів, які отримували HIVEC, був значно вищим, ніж у пацієнтів групи БЦЖ, а саме: 31,5 міс (95% ДІ: 29,1–34,0) проти 26,0 міс (95% ДІ: 22,7–29,3) відповідно (p=0,034). Регресійний аналіз Кокса продемонстрував, що співвідношення ризиків для HIVEC проти БЦЖ терапії для БРВ через 36 міс становило 0,48 (95% ДІ: 0,24–0,96; p=0,04). Показники БРВ та БПВ протягом 36-місячного періоду спостереження у пацієнтів, які отримали додаткове уведення ДМСО внутрішньоміхурово, істотно не відрізнялися від інших пацієнтів у групі HIVEC.
Висновки. Гіпертермічна внутрішньоміхурова хіміотерапія з мітоміцином з додаванням диметилсульфоксиду є безпечним варіантом лікування пацієнтів з неінвазивним раком сечового міхура високого ризику з ефективністю, що порівняна з терапією БЦЖ.
Ключові слова: *м'язово-неінвазивний рак сечового міхура, гіпертермічна внутрішньоміхурова хіміотерапія, диметилсульфоксид.*

Bladder cancer is the sixth most common cancer in males worldwide and the twelfth most common cancer [1]. In the European Union the age-standardised incidence rate was 20 for men and 4.6 for women in 2020, respectively [2]. In Ukraine the age-standardized incidence rate was 11.1 for men and 1.5 for women in 2020, respectively [3]. Approximately 75% of newly diagnosed bladder cancer patients have a non-muscle-invasive tumor (NMIBC) [2].

In patients at high risk for NMIBC, adjuvant intravesical instillation of the Bacillus Calmette-Gu rin (BCG) vaccine

with supportive care is recommended as an effective way to preserve the bladder [4–6]. A separate category includes patients of highest-risk group and patients who have undergone unsuccessful BCG therapy (BCG failure). According to the European Association Urology (EAU) Guidelines one of the treatment options for these patients is immediate radical cystectomy (RC) [2]. But many patients are elderly and have comorbidities, that makes them unsuitable for RC [7–9]. Thus, the alternative bladder-sparing intravesical therapy for patients with NMIBC is necessary.

One of the ways to increase the effectiveness of intravesical chemotherapy to reduce the risks of recurrence and progression is the use of physical methods like local hyperthermia (one of them is hyperthermic intravesical chemotherapy – HIVEC) [10–12] or chemical methods (dimethyl sulfoxide – DMSO) [13, 14] to get drugs across bladder penetrating barriers.

The objective: of this work is to analyze the experience of using hyperthermic intravesical chemotherapy with Mitomycin C in the adjuvant treatment of high-risk NMIBC patients and to compare oncological results with BCG therapy.

MATERIALS AND METHODS

This non-randomized, ambispective, observational and single center study was carried out according to the "Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine by the Council of Europe (ETS #164, April 1997), the "Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects" by the World Medical Association (October 2013) and approved by the Bioethics Commission of the Odessa National Medical University (Protocol #135A, 03.07.2019). Before including any patient to the study protocol, their personal written informed consent to participate in the study was obtained and all measures to ensure their anonymity were taken.

From March 2018 to January 2021, 53 prospective patients underwent HIVEC-MMC adjuvant regimen in University Clinic of Odessa National Medical University (UC ONMedU). The patients who received adjuvant intravesical BCG therapy in UC ONMedU from 2015 to 2019 were used as a retroprospective control group (Fig. 1).

The inclusion criteria were the diagnosis of high-risk NMIBC as defined by the 2018 version of the EAU guidelines and Karnofsky status from 100 to 60 percent. Patients were excluded if they had a history of hypersensitivity to MMC or any contraindication to BCG. Before the start of intravesical therapy, both groups underwent transurethral resection of all visible bladder tumors (TURBT) under general anesthesia using endoscopic mono- or bipolar resection. Intravesical instillations started 3–4 weeks after TURBT/Re-TURBT.

Table 1

Comparison characteristics HIVEC subgroups of the EORTC stratification

Parameter	Subgroup with DMSO n=16 (%)	Subgroup without DMSO n=37 (%)
Sex: Male Female	 11 (68,8) 5 (31,2)	 29 (78,4) 8 (21,6)
Age	72,25±11,69 (range 48-85)	62,24 ±11,72 (range 37-81)
Primary Recurrent	5 (31,2) 11 (68,8)	35 (94,6) 2 (5,4)
Ta T1	1 (6,3) 15 (93,7)	2 (5,4) 35 (94,6)
№ of tumors Single Multiple	 5 (31,3) 11 (68,7)	 26 (70,3) 11 (29,7)
Diameter of tumors < 3 ≥ 3	 8 (50,0) 8 (50,0)	 15 (40,5) 22 (59,5)
Concomitant CIS	5 (31,3)	5 (13,5)
G2 G3	- 16 (100)	23 (62,2) 14 (37,8)
Low grade High grade	 16 (100)	22 (59,5) 15 (40,5)

Note: Ta, T1 – pathologic stage; CIS – carcinoma in situ; G1-G2, Low grade – High grade – grade of differentiation;
* – Independent sample T test – data are expressed as «mean ± standard deviation», p statistical significance level;
EORTC – European Organisation for Research and Treatment of Cancer.

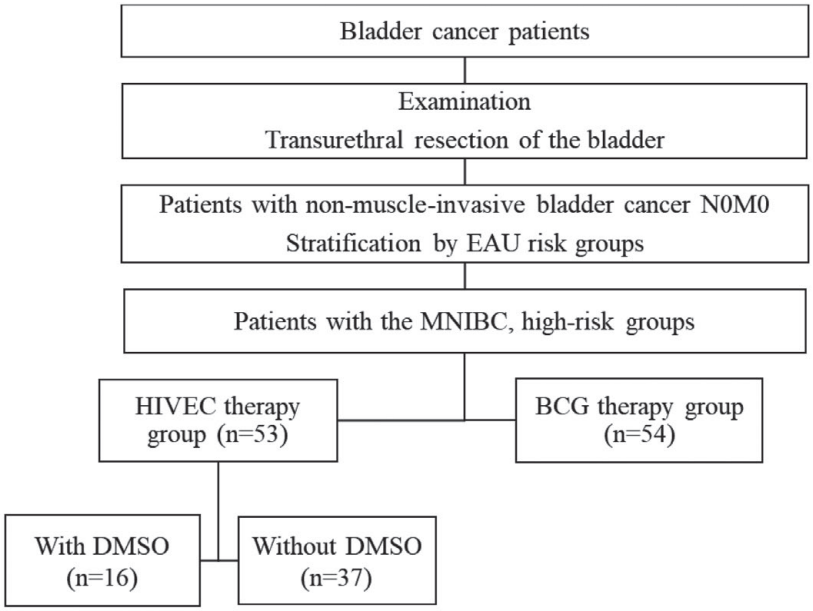


Fig. 1. Study design scheme
Note: EAU – European association of urology; NMIBC – non-muscle-invasive bladder cancer; HIVEC – hyperthermic intravesical chemotherapy; BCG – Bacillus Calmette-Guerin, MMC – Mitomycin C; DMSO – dimethyl sulfoxide.

HEALTH OF MAN / ЗДОРОВ'Я ЧОЛОВІКА • №2 (89)/2024
ISSN 2787-7315 (Print) | ISSN 2786-7373 (Online)

Patient characteristics

Of the 107 patients included in the study, 84 (78.5%) were men, 23 (21.5%) were women. There were no statistical differences by sex among the patients of the studied groups (p=0.45). The average age of patients in the HIVEC-therapy group was (65.26±12.50) years old, in the BCG-therapy group – (64.65±12.00) years old (p=0.8). In addition, there were no significant imbalances in tumor characteristics such as size, number of tumors, depth of invasion into the bladder mucosa, histological classification, and the presence of concomitant CIS, which was reflected in the earlier article [15]. This publication reflects the continuation of our work and is devoted to the analysis of the oncological results obtained depending on the type of intravesical therapy used, as well as depending on the addition of DMSO. The initial characteristics of patients in the HIVEC therapy group, depending on the addition of DMSO, are presented in Table 1.

Treatment

The protocol of HIVEC treatment included the Mitomycin-C use at a dose of 40 mg once a week for 6 weeks. The instillations were performed using a Combat BRS system V2.0 for hyperthermic chemotherapy (Combat Medical, Wheathampstead, UK) that heated the solution to the temperature of 41–43 °C extravesically and recirculated it for 60 minutes at a stable pressure and a rate of 200 ml/minute. In the chemohyperthermia group, 16 (30.2%) patients with reduced bladder capacity due to repeated or large TUR, according to our methodology, underwent the HIVEC session with prior injection of DMSO solution into the bladder. The bladder capacity decrease below 200 ml was determined on the basis of patient complaints and confirmed by ultrasound.

All patients underwent the penetrant dose titration to ensure better tolerability. The first instillation was carried out with a preliminary injection of 50 ml of 5% DMSO solution, in further instillations the concentration of DMSO solution was brought up to 10% with an intravesical exposure time of 5 minutes.

The treatment for patients in the BCG cohort was based on the use of Uro-BCG applied to an emptied bladder. The patient had to withstand a least 1 hour before urinating. The main course of treatment is 6 weekly instillations and a maintenance course of 3 weekly instillations at 3, 6, and 12 months.

Surveillance

Every three months, all patients underwent cystoscopy and urine cytology. Computed tomography-intravenous urography was performed at the screening visit, and then once a year or as clinically indicated. In case of endoscopic suspicion of the tumor recurrence or the positive cytology was detected a "cold" bladder biopsy was performed. TURBT was performed if cystoscopy revealed a tumor or imaging suggested a possible recurrence of cancer.

Outcomes

The primary outcome was recurrence-free survival (RFS), defined as a diagnosis of urothelial carcinoma in the time from the end of intravesical adjuvant treatment to histologically confirmed tumor recurrence. The secondary outcome was progressive-free survival (PFS), that was defined as the time from the end of intravesical adjuvant treatment to a histologically or radiologically confirmed diagnosis of muscle-invasive bladder cancer or metastatic disease, the mean time to recurrence (TTR), cancer-specific (CSS) and overall survival (OS) at 36 months.

Statistical analysis

A comparative analysis of the corresponding parameters in both groups was carried out according to the χ^2 method and using the t-test for independent samples. The Kaplan-Meier method was used to obtain estimates of the RFS, PFS, CSS, and OS. The indicators were compared with each other using a log-rank test. A univariate and multivariate Cox proportional hazards regression model was used to analyze potential risk factors for intravesical recurrence and progression. The hazard ratio and its 95% confidence interval were calculated. IBM SPSS Statistics for Windows (version 28.0) was used as a program for calculating statistical indicators. A p-value <0.05 was considered an indicator of statistical significance.

RESEARCH RESULTS AND THEIR DISCUSSION

The median follow-up period was 28 months (range 8–46) in the HIVEC group and 34 months (range 9–68) for the BCG group. There were 35 recurrences (BCG = 23, HIVEC = 12), 15 disease progressions (BCG = 11, HIVEC = 4) and 6 deaths (BCG = 4; HIVEC = 2) due to bladder cancer during the 36 months follow-up.

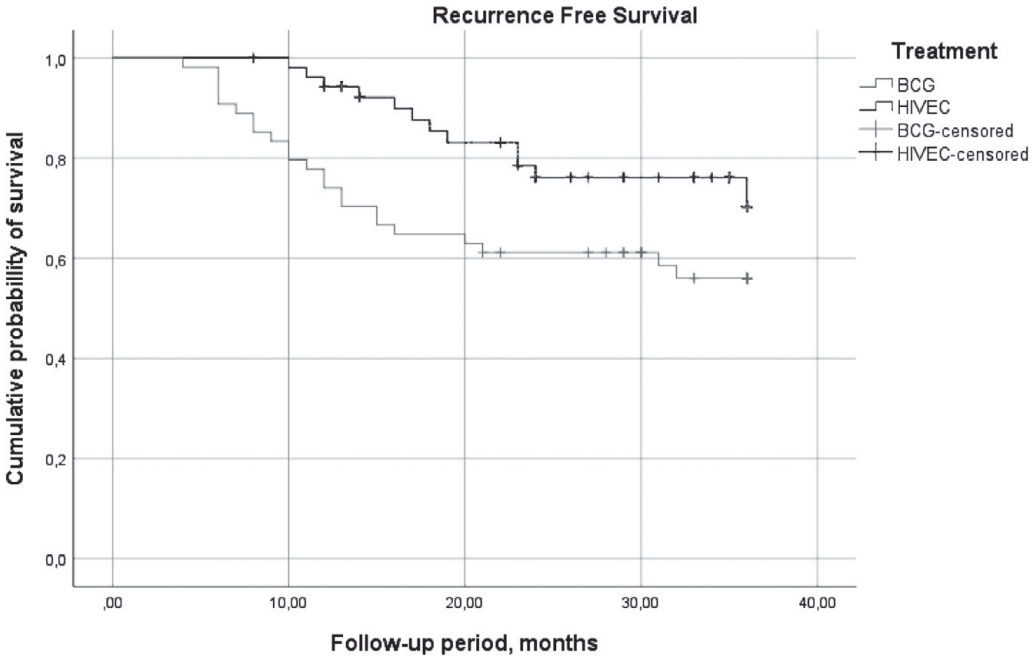
Survival analysis

The recurrences rates were significantly different between the two groups (42.6% versus 22.6%; p=0.028), respectively. The 12-month RFS was 94.2% for the HIVEC group and 77.8% for the BCG group (HR 0.32;95% CI: 0.13–0.80; p=0.02), and the 24-month RFS was 79.1% for the HIVEC group and 66.1% for the BCG group (HR 0.86;95% CI: 0.48–1.55; p=0.24). The Kaplan-Meier analysis of recurrence-free survival for two adjuvant treatment strategies is shown in Fig. 2.

The mean time to recurrence (TTR) in patients who received HIVEC MMC was significantly higher than in patients of the BCG group: 31.5 months (95% CI: 29.1–34.0) versus 26.0 months (95% CI: 22.7–29.3), respectively (p=0.034). Recurrent tumor, concomitant Carcinoma in citu (CIS), high grade of differentiation, the BCG treatment, and the number of intravesical instillations were independent prognostic factors for tumor recurrence by the Cox hazards regression model.

The incidence of the disease progression was different between the two groups (20.4% versus 7.5%; p=0.050), respectively. The 12-month PFS was 100% for HIVEC and 92.5% for BCG (HR 0.39;95% CI: 0.09–1.73; p=0.25), and the 24-month PFS was 93.1% for HIVEC and 82.9% for BCG (HR 1.38 ;95% CI: 0.70–2.75; p=0.35). The PFS analysis using the Kaplan-Meier method for two adjuvant treatment strategies is shown in Fig. 3.

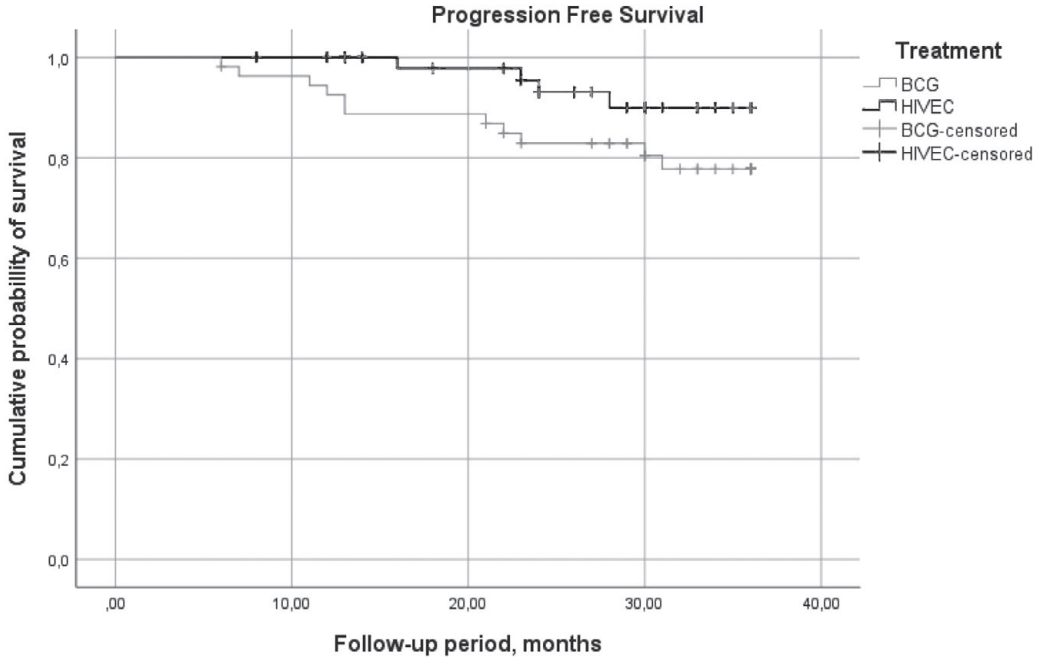
Although the incidence of the disease progression in patients who received HIVEC MMC was higher than in patients who received the intravesical BCG, the mean time to progression did not differ significantly: 32.0 (95% CI: 29.7–34.3) versus 34.7 (95% CI: 33.5–35.9), respectively (p=0.084). Recurrent tumor, concomitant CIS, and



Number at risk

HIVEC	53	52	37	23
BCG	54	45	35	27

Fig. 2. Recurrence-free survival (RFS) curves in both treatment groups



Number at risk

HIVEC	53	52	43	27
BCG	54	51	47	33

Fig. 3. Progression-free survival (PFS) curves in both treatment groups

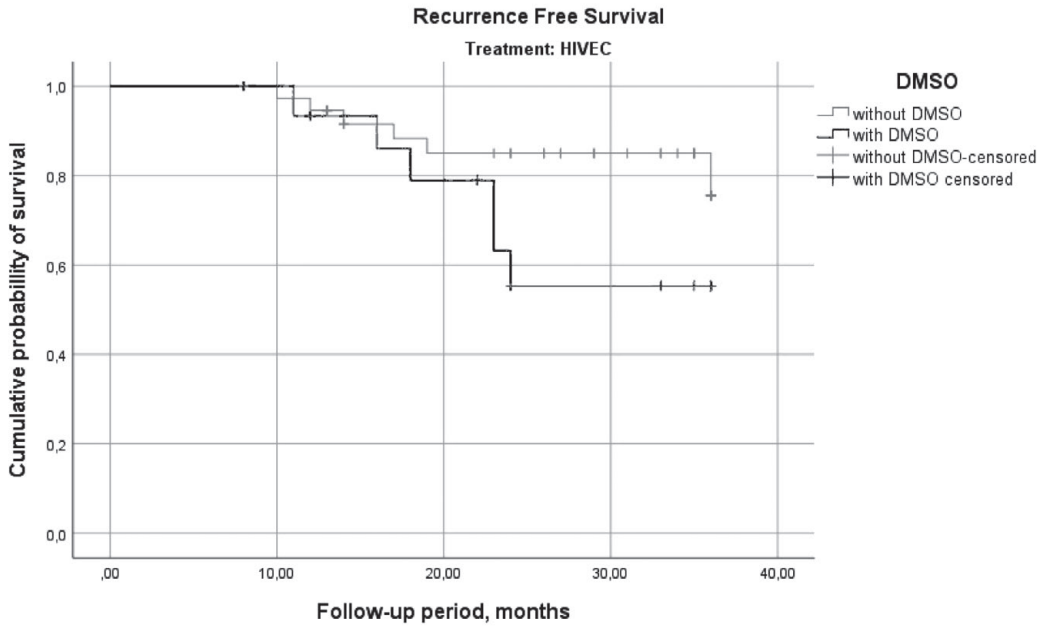


Fig. 4. Kaplan-Meier curves of RFS indicators of patients in the HIVEC therapy group depending on the addition of DMSO to the treatment regimen

high grade of differentiation were independent prognostic factors for tumor progression after the adjuvant treatment by the Cox hazards regression model.

The 12-month CSS was 100% for both groups, the 24-month CSS was 94.5% for HIVEC and 93.2% for BCG. Overall survival rates during follow-up were not statistically different and amounted to 77.8% in the BCG therapy group and 86.8% in the HIVEC therapy group (p=0.222). The 12-month OS was 98.1% for HIVEC and 100% for BCG, the 24-month OS was 90% for HIVEC and 87% for BCG. The mean time to death did not differ either from 33.7 (95% CI: 32.0–35.4) versus 33.5 (95% CI: 32.1–34.9; p=0.458), respectively. Cox regression analysis showed hazard ratios for HIVEC vs BCG for the RFS, PFS and OS at 36 months to be 0.48 (95% CI: 0.24–0.96; p=0.04), 0.38 (95% CI: 0.12–1.19; p=0.10) and 0.83 (95% CI: 0.33–2.12; p=0.67), respectively.

DMSO subgroup results

The average bladder capacity in the DMSO subgroup was 184±8.6 ml. The time of the instillation session was shortened depending on the patient's ability to withstand the solution in the bladder until a strong urge to urinate occurred. The average time of the instillation session in the subgroup with previous administration of DMSO was 40.4±4.8 minutes (95% CI: 38,1–42.8) (range 32–48 minutes). In the subgroup without DMSO administration it was significantly higher: 57.1±3.1 minutes (95% CI: 56.1–58.1) (range 51–60 minutes; p=0.013).

DMSO subgroup survival analysis

During the follow-up period, 6 cases of relapse and 3 cases of disease progression were registered in the subgroup received hyperthermic chemoperfusion with DMSO (respectively, 12 and 4 in the total group of HIVEC therapy).

Although the frequency of relapses was significantly higher in the subgroup with DMSO ($p<0.05$; χ^2-test), the RFS indicators during the 36-month follow-up period in patients who received additional intravesical DMSO did not differ significantly from other patients in the HIVEC therapy group during the follow-up period after the end of the induction course therapy: 83.8% vs. 62.5%, respectively (HR 0.12; 95% CI: 0.13–1.28; p=0.41). The mean time to relapse was also comparable among patients of the studied subgroups: 32.8 months (95% CI: 29.9–35.6) versus 28.6 months (95% CI: 23.9–33.2), respectively (Log Rank test; p=0.107) (Fig. 4)

The RFS indicators of patients who received DMSO instillations before the start of chemohyperthermia were also not significantly different from other patients in the HIVEC therapy group during the follow-up period after the end of the induction therapy course: 80.0% vs. 95.3%, respectively (HR 0.15; 95% CI: 0.02–1.427; p=0.1). Median time to progression was also comparable among patients in the studied subgroups: 33.0 months (95% CI: 29.8–36.2) versus 35.6 months (95% CI: 34.7–36.4), respectively (Log Rank test; p=0.107) (Fig. 5).

In the subgroup of HIVEC therapy with the addition of DMSO, 3 patients died, in the subgroup without prior administration of DMSO, 4 deaths were recorded during the observation period. A total of 1 death due to bladder cancer was recorded during the 36-month follow-up in each of the subgroups. The overall and cancer-specific survival rates during the 36-month follow-up were not statistically different.

Treatment surveillance

Six-week therapy courses were not fully completed due to the side effects: 13 (24.1%) patients in the BCG therapy group (7 patients received 4 instillations, 6–5 ones); 4 patients (7.5%) in the HIVEC group did not undergo a full course therapy (1 patient received 4 instillations, 3–5 ones) (p=0.005). In 18 (33.3%) patients from

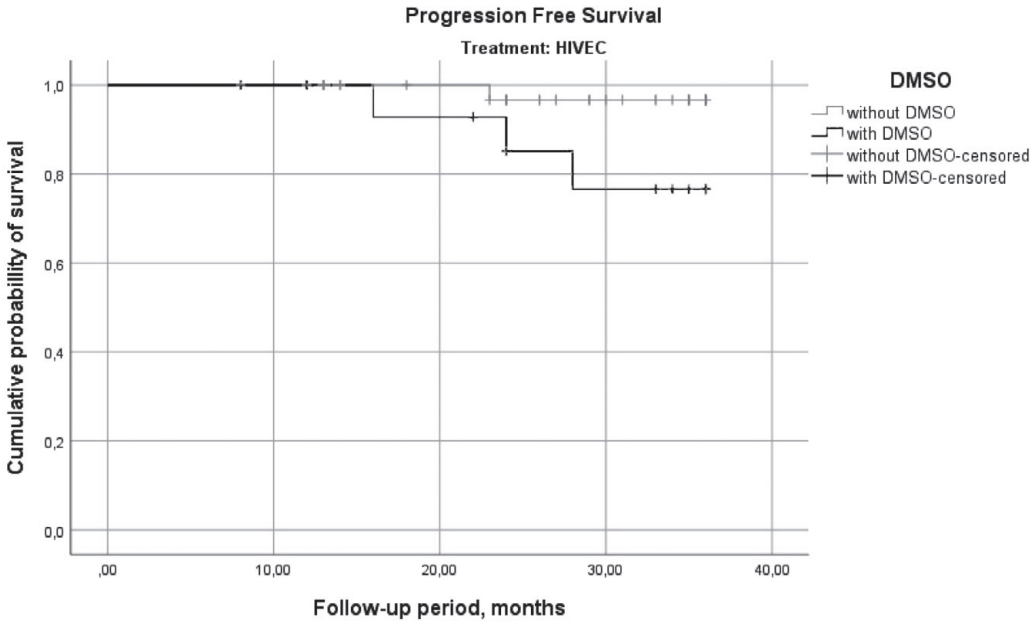


Fig. 5. Kaplan-Meier curves of PFS indicators of patients in the HIVEC therapy group depending on the addition of DMSO to the treatment regimen

the BCG group and 8 (15.1%) patients from the HIVEC group, the instillation schedule was shifted for a week once due to moderate local toxicity ($p<0.05$), twice – in 8 (14.8%) and 2 (3.8%), respectively. In the subgroup with previous administration of DMSO, 2 patients from 4 HIVEC groups did not complete the full induction course of chemohyperthermia (one patient received 4 instillation sessions, 1 patient – 5 sessions).

The mechanism of action of local intravesical hyperthermia in the treatment of bladder cancer is well understood. It is based on an increase in the permeability of cell membranes since heating causes instability of the phospholipid bilayer of cancer cells and increases the concentration and depth of penetration of chemotherapy drugs into the tissues of the bladder wall [16]. This results in the denaturation of cellular proteins and the release of heat shock proteins during cell necrosis, especially HSP70, as well as an increase in circulating tumor antigen, which stimulates an adaptive T cell response that induces both the adaptive and innate immune systems [17]. It is known that hyperthermia promotes both direct and indirect processes of DNA damage, which enhances the anticancer immune response [18–20].

Preliminary results from the use of HIVEC show the promise of this method [21]. Alejandro Sousa et al., in their adjuvant group with HIVEC treatment in intermediate and high-risk patients, reported a 2-year cumulative incidence of recurrence of 12.5% (95% CI: 7.8–19.3%) with the earliest recurrence at 7 months in one patient, who was successfully retreated with HIVEC [22]. There were more publications of the HIVEC results in patients with high-risk NMIBC in 2021 and 2022.

Zhao et al. published a systematic review and meta-analysis comparing chemohyperthermia and BCG in patients with intermediate- and high-risk NMIBC. The meta-analysis included 5 studies, 1 of which focused on HIVEC in high-risk patients [23]. The authors presented results of the randomized clinical trial «Hyperthermic intravesical chemotherapy – High Risk» of the high-risk NMIBC patients who were randomized to receive adjuvant BCG or HIVEC: RFS at 24 months was 86.5% for HIVEC and 71.8% for BCG (p=0.184), PFS survival for HIVEC vs BCG was 95.7% vs 71.8% (p=0.043). The results of the first randomized trial show that HIVEC did not worse than BCG on any of the clinical efficacy endpoints [24].

In August 2021 the group of authors from Spain presented data of the results of a multicenter prospective study of the 205 patients with high-risk NMIBC who received the adjuvant chemohyperthermia MMC by the COMBAT BRS system [25]. For high-risk NMIBC patients the 1-year recurrent-free survival rate was 80.34%, the 2-year recurrent-free survival rate was 64.88%, and the 1-year and 2-year progression-free survival rate was 93,99% and 86,52% respectively. Tan et all reported the result of 2-year outcomes of a HIVEC-E multicenter study. It was 557 BCG naïve patients in this study, and 358 patients from this cohort were WHO 2004 High Grade. The RFS at 12 months and 24 months for BCG naïve was 87.6% and 75.0%, respectively. The PFS at 12 months and 24 months was 95.5% and 90.8%, respectively [26].

The results of the HIVEC treatment in high-risk NMIBC also have been published. The 1-year RFS rate was 60,5%, 67,5%, 91,1%, and 94,1% respectively [27–30]. The worst RFS results were obtained in studies with a big number of the patients who were previously BCG treated.

Hyperthermic chemotherapy with the Combat BRS system might be an excellent alternative to BCG therapy for high-risk NMIBC patients. The results of our study

HEALTH OF MAN / ЗДОРОВ'Я ЧОЛОВІКА • №2 (89)/2024
ISSN 2787-7315 (Print) | ISSN 2786-7373 (Online)

demonstrate that the RFS for the HIVEC group at 12 months and 24 months was 94.2% and 76.1%, respectively, and the PFS for the HIVEC group at 12 months and 24 months was 100.0% and 93.1%, respectively. This treatment method has a good tolerability. Only 4 patients (8.7%) discontinued the treatment due to adverse events, that is consistent with published data from other authors (4–28%) [24–31].

Also, the data obtained by us indicate that the addition of a penetrant substance to the therapeutic instillation scheme in patients with limited ability to withstand a full session of chemoperfusion allows obtaining oncological results similar to the results of the full treatment group.

DMSO is a dipolar solvent, miscible with lipid and water. DMSO can affect the lipid bilayer, thereby increasing the drug penetration in cytomembrane and biological barriers. DMSO has also been approved by U.S. Food and Drug Administration (FDA) for interstitial cystitis/bladder pain syndrome, which proved DMSO is safe for intravesical instillation [32]. Co-administration of DMSO (10–50%) promoted the penetration of water-soluble drugs (e.g., cisplatin, pirarubicin, doxorubicin) [33–35] and a lipophilic drug paclitaxel [36] across the urothelium in dogs or rats [13, 14, 36]. Yaman et. found intravesical instillation of epirubicin with DMSO enhanced the epirubicin absorption of the bladder wall, the fluorescence of epirubicin was observed throughout the bladder tumor and in the deeper muscle layers. In contrast, epirubicin's fluorescence was only seen in the bladder mucosa in the epirubicin without DMSO group [37].

All patients in the DMSO-pretreated HIVEC subgroup were at ultra-high risk of recurrence and progression (according to EAU 2019 guidelines), in contrast to the monochemotherapy subgroup, where only 11 (29.7%) of 37 patients were classified as ultra-high-risk. This factor also explains the rather high absolute numbers of relapses and progressions in the subgroup with DMSO. Thanks to the course of intravesical chemohyperthermia modernized due to the previous administration of DMSO, the biology of recurrent tumors turned out to be quite favorable (absence of CIS; Low Grade stage of differentiation, low level of proliferative activity marker Ki-67). A study on the dynamics of changes in the biology of recurrent tumors under the influence of intravesical therapy was published by us earlier [15]. This made it possible to conduct repeated courses of hyperthermic chemoperfusion in three cases, and in two cases of muscle-invasive relapses, taking into account the absence of signs of lymphadenopathy and metastases, the presence of local symptoms associated with low bladder capacity, a radical rescue cystectomy was performed.

Practical meaning. The use of hyperthermic chemotherapy in high-risk patients is an effective and safe first-line treatment option for intravesical therapy. When BCG therapy is ineffective, it is recommended to carry out HIVEC therapy in patients who cannot undergo radical cystectomy. In this study we reflected our experience in the treatment of high-risk NMIBC in elderly patients, most of them were not tolerable to RC.

Limitations of this study include the small cohort of the patients, the non-randomized nature of the study and shot follow-up. The comparison group was recruited primarily retrospectively, while the HIVEC therapy group was recruited prospectively, which may have an impact on the obtained results. Unfortunately, since February 2022, the patient follow-up has been difficult due to the all-out war in Ukraine.

Prospects for further research. The obtained research results are the basis for further analysis of the influence of the methods to get drugs across bladder penetrating barriers, on the effectiveness of intravesical chemotherapeutic drugs of the new generation.

CONCLUSIONS

Hyperthermic intravesical chemotherapy with MMC is a safe treatment option for patients with high-risk noninvasive bladder cancer, with efficacy comparable to BCG therapy. The combination of dimethyl sulfoxide and HIVEC may improve oncological treatment outcomes in patients with limited chemotherapy exposure time.

Conflicts of interest. The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

Funding. The study was performed without financial support.

Data availability. Data will be made available on reasonable request

Information about the authors

Kostyev Fedir I. – Professor of the Department of Urology, Odesa National Medical University; tel.: (048) 723-33-24. *E-mail: prof.kostev@g,ail.com*

ORCID: 0000-0001-6480-564X

Chystiakov Roman S. – Assistant Professor of the Department of radiation diagnostic, therapy and oncology, Odesa National Medical University; tel.: (048) 723-33-24. *E-mail: romanchystiakov@gmail.com*

ORCID: 0000-0002-7049-7628

Lysenko Viktoria V. – Head of Urologic service of University clinic, Odesa National Medical University; tel.: (048) 723-33-24. *E-mail: viktoriyalisenko1966@gmail.com*

ORCID: 0000-0002-7200-4954

Bondar Oleksandr V. – Professor of the Department of radiation diagnostic, therapy and oncology, Odesa National Medical University; tel.: (048) 723-33-24. *E-mail: ovbondar0708@gmail.com*

ORCID: 0000-0001-8746-1878

Varbanets Valeriia O. – Assistant Professor of Department of surgery, Odesa National Medical University; tel.: (048) 723-33-24. *E-mail: valeria.varb@gmail.com*

ORCID: 0000-0001-7216-7203

Відомості про авторів

Костєв Федір Іванович – д-р мед. наук, професор кафедри урології, Одеський національний медичний університет; тел.: (048) 723-33-24. *E-mail: prof.kostev@g,ail.com*
ORCID: 0000-0001-6480-564X

Чистяков Роман Сергійович – асистент, кафедра променевої діагностики, терапії та онкології, Одеський національний медичний університет; тел.: (048) 723-33-24. *E-mail: romanchystiakov@gmail.com*
ORCID: 0000-0002-7049-7628

Лисенко Вікторія Володимирівна – голова урологічної служби Університетської клініки, Одеський національний медичний університет; тел.: (048) 723-33-24. *E-mail: viktoriyalisenko1966@gmail.com*
ORCID: 0000-0002-7200-4954

Бондар Олександр Вадимович – д-р мед. наук, професор кафедри променевої діагностики, терапії та онкології, Одеський національний медичний університет; тел.: (048) 723-33-24. *E-mail: ovbondar0708@gmail.com*
ORCID: 0000-0001-8746-1878

Варбанець Валерія Олександрівна – асистент, кафедра хірургії, Одеський національний медичний університет; тел.: (048) 723-33-24. *E-mail: valeria.varb@gmail.com*
ORCID: 0000-0001-7216-7203

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49. doi: 10.3322/caac.21660.
2. Babjuk M, Burger M, Capoun O, Cohen D, Compérat EM, Dominguez Escrig JL, et al. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (Ta, T1, and Carcinoma in Situ). Eur Urol. 2022;81(1):75-94. doi: 10.1016/j.eururo.2021.08.010.
3. Fedorenko Z, Michailovich Yu, Goulak L, Gorokh Ye. Cancer in Ukraine 2020–2021: Incidence, mortality, prevalence and other relevant statistics. Bull National Cancer Reg Ukr. Kyiv; 2022. 23 p.
4. Cambier S, Sylvester RJ, Collette L, Gontero P, Brausi MA, van Andel G, et al. EORTC Nomograms and Risk Groups for Predicting Recurrence, Progression, and Disease-specific and Overall Survival in Non-Muscle-invasive Stage Ta-T1 Urothelial Bladder Cancer Patients Treated with 1-3 Years of Maintenance Bacillus Calmette-Gu rin. Eur Urol. 2016;69(1):60-9. doi: 10.1016/j.eururo.2015.06.045.
5. Schmidt S, Kunath F, Coles B, Draeger DL, Krabbe LM, Dersch R, et al. Intravesical Bacillus Calmette-Guérin versus mitomycin C for Ta and T1 bladder cancer. Cochrane Database Syst Rev. 2020;1(1):CD011935. doi: 10.1002/14651858.CD011935.pub2.
6. Oddens J, Brausi M, Sylvester R, Bono A, van de Beek C, van Andel G, et al. Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette-Guérin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. Eur Urol. 2013;63(3):462-72. doi: 10.1016/j.eururo.2012.10.039.
7. Hautmann RE, de Petriconi RC, Volkmer BG. Lessons learned from 1,000 neobladders: the 90-day complication rate. J Urol. 2010;184(3):990-4. doi: 10.1016/j.juro.2010.05.037.
8. Catto JWF, Gordon K, Collinson M, Poad H, Twiddy M, Johnson M, et al. Radical Cystectomy Against Intravesical BCG for High-Risk High-Grade Nonmuscle Invasive Bladder Cancer: Results From the Randomized Controlled BRAVO-Feasibility Study. J Clin Oncol. 2021;39(3):202-14. doi: 10.1200/JCO.20.01665.
9. Parker WP, Smelser W, Lee EK, Habermann EB, Thapa P, Zaid HB, Frank I, et al. Utilization and Outcomes of Radical Cystectomy for High-grade Non-muscle-invasive Bladder Cancer in Elderly Patients. Clin Genitourin Cancer. 2017:S1558-7673(17)30208-2. doi: 10.1016/j.clgc.2017.07.011.
10. Grimberg DC, Shah A, Tan WP, Etienne W, Spasojevic I, Inman BA. Hyperthermia Improves Solubility of Intravesical Chemotherapeutic Agents. Bladder Cancer. 2020;6(4):461-70. doi: 10.3233/BLC-200350.
11. Vartolomei MD, Ferro M, Roth B, Teoh JY, Gontero P, Shariat SF. Device-assisted intravesical chemotherapy treatment for nonmuscle invasive bladder cancer: 2022 update. Curr Opin Urol. 2022;32(5):575-83. doi: 10.1097/MOU.0000000000001010.
12. Zhou W, Liu J, Mao D, Hu C, Gao D. The clinical efficacy and safety of equipment-assisted intravesical instillation of mitomycin C after transurethral resection of bladder tumour in patients with nonmuscular invasive bladder cancer: A meta-analysis. PLoS One. 2022;17(10):e0276453. doi: 10.1371/journal.pone.0276453.
13. Wang S, Jin S, Shu Q, Wu S. Strategies to Get Drugs across Bladder Penetrating Barriers for Improving Bladder Cancer Therapy. Pharmaceutics. 2021;13(2):166. doi: 10.3390/pharmaceutics13020166.
14. Shen Z, Shen T, Wientjes MG, O'Donnell MA, L. Intravesical treatments of bladder cancer: review. Pharm Res. 2008;25(7):1500-10. doi: 10.1007/s11095-008-9566-7.
15. Kostyev F, Bondar O, Chystiakov R, Lysenko V, Stavnychyi O, Varbanets V. The impact of different adjuvant intravesical therapy methods on tumor biology in patients with high-risk non-muscle-invasive bladder cancer. Cent European J Urol. 2021;74(4):496-502. doi: 10.5173/ceju.2021.0122.
16. Multhoff G, Habl G, Combs SE. Rationale of hyperthermia for radio(chemo) therapy and immune responses in patients with bladder cancer: Biological concepts, clinical data, interdisciplinary treatment decisions and biological tumour imaging. Int J Hyperthermia. 2016;32(4):455-63. doi: 10.3109/02656736.2016.1152632.
17. Milani V, Noessner E, Ghose S, Kuppner M, Ahrens B, Scharner A, et al. Heat shock protein 70: role in antigen presentation and immune stimulation. Int J Hyperthermia. 2002;18(6):563-75. doi: 10.1080/02656730210166140.
18. Mantso T, Goussetis G, Franco R, Botaitis S, Pappa A, Panayiotidis M. Effects of hyperthermia as a mitigation strategy in DNA damage-based cancer therapies. Semin Cancer Biol. 2016;37-38:96-105. doi: 10.1016/j.semcancer.2016.03.004.
19. Chiancone F, Fabiano M, Carrino M, Fedelini M, Meccariello C, Fedelini P. Impact of systemic inflammatory markers on the response to Hyperthermic IntraVEsical Chemotherapy (HIVEC) in patients with non-muscle-invasive bladder cancer after bacillus Calmette-Gu rin failure. Arab J Urol. 2021;19(1):86-91. doi: 10.1080/2090598X.2021.1874627.
20. Dayanc BE, Beachy SH, Ostberg JR, Repasky EA. Dissecting the role of hyperthermia in natural killer cell mediated anti-tumor responses. Int J Hyperthermia. 2008;24(1):41-56. doi: 10.1080/02656730701858297.
21. Guerrero-Ramos F, Castellano-Gauna D, García-Rojo E, Duarte- M, de la Rosa-Kehrmann F, Villacampa-Aubá F. HIVEC con mitomicina C. Mitomycin C HIVEC. Update and results in high risk patients. Arch Esp Urol. 2018;71(4):417-425.
22. Sousa A, Piñeiro I, Rodríguez S, Aparici V, Monserrat V, Neira P, et al. Recirculant hyperthermic IntraVEsical chemotherapy (HIVEC) in intermediate-high-risk non-muscle-invasive bladder cancer. Int J Hyperthermia. 2016;32(4):374-80. doi: 10.3109/02656736.2016.1142618.
23. Zhao H, Chan VW, Castellani D, Chan EO, Ong WLK, Peng Q, et al. Intravesical Chemohyperthermia vs. Bacillus Calmette-Guerin Instillation for Intermediate- and High-Risk Non-muscle Invasive Bladder Cancer: A Systematic Review and Meta-Analysis. Front Surg. 2021;8:775527. doi: 10.3389/fsurg.2021.775527.
24. Guerrero-Ramos F, González-Padilla DA, González-Díaz A, de la Rosa-Kehrmann F, Rodríguez-Antolín A, Inman BA, et al. Recirculating hyperthermic intravesical chemotherapy with mitomycin C (HIVEC) versus BCG in high-risk non-muscle-invasive bladder cancer: results of the HIVEC-HR randomized clinical trial. World J Urol. 2022;40(4):999-1004. doi: 10.1007/s00345-022-03928-1.
25. Plata A, Guerrero-Ramos F, Garcia C, González-Díaz A, Gonzalez-Valcárcel I, de la Morena JM, et al. Long-Term Experience with Hyperthermic Chemotherapy (HIVEC) Using Mitomycin-C in Patients with Non-Muscle Invasive Bladder Cancer in Spain. J Clin Med. 2021;10(21):5105. doi: 10.3390/jcm10215105.
26. Tan WP, Bello AP, Alvarez CG. A Multicenter Study of 2-year Outcomes Following Hyperthermia Therapy with Mitomycin C in Treating Non-Muscle Invasive Bladder Cancer: HIVEC-E. Bladder Cancer. 2022;8(4):379-93. doi: 10.3233/BLC-220026.
27. Doisy L, Cimier A, Adypagavane A, Walz J, Marquette T, Maubon T, et al. Efficacy of HIVEC in patients with high-risk non-muscle invasive bladder cancer who are contraindicated to BCG and in patients who fail BCG therapy. Int J Hyperthermia. 2021;38(1):1633-8. doi: 10.1080/02656736.2021.2002435.
28. Conroy S, Pang K, Jubber I, Hussain SA, Rosario DJ, Cumberbatch MG, et al. Hyperthermic intravesical chemo-

therapy with mitomycin-C for the treatment of high-risk non-muscle-invasive bladder cancer patients. BJUI Compass. 2022;4(3):314-21. doi: 10.1002/bco2.203.
29. Melgarejo Segura MT, Morales MA, Yáñez CY, Arrabal Polo MÁ, Gómez LP, Pareja VM, et al. Conductive hyperthermic chemotherapy versus electromotive drug administration of mitomycin C as intravesical adjuvant treatment of patients with intermediate or high-risk non-muscle invasive bladder cancer. Urol Oncol. 2023;41(2):109.e1-109.e8. doi: 10.1016/j.urolonc.2022.10.019.
30. Thyavihally YB, Waigankar SS, Dev P, Asari A, Pednekar AP, Athikari N, et al. Comparing adverse effects, short term outcomes, and cost implications of hyperthermic intravesical chemotherapy with Mitomycin-C and intravesical bacillus Calmette-Guerin instillation (Moscow-I strain) in the management of intermediate and high-risk nonmuscle invasive bladder cancer. Urol Ann. 2021;13(4):424-30. doi: 10.4103/UA.UA_139_20.
31. Thomsen JA, Nielsen DH, Lindgren MS, Jensen JB. Adverse events of hyperthermic intravesical chemotherapy for non-muscle invasive bladder cancer patients. Scand J Urol. 2021;55(4):281-6. doi: 10.1080/21681805.2021.1938664.
32. Lim YN, Dwyer P, Murray C, Karmakar D, Rosamilia A, Thomas E. Long-term outcomes of intravesical dimethyl sulfoxide/heparin/hydrocortisone therapy for interstitial cystitis/bladder pain syndrome. Int Urogynecol J. 2017;28(7):1085-9. doi: 10.1007/s00192-016-3232-0.
33. Schoenfeld RH, Belville WD, Jacob WH, Buck AS, Dresner ML, Insalaco SJ, et al. The effect of dimethyl sulfoxide on the uptake of cisplatin from the urinary bladder of the dog: a pilot study. J Am Osteopath Assoc. 1983;82(8):570-3.
34. Hashimoto H, Tokunaka S, Sasaki M, Nishihara M, Yachiku S. Dimethylsulfoxide enhances the absorption of chemotherapeutic drug instilled into the bladder. Urol Res. 1992;20(3):233-6. doi: 10.1007/BF00299723.
35. See WA, Xia Q. Regional chemotherapy for bladder neoplasms using continuous intravesical infusion of doxorubicin: impact of concomitant administration of dimethyl sulfoxide on drug absorption and antitumor activity. J Natl Cancer Inst. 1992;84(7):510-5. doi: 10.1093/jnci/84.7.510.
36. Chen D, Song D, Wientjes MG, Au JL. Effect of dimethyl sulfoxide on bladder tissue penetration of intravesical paclitaxel. Clin Cancer Res. 2003;9(1):363-9.
37. Wirth M, Plattner VE, Gabor F. Strategies to improve drug delivery in bladder cancer therapy. Expert Opin Drug Deliv. 2009;6(7):727-44. doi: 10.1517/17425240903022758.
38. Kostyev F, Bondar O, Chystiakov R, Lysenko V, Stavnychyi O, Varbanets V. The impact of different adjuvant intravesical therapy methods on tumor biology in patients with high-risk non-muscle-invasive bladder cancer. Cent European J Urol. 2021;74(4):496-502. doi: 10.5173/ceju.2021.0122.

Стаття надійшла до редакції 23.05.2024. – Дата першого рішення 29.05.2024. – Стаття подана до друку 26.06.2024