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3-YEARS EXPERIENCE OF HYPERTHERMIC INTRAVESICAL CHEMOTHERAPY USE IN PATIENTS WITH HIGH-RISK NON-MUSCULAR-INVASIVE BLADDER CANCER

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Ключові слова: *м'язово-неінвазивний рак сечового міхура, гіпертермічна внутрішньоміхурова хіміотерапія*

Abstract. 3-year experience of hyperthermic intravesical chemotherapy use in patients with high risk non-muscular-invasive bladder cancer. Chystiakov R.S., Kostyev F.I., Bondar O.V., Lysenko V.V., Varbanets V.O. *Cur rently, the search for additional organ-sparing methods of intravesical therapy for non-muscular-invasive bladder cancer (NMIBC) is actively continuing, which could become an effective alternative to standard treatment using the Bacillus Calmette-Guérin (BCG) vaccine. The aim of this work was to analyze the safety profile and long-term results of treatment of patients with the high-risk non-muscular-invasive bladder cancer who received adjuvant intravesical chemotherapy using the Combat BRS HIVEC® device for local hyperthermia (HIVEC® therapy group; n=53) in comparison with patients who received adjuvant therapy after transurethral resection of bladder performed with the Bacillus Calmette-Guérin vaccine (BCG therapy group; n=54). As a result, the median follow-up was 30 months (range 7-36). According to Common Terminology Criteria for Adverse Events (CTCAE) v 5.0, the most relevant side effects in HIVEC®/BCG therapy groups were adverse events grade 1-2: fever – 1%/8%; dysuria – 9%/13%; bladder spasms – 7%/12%; hematuria – 3%/4% and urinary tract infection – 3%/10%. Tumor recurrence was reported in 23 patients receiving intravesical BCG therapy and in 10 patients receiving intravesical hyperthermic chemotherapy (42.6% versus 18.9%, p=0.008). Tumor progression was recorded in 11 patients receiving intravesical BCG therapy and in 4 patients receiving intravesical hyperthermic chemotherapy (20.4% versus 7.5%, p=0.046). The study allows us to conclude that the method of hyperthermic intravesical chemotherapy has a better safety profile compared to intravesical Bacillus Calmette–Guérin vaccine therapy, while such indicators of oncological efficacy as 3-year recurrence-free survival and the incidence of progression were better in the HIVEC® therapy group.*

Реферат. Трирічний досвід застосування гіпертермічної внутрішньоміхурової хіміотерапії в пацієнтів з м'язово-неінвазивним раком сечового міхура високого ризику. Чистяков Р.С., Костєв Ф.І., Бондар О.В., Лисенко В.В., Варбанець В.О. *На цей час активно триває пошук додаткових органозберігаючих методик внутрішньоміхурової терапії м'язово-неінвазивного раку сечового міхура, які могли б стати ефективною альтернативою стандартному лікуванню з використанням вакцини Бацили Кальметта-Герена (БЦЖ, лат. BCG). Метою цієї роботи був аналіз профіля безпеки і віддалених результатів лікування пацієнтів з м'язово-неінвазивним раком сечового міхура високого ризику, яким ад'ювантна внутрішньоміхурова хіміотерапія проводилась за допомогою апарата для локальної гіпертермії Combat BRS HIVEC® (група HIVEC® терапії; n=53) порівняно з пацієнтами, яким ад'ювантна терапія після трансуретральної резекції проводилася за допомогою вакцини Бацили Кальметта-Герена (група BCG терапії; n=54). У результаті медіана періоду спостереження становила 30 місяців (діапазон 7-36). Згідно зі шкалою Common Terminology Criteria for Adverse Events v 5.0, найбільш актуальними побічними ефектами в групах HIVEC®/BCG терапії були побічні явища 1-2 ступеня: лихоманка 1%/8%; дизурія 9%/13%; спазми сечового міхура 7%/12%; гематурія 3%/4% та інфекція сечовидільних шляхів 3%/10%. Рецидив пухлини був зареєстрований у 23 пацієнтів, які отримували внутрішньоміхурову BCG терапію, і в 10 пацієнтів, які отримували внутрішньоміхурову гіпертермічну хіміотерапію (42,6% проти 18,9%, p=0,008). Прогресія пухлини була зареєстрована в 11 пацієнтів, які отримували внутрішньоміхурову BCG терапію, і в 4 пацієнтів, які отримували внутрішньоміхурову гіпертермічну хіміотерапію (20,4% проти 7,5%, p=0,046). Проведене дослідження дозволяє зробити висновок, що метод*

гіпертермічної внутрішньоміхурової хіміотерапії має кращий профіль безпеки порівняно з внутрішньоміхуровою терапією вакциною Бацили Кальметта-Герена, при цьому такі показники онкологічної ефективності, як трирічна безрецидивна виживаність і частота випадків прогресії, були кращі в групі HIVEC® терапії.

Bladder cancer is the most common urothelial tumor and according to the International Agency for Research on Cancer (IARC), it is 5th cancer in men's oncology and the 17th in women's one. In the male population, it occurs 4.5 times more often than in the female (9 cases versus 2 per 100 000 people). Approximately 75% of patients with newly diagnosed bladder cancer have a non-muscle invasive tumor (NMIBC) – stages Tis, Ta, and T1 according to the TNM classification [9].

Transurethral resection of the bladder (TURB) with subsequent histological examination of the neoplasm is a method that allows to make the final diagnosis of NMIBC and stratifying the patient by risk groups according to the EORTC criteria (depth of invasion, tumor diameter, number of tumors, recurrent nature, presence of concomitant carcinoma in situ (CIS), degree of differentiation) [5].

The TURB with one of the adjuvant intravesical therapy types can be a radical organ-sparing treatment for low- and medium-risk patients [3]. A separate category includes patients of high- and highest-risk groups (any of the following: T1 tumor; G3 (High Grade) tumor; carcinoma in situ (CIS); multiple, recurrent, and large (>3 cm) TaG1G2/LG tumors (all features must be present)), as well as patients who had unsuccessful BCG therapy (BCG-failure). In such situations, one of the management options is an early radical cystectomy with the definite urinary diversion way that makes the NMIBC treatment extremely difficult [1, 7].

Hyperthermic intravesical chemotherapy is an apparatus technique that allows the continuous recirculation of a hot liquid through a definite isolated space [8]. As a drug for use as an antitumor antibiotic – Mitomycin-C (MMC) in an aqueous solution. The substance was heated to the temperature of 41-44◦C to increase the intravesical chemotherapy effectiveness. The technique has shown some encouraging results in the NMIBC patients' treatment [8].

Following current European Association of Urology (EAU) guidelines, hyperthermic chemotherapy may be considered in patients with NMIBC who had unsuccessful previous intravesical treatment (BCG failure), so, it is appropriate in ones who cannot or do not want to undergo radical cystectomy, however, it is not currently considered as an alternative to the BCG therapy in high-risk patients [3].

Aim – to assess the safety profile and long-term results of adjuvant treatment in patients with high-risk non-muscular-invasive bladder cancer.

MATERIALS AND METHODS OF RESEARCH

A retroprospective study included 107 outpatients with high-risk NMIBC according to EAU Guidelines 2018 with an average age of 65.01±12.23 (95% CI: 62.72-67.35) who received adjuvant intravesical therapy at the University Clinic of Odessa National Medical University from 2013 to 2021.

All studies were 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 No. 164, April 1997), the "Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects" by the World Medical Association (October 2008) and approved by the Bioethics Commission of the Odessa National Medical University, Protocol No. 135A, 03.07.2019). Before including patients in the study protocol, their personal written voluntary consents to participate in the study were obtained and all measures to ensure their anonymity were taken.

Depending on the type of treatment, the patients were divided into 2 groups. Group 1 included patients who received adjuvant therapy after TURB with the BCG vaccine (BCG therapy group; n=54). Group 2 included patients who received adjuvant intravesical chemotherapy using a Combat BRS HIVEC® device for local hyperthermia (HIVEC® therapy group; n=53).

The treatment of patients in the BCG group was based on the of use Uro-BCG applied to an emptied bladder. The soluted lyophilisate containing from 2×10^8 to 8×10^8 viable BCG bacteria with a temperature of 20-21ºC was inserted once a week with a disposable urethral catheter. The patient had to withstand 1 hour before urinating. The main course of treatment is supposed 6 weekly instillations and a maintenance course of 3 weekly instillations at 3, 6, and 12 months.

The protocol for patients in group 2 included the Mitomycin-C use at a dose of 40 mg once a week for 6 weeks. The installations were performed using a Combat BRS system V2.0 for hyperthermic chemotherapy (Combat Medical, Whithamstead, 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.

No significant differences in demographic variables between patients in both groups were revealed. In addition, there were no significant imbalances in the tumor process characteristics, such as tumor size, number of neoplasms, depth of invasion into the

bladder mucosa, histological gradation, and the presence of concomitant CIS.

The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 adverse event rating scale was used to assess immediate treatment outcomes. Safety endpoints included: type, frequency, and severity of adverse events (AE) according to the CTCAE v 5.0. The frequency of adverse events was calculated by the number of detected cases of toxicity per the number of intravesical instillations performed.

The primary outcome was recurrence-free survival (RFS), defined as the time from the end of intravesical adjuvant treatment to intravesical tumor recurrence. The recurrence was defined as a histologically confirmed diagnosis of urothelial carcinoma. The secondary outcome was progressive-free survival (PFS), which 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.

A comparative analysis of the corresponding parameters in both groups was carried out according to the $\chi 2$ method and using the t-test for independent samples. The Kaplan-Meier method was used to obtain estimates of the RFS, PFS, and OS (overall survival). The indicators were compared with each other using a log-rank test. A Cox proportional hazards regression model was used to analyze potential risk factors for intravesical recurrence and progression. IBM SPSS Statistics for Windows (version 28.0, license number: 8VHCOJ4SWTANT8W3AATBHOOBMICU6KR5 TKGQ42AU948MQM2ZK8FTSGZ8XI6VKD4WP 9UKFRKGWVHA7WRA92I9RERFJBVRXW2UU 3WK23) was used as a program for calculating statistical indicators. A p-value <0.05 was considered an indicator of statistical significance [1].

RESULTS AND DISCUSSION

The median follow-up period was 30 months (range 7-36) – 33 versus 27 months in the first and second groups, respectively (p=0.015).

7 patients (2 in the HIVEC® group and 5 in the BCG group) who discontinued treatment in the first and second cycles of intravesical therapy were not included in the analysis. Six-week therapy courses were not fully completed due to the side effects: 13 (26%) patients in the BCG therapy group (7 patients received 4 instillations, 6-5 ones); 4 patients (8.7%) in the HIVEC® group did not undergo a full course therapy (1 patient received 4 instillations, 3-5 ones) (p=0.005). In 18 (36%) patients from the first group and 8 (17.4%) patients from the second group, the instillation schedule was shifted for a week once due to moderate local toxicity, twice – in 8 (16%) and 2 (4.3%), respectively) patients (p<0.05).

According to the CTCAE, the most relevant side effects in HIVEC®/BCG therapy groups were AE grade 1-2: fever – 1%/8%; dysuria – 9%/13%; bladder spasms – 7%/12%; hematuria – 3%/4% and urinary tract infection – 3%/10%. When comparing the frequency of adverse events of 1-2 degrees, a significant difference was found in the higher frequency of fever, bladder spasms, and urinary tract infection in the BCG therapy group (Table 1).

Table 1

Comparison of adverse events of 1-2 degrees in both groups

Adverse event	The BCG group Grade 1, n (%)	The HIVEC® group Grade 1, n (%)	*p-value*
Fever	**17 (6%)**	**2 (0.6%)**	**<0.001**
Bladder spasms	**25 (8%)**	**11 (4%)**	**0.005**
Hematuria	**8 (3%)**	**6 (2%)**	**0,592**
Dysuria	**27 (9%)**	**20 (6%)**	**0.201**
Urinary tract infection	**18 (6 %)**	**5 (2%)**	**0.003**
Adverse event	**The BCG group Grade 2, n (%)**	**The HIVEC® group Grade 2, n (%)**	***p-value***
Fever	**8 (3%)**	**1 (0.3%)**	**0.016**
Bladder spasms	**11 (4%)**	**9 (3%)**	**0.653**
Hematuria	**3 (1%)**	**3 (1%)**	
Dysuria	**12 (4%)**	**10 (3%)**	**0.668**
Urinary tract infection	**11 (4 %)**	**3 (1%)**	**0.024**

Notes: Grade 1, 2 – grade of adverse events; p – statistical significance level.

The number of such adverse events of grade 3 as fever and urinary tract infection was higher in the group of BCG therapy, also in this group there was 1 case of these adverse events of grade 4 (Table 2).

Table 2

Comparison of adverse events of 3-4 degrees in both groups

Adverse effect	The BCG group		The HIVEC® group	
	grade 3	grade 4	grade 3	grade 4
Fever	**5**	**1**	**0**	**0**
Bladder spasms	**4**	**0**	**1**	**0**
Hematuria	**1**	**0**	**1**	**0**
Dysuria	**4**	**0**	**3**	**0**
Non-infectious cystitis	**4**	**1**	**1**	**0**
Total number AEs	**18**	**2**	**6**	**0**

Note. Grade 3, 4 – grade of adverse events.

Tumor recurrence was reported in 23 patients who received intravesical BCG therapy and in 10 patients who received intravesical hyperthermic chemotherapy. The recurrence rate was significantly different between the two groups (respectively 42.6% versus 18.9%, p=0.008). The Kaplan-Meier analysis of recurrence-free survival for two adjuvant treatment strategies is shown in Figure 1. The mean RFS time in patients receiving intravesical hyperthermic chemotherapy was significantly higher than in patients receiving intravesical BCG therapy 26.2 (95% CI: 22.9-29.5) versus 31.6 (95% CI: 29.3-34.0) (the result of the log-rank test: p=0.023). Recurrent tumor, concomitant CIS, high grade of differentiation, the BCG treatment, and the number of therapy cycles performed were independent prognostic factors for tumor recurrence after the adjuvant treatment by the Cox hazards regression model.

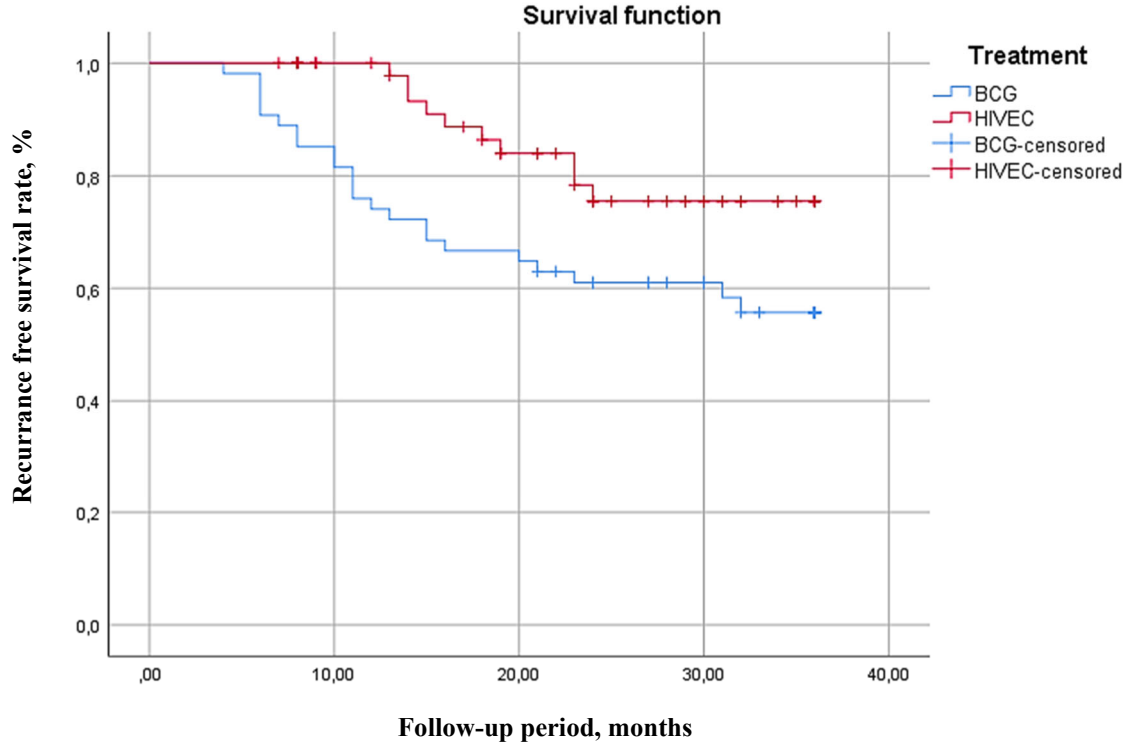

Fig. 1. The Kaplan-Meier curves of RFS indices in the studied groups

Tumor progression was recorded in 11 patients who received intravesical BCG therapy and in 4 patients who received intravesical hyperthermic chemotherapy. The incidence of the disease progression was significantly different between the two groups (respectively 20.4% versus 7.5%, p=0.046). The PFS analysis using the Kaplan-Meier method for two adjuvant treatment strategies is shown in Figure 2. Although the incidence of PFS in patients who received intravesical hyperthermic chemotherapy was significantly higher than in patients who received the intravesical BCG therapy, the mean PFS time did not differ significantly: 31.6 (95% CI: 29.1-34.1) versus 34.5 (95% CI: 33.2-35.9) (log-rank test result: p=0.126). Recurrent tumor, concomitant CIS, and high grade of differentiation were independent prognostic factors for tumor progression after the adjuvant treatment by the Cox hazards regression model.

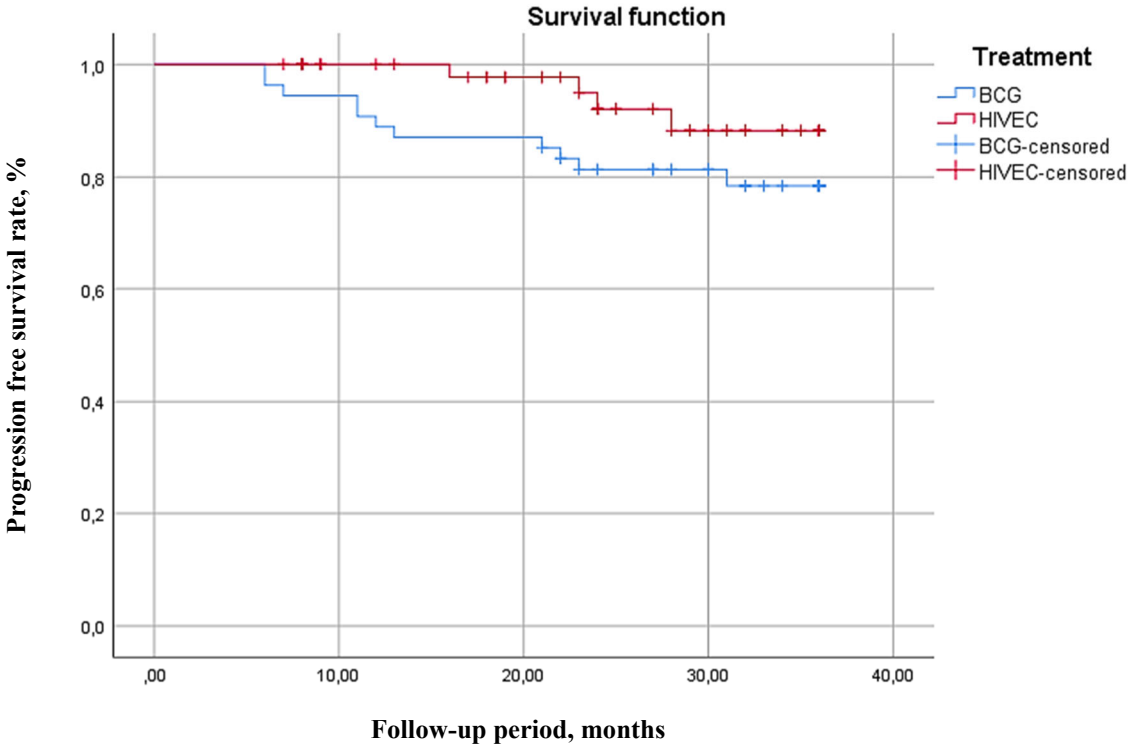

Fig. 2. The Kaplan-Meier curves of PFS indices in the studied groups

Overall survival rates during follow-up were not statistically different and amounted to 83.3% in the BCG therapy group and 90.6% in the HIVEC® therapy group (p=0.267). The mean OS time did not differ either from 33.6 (95% CI: 32.1-35.1) versus 34.0 (95% CI: 32.3-35.7) (p=0.591) (Fig. 3).

At the moment, in the world, there are no publications devoted to the final results of randomized trials of the use of hyperthermic chemotherapy in the first line of adjuvant treatment of high-risk NMIBC compared with the standard BCG therapy (HIVEC® HR study is ongoing – EudraCT 2016-001186-85). However, there are data from long-term studies of apparatus-assisted chemohyperthermia with which analogies can be drawn.

In 2019, Tan B.S. and co-authors published the results of a randomized study of the HYMN where they compared treatment with the radiofrequency chemohyperthermia using the MMC (6-week induction installations followed by maintenance installations) with adjuvant therapy with the BCG vaccine (induction installations with maintenance courses for one year) in patients with the moderate and high-risk recurrent NMIBC. Analysis of the results did not reveal any difference in either the complete response after 3 months or the disease-free survival between both study groups [10]. Subgroup analysis in this study showed that patients with CIS had lower disease-free survival in the chemohyperthermia group.

In our experience, patients without the CIS who receive the HIVEC MMC therapy show better results than patients with the CIS, both in terms of recurrence and progression – while analyzing risk factors, the CIS is an independent predictor of recurrence/progression.

In August 2021, a group of authors from Spain presented data on the results of a multicenter prospective HIVEC-E study, performed from 2012 to 2020, in which 502 patients with the medium and

high-risk NMIBC received the adjuvant chemohyperthermia MMC using the COMBAT BRS system [8]. The 5-year recurrent-free survival rate in this study was 50.37% (53.3% in medium-risk patients and 47.14% in high-risk patients), the progression-free survival rate was 89.83% (94.02% in the middle-risk group and 84.23% in the high-risk group, respectively). Authors noted a good tolerance to this type of therapy, 68.58% of patients did not have any adverse events and serious toxicity was noted only in 2.7%. No case was found to be life-threatening toxicity.

Our data about the safety of chemohyperthermia are consistent with the HIVEC-E study data.

The ability to tolerate the full course of intravesical therapy is an important factor when choosing a method of treatment, which can also affect on oncological indicators. The BCG vaccine therapy is associated with more side effects compared to intravesical chemotherapy (LoE 1a) and serious side effects occur in about 5% [4]. Adverse events which require discontinuation of treatment are more common during the first year of therapy and more common in elderly patients [6].

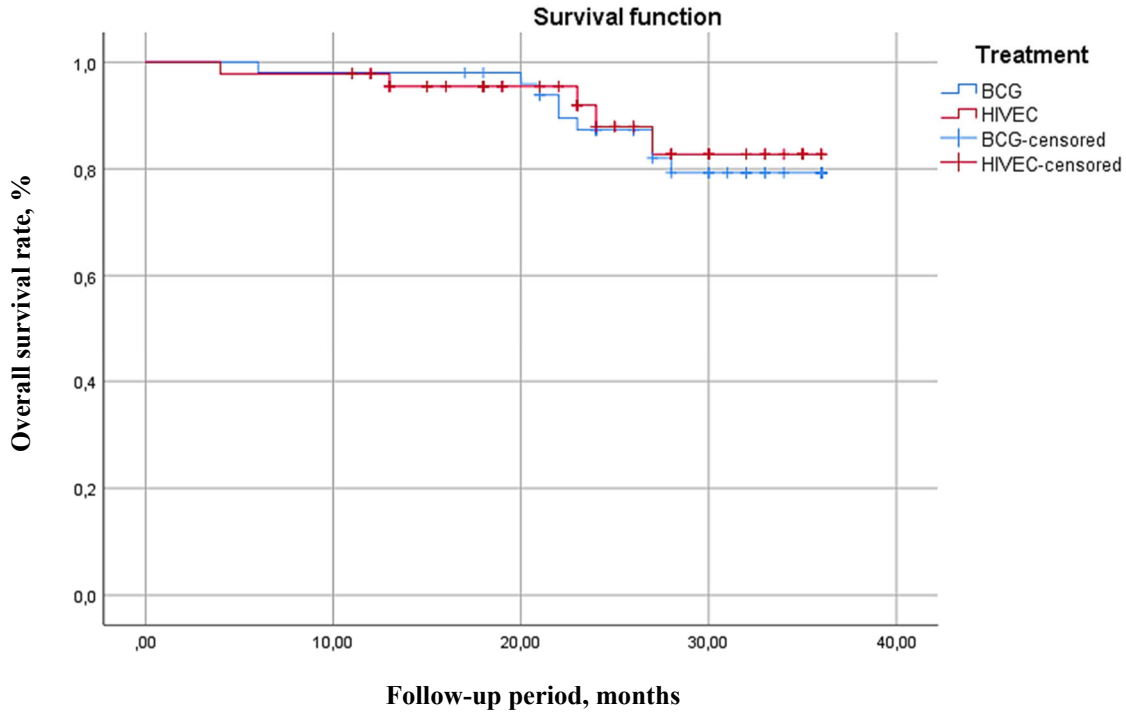

Fig. 3. The Kaplan-Meier curves of OS indices in the studied groups

CONCLUSIONS

1. Hyperthermic intravesical chemotherapy is a safe option for the high-risk non-muscular-invasive bladder cancer adjuvant treatment with side effects mainly of 1-2 degrees. It allows patients even the elderly ones to undergo a full course of adjuvant therapy without the quality-of-life loss.
2. The use of hyperthermic chemotherapy increases the 3-year recurrence-free survival of patients with high-risk non-muscular-invasive bladder cancer compared with the standard Bacillus Calmette-Guérin vaccine vaccine-based adjuvant treatment.
3. Cases of bladder cancer progression were statistically more frequent in patients after the standard Bacillus Calmette-Guérin vaccine therapy during the observation period.

Contributors:

Chystiakov R.S. – investigation, resources, data curation, software, formal analysis, writing – original draft;

Kostyev F.I. – methodology, validation, supervision;

Bondar O.V. – project administration;

Lysenko V.V. – conceptualization, validation;

Varbanets V.O. – data curation, writing – review & editing, visualization.

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