Adjuvant intravesical chemotherapy with titanium glycerosolvate aquacomplex versus BCG therapy in patients with high risk nonmuscle-invasive bladder cancer

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Objective: *to compare recurrence rate, progression rate and recurrence-free survival in patients with high-risk non-muscle-invasive bladder cancer (NMIBC) after adjuvant intravesical chemotherapy (IVCT) with titanium glycerosolvate aquacomplex (TGA) versus intravesical BCG therapy.*

Material and methods. *In a retrospective multicenter clinical study initially were included 126 patients with NMIBC. Of all 126 patients, 94 patients with high-risk NMIBC were selected and divided into 2 groups using a pseudo randomization with propensity score matching to minimize systematic differences in the process of forming groups. The treatment group (n = 55) consisted of patients with high-risk NMIBC who received a 6-week course of adjuvant IVCT with TGA. In the control group (n = 39) patients received an induction 6-week course of adjuvant intravesical BCG therapy, 19 (49 %) of 39 patients received maintenance therapy. Both methods were compared according to recurrence rate, progression rate and recurrence-free survival. Significance of difference was set at p <0.05.*

Results. *The compared groups of patients were well balanced in terms of clinical and morphological characteristics and the main risk factors for recurrence and progression of non-muscle-invasive bladder cancer, no significant differences were found between the groups (p >0.5). The recurrence rate in treatment and control groups was 33 % and 23 %, respectively (p = 0.31). The disease progression was observed in 1 (2 %) patient in the treatment group and in 4 (13 %) patients in the control group (p = 0.08). The median disease-free survival in both groups of patients was not reached at the time of analysis. Three- and five-year recurrence-free survival in the treatment group of patients were 71 % and 62 %, respectively; in the control group – 76 % and 72 %, respectively. There were no significant differences between recurrence-free-survival curves of the treatment and control groups (p = 0.58).*

Conclusion. *Adjuvant IVCT with TGA has demonstrated a clinical effectiveness comparable to intravesical BCG therapy and it can be used as an alternative method of treatment in patients with high-risk NMIBC.*

Key words: *adjuvant intravesical chemotherapy, hydrogel, titanium glycerosolvate aquacomplex, intravesical BCG, high risk non-muscle invasive bladder cancer, propensity score matching, pseudo randomization*

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Background

According to current Russian and foreign clinical guidelines, all patients with non-muscle invasive bladder cancer (NMIBC) with a high risk of recurrence and disease progression (stage pT1, G3 tumors, multifocal recurrent stage Ta tumors, carcinoma *in situ* (CIS)) after transurethral or open resection should undergo adjuvant intravesical Bacillus Calmette-Guérin (BCG) therapy given as a 6-week induction course followed by supportive therapy for up to 3 years; patients with very high risk of progression should undergo radical cystectomy [1–3].

Despite adjuvant intravesical BCG therapy in high-risk patients, the recurrence rate and the frequency of disease progression remains quite high reaching 40 % – 80 % and 15–40 %, respectively, over 5 years [4–6]. Moreover, there are serious limitations for intravesical BCG therapy in routine clinical practice, such as high toxicity compared to intravesical chemotherapy (IVCT), BCG vaccine shortage, and some legal aspects of its use [7–9].

A randomized clinical trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) has demonstrated that in case of BCG vaccine shortage or BCG intolerance in high-risk patients with NMIBC, it is possible to use lower BCG doses (up to one-third) and a shorter course (up to 1 year), because it affects only the probability of relapses, but does not lead to a significant increase the probability of disease progression to muscle-invasive forms [10].

Adjuvant IVCT significantly reduces the incidence of NMIBC relapses, but does not really prevent disease progression to muscle-invasive forms and is not effective for CIS. Therefore, it cannot be recommended as a standard treatment for high-risk patients [11, 12].

One of the most promising ways to improve IVCT efficacy is the implementation of optimized methods of intravesical instillation of chemotherapeutic agents aimed to increase bladder wall permeability and ensure longer contact between the drug and the tumor (such as hyperthermia, electrophoresis) [13].

In previous studies, we have analyzed the possibility of enhancing diffusion of chemotherapeutic agents into the bladder wall using titanium glycerosolvate aquacomplex (TGA), an original gel medication. TGA has a unique property: it can penetrate into tissues through the skin and mucous membranes and deliver drugs to the pathological site without losing their efficacy [14, 15].

The results of a recently published clinical trial involving high-risk NMIBC patients suggest that adjuvant IVCT with TGA ensures a 17 % increase in the 5-year relapse-free survival (RFS) compared to standard IVCT (64.9 % *vs* 47.9 %; $p = 0.068$). All adverse events associated with IVCT with TGA were mild or moderate and did not last for a long time, which ensured treatment completion [16].

High efficacy and low toxicity of IVCT with TGA in high-risk NMIBC patients suggest that this treatment can be used as an alternative to standard intravesical BCG therapy.

In this study, we compared the efficacy of IVCT with TGA and BCG therapy in high-risk NMIBC patients using propensity score matching in order to reduce biases associated with systematic differences at formation of groups (by different treatments) and affecting treatment outcomes [17, 18].

This study was undertaken to compare relapse-free survival, recurrence rate, and frequency of disease progression in high-risk NMIBC patients after adjuvant IVCT with TGA compared to conventional intravesical BCG therapy.

Materials and methods

This retrospective, multicenter, comparative, clinical study included 126 patients with confirmed bladder cancer who received adjuvant IVCT with TGA ($n = 72$) or intravesical BCG therapy ($n = 54$) in Sverdlovsk Regional Oncology Dispensary or Sverdlovsk Regional Clinical Hospital No. 1 between 2007 and 2019. The exclusion criteria were as follows: ≥T2 invasion of the primary tumor ($n = 2$), regional or distant metastases ($n = 1$), history of upper urinary tract tumors ($n = 6$), IVCT or BCG therapy within the preceding 3 months ($n = 3$). Separate analysis was performed for a group of 114 high-risk NMIBC patients (according to the European Association of Urology) [1].

These 114 patients were divided into two groups: experimental and control. To eliminate systematic differences between the groups compared, we selected patients using propensity score matching. It was based on clinical and morphological characteristics of patients and risk factors believed to be the main predictors of NMIBC recurrence and progression, such as age, gender; tumor size, number of tumors, depth of invasion, and tumor differentiation grade; presence of CIS; single postoperative instillation of a chemotherapeutic agent; type of primary surgical treatment and repeated transurethral resection of the bladder.

Ninety-four patients (80 men and 14 women) with stage pT1 or pTaG3 non-muscle-invasive urothelial carcinoma, or stage pTa recurrent multifocal tumors, or CIS who received adjuvant IVCT with TGA or intravesical BCG therapy were included into the final analysis.

The experimental group included 55 patients who received adjuvant IVCT with TGA, whereas the control group included patients treated using intravesical BCG therapy. Patients in the experimental group received treatment within a prospective clinical trial assessing the efficacy and safety of IVCT with TGA in NMIBC patients. Controls were retrospectively selected from the database of Sverdlovsk Regional Oncology Dispensary using the information and analytical system "Medofis".

At the first stage, all participants underwent either transurethral ($n = 84$) or open ($n = 10$) resection of the bladder using the standard method with the removal of all visible tumors.

In the experimental group, instillations were performed once a week for 6 weeks (50 mg doxorubicin or 40 mg mitomycin per installation). Drugs were dissolved in 50 mL of 40 % water solution of TGA.

Patients in the control group received a course of intravesical BCG therapy with Imuron ($n = 38$) or Uro-BCG Medac ($n = 1$). All of them had an induction 6-week course of BCG therapy with 1 installation per week (100 mg of vaccine per installation). Supportive BCG therapy was administered to 19 out of 39 patients (49 %) as follows: 1 installation per month with a total of 10 installations given during up to a year ($n = 2$; 5 %) or 3 weekly installation given once ($n = 8$; 21 %), twice ($n = 6$; 15 %) or thrice ($n = 3$; 7 %). BCG vaccine was diluted in saline (0.9 % NaCl) before instillation.

The course of intravesical instillations was initiated 8–30 days after surgery. The exposure time for both chemotherapeutic agents and BCG vaccine was 1 hour. The duration of adjuvant intravesical therapy was 6–8 weeks in the experimental group and 2–16 months in the control group. The ECOG performance status of all patients who received adjuvant intravesical therapy was 0–1

After the completion of adjuvant intravesical therapy, patients were examined every 3–6 months for the first 2 years, then once every 6 months for the next 3 years, and then annually. Each follow-up visit included physical examination, cystoscopy with biopsy of suspicious areas of the mucous membrane, computed tomography (CT) or ultrasonography of the abdominal cavity, kidneys, bladder, retroperitoneal and regional lymph nodes, chest X-ray or CT, urinalysis, cytology, and magnetic resonance imaging (when indicated). Patients suspected of having a relapse or disease progression underwent transurethral resection of the bladder.

In case of relapse and/or disease progression, we evaluated depth of invasion (rpT) and tumor differentiation grade (G). The development of muscle invasion (≥T2), regional (N+) or distant metastases (M+) was considered as disease progression. The efficacy of various methods of adjuvant intravesical therapy was evaluated by assessing relapse-free survival, recurrence rate, and frequency of disease progression. We calculated the time to relapse and/or disease progression from the moment of surgery.

Data analysis was conducted using the Microsoft Word, Excel, and SPSS v. 21 software. Propensity score matching was performed using logistic regression modeling. We used the two-tailed Fisher's exact test and χ^2 test to estimate the differences between categorical variables and Mann–Whitney U-test for continuous variables. We also performed Kaplan–Meier analysis to assess survival and log-rank-test to compare the survival curves. The differences were considered significant at $p < 0.05$.

Results

Table 1 demonstrates clinical and morphological characteristics of patients in the experimental and control groups, including the main risk factors for disease recurrence and progression that were taken into account in propensity score matching.

The groups compared were matched for the main clinical and morphological characteristics without significant differences between them. The median age of patients in the experimental and control groups was 58 and 60 years, respectively ($p = 0.89$). The male to female ratio in the experimental and control groups was 5.9:1 and 5.5:1, respectively ($p = 0,91$). In the experimental group, 44 patients (80 %) received IVCT

Table 1. *Characteristics of patients in the experimental and control groups*

Characteristic	Experimental group ($n = 55$)	Control group ($n = 39$)	p
Median follow-up time, months	59	42	0.07
Median age, years	58	60	0.89
Gender, *n* (%): male female	 47 (85) 8 (15)	 33 (82) 6 (18)	0.91
Surgery, *n* (%): transurethral resection resection	 50 (91) 5 (9)	 37 (94) 2 (6)	0.7
Repeated transurethral resection 4–8 weeks after the first resection, *n* (%): yes no	 3 (5) 52 (95)	 6 (15) 33 (85)	0.11
Tumor invasion, *n* (%): pTa pT1	 1 (2) 54 (98)	 2 (5) 37 (95)	0.57
Tumor size, *n* (%): <3 cm ≥3 cm	 41 (75) 14 (25)	 28 (72) 11 (28)	0.57
Number of tumors, *n* (%): single multifocal	 16 (29) 39 (71)	 11 (28) 28 (72)	0.93
Differentiation grade, *n* (%): G_1 G_2 G_3	 23 (42) 23 (42) 9 (16)	 13 (33) 16 (41) 10 (26)	>0.18
Primary tumor, *n* (%) Relapse, *n* (%)	 33 (60) 22 (40)	 22 (56) 17 (44)	0.73
Carcinoma *in situ*, *n* (%)	4 (7)	3 (8)	
Single postoperative instillation of a chemotherapeutic agent, *n* (%)	31 (56)	16 (41)	0.14

Table 2. *Relapse rate, median relapse-free survival, 3-year and 5-year relapse-free survival in the experimental and control groups (comparative analysis)*

Characteristic	Experimental group (n = 55)	Control group (n = 39)	p
Relapse rate, n (%)	18 (33)	9 (23)	0,31
Rate of disease progression, n (%)	1 (2)	5 (13)	0,08
Median relapse-free survival, months	Not reached	Not reached	–
3-year relapse-free survival rate, %	71	76	0,68
5-year relapse-free survival rate, %	62	72	0,63

with doxorubicin, whereas 11 patients (20 %) received IVCT with mitomycin. Of note, there were no significant differences in the duration of follow-up between the groups, although participants in the experimental group were followed-up longer (42 months vs 59 months; $p = 0.07$).

The recurrence rates, frequency of disease progression, and RFS in the groups are shown in Table 2.

Median RFS in both groups was not reached by the time of analysis. The 3-year and 5-year RFS rates in the experimental group were 71 % and 62 %, respectively; in the control group, they were 76 % and 72 % respectively. The comparison of survival curves of the experimental and control groups demonstrated no significant differences between them ($p = 0.58$) (Fig. 1).

The recurrence rate in the experimental and control groups was 33 % and 23 %, respectively ($p = 0.31$). Disease progression was observed in 1 patient from the experimental group (2 %) and 4 patients from the control group (13 %). The frequency of disease progression in the control group was 7 times higher than that in the experimental group; however, the difference failed to reach statistical significance ($p = 0.08$) (Fig. 2).

Thus, comparative analysis of the outcomes of adjuvant intravesical therapy in patients from the experimental and control groups, matched for the main clinical and morphological parameters using propensity score matching, did not show any significant differences in RFS, recurrence rate, and frequency of disease progression between the groups.

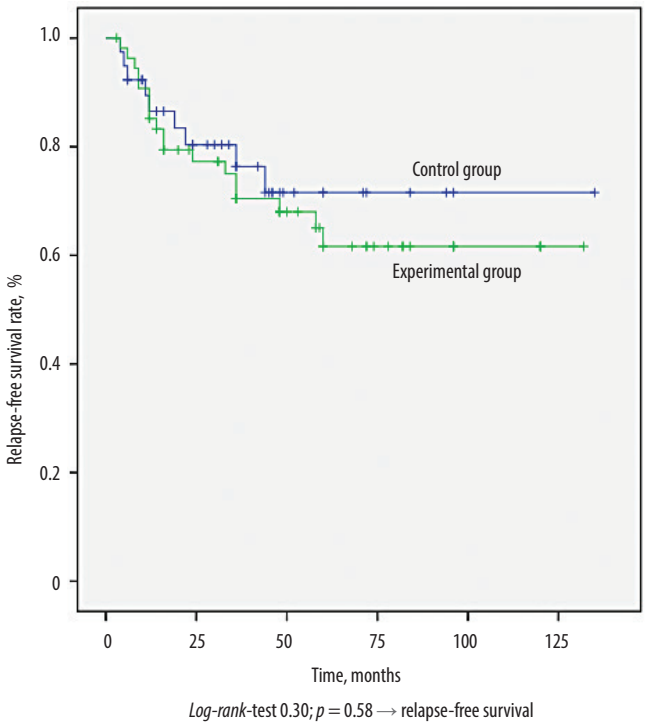

Fig. 1. *Relapse-free survival in the experimental and control group*

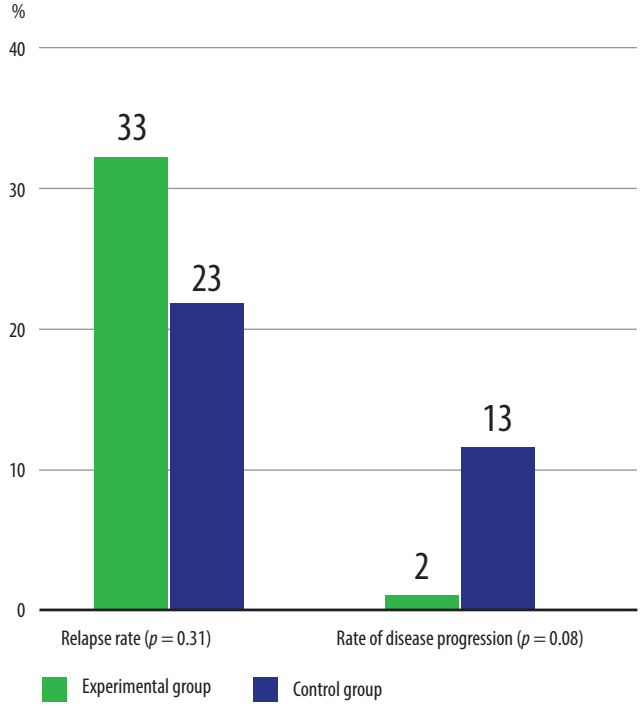

Fig. 2. *Rates of relapses and disease progression in the experimental and control group*

Discussion

It is well known that BCG vaccine is the most effective drug for adjuvant intravesical therapy for intermediate-risk and high-risk NMIBC patients (1a level of evidence) [19, 20].

Previous comparative randomized trials and meta-analyses demonstrated significant advantages of intravenous BCG therapy over standard IVCT with anthracyclines (such as doxorubicin, epirubicin, adriamycin) or mitomycin in high-risk patients for the prevention of both recurrence and disease progression [21–23].

BCG vaccine shortage, as well as limitations associated with its administration (including intolerance and complex epidemiological requirements) stimulated the development of alternative techniques of intravesical therapy for NMIBC, including those that can increase the efficacy of standard IVCT.

Currently, the most studied ways of improving standard IVCT are hyperthermic chemotherapy and electrophoresis with chemotherapeutic agents. These methods increase permeability of the bladder wall and enhance antitumor activity of drugs [24, 25]. In addition to that, IVCT efficacy can be increased by administration of chemotherapeutic agents that are not normally used in intermediate/high-risk patients, such as gemcitabine and docetaxel [26, 27]. However, these optimized IVCT techniques are not considered as a standard treatment for high-risk NMIBC patients and are recommended only as an alternative to intravesical BCG therapy in cases when it is impossible or ineffective [28].

In this study, we demonstrated high efficacy of adjuvant IVCT with chemotherapeutic agents and TGA for high-risk patients with NMIBC.

We found that despite higher efficacy of adjuvant intravesical BCG therapy for preventing disease recurrence compared to adjuvant IVCT with TGA, the differences in the recurrence rates, 3-year RFS, and 5-year RFS between the groups were 5 %, 10 %, and 10 %, respectively, and failed to reach statistical significance (p >0.5).

Of note, patients receiving adjuvant IVCT with TGA were less likely to have disease progression than those receiving BCG therapy: the difference between the groups was 11 % and almost reached statistical significance (2 % in the experimental group and 13 % in the control group; $p = 0.08$).

To minimize biases and to reduce the impact of the main clinical and morphological characteristics of patients on treatment outcomes, we used propensity score matching, a multi-stage statistical analysis based on the calculation and matching of propensity scores (PSs), i. e., the probability of patient enrollment in the experimental or control group according to his/her characteristics. Propensity score matching allowed us to balance the groups studied and to obtain more reliable results when comparing the efficacy of adjuvant IVCT with TGA and BCG therapy.

Despite the use of propensity score matching, our study still has some methodological limitations due to its retrospective nature and relatively small number of patients in the groups compared.

This suggests the need for further and larger prospective randomized clinical trials assessing the efficacy of IVCT with TGA compared to standard adjuvant intravesical therapy in NMIBC patients, including supportive IVCT with TGA.

Conclusion

Our findings suggest that the efficacy of adjuvant IVCT with TGA is close to the efficacy of intravesical BCG therapy and, therefore, can be used as an alternative treatment in in high-risk NMIBC patients.

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A.V. Zamyatin: developing the research design, obtaining data for analysis, analysis of the obtained data (including statistical), reviewing of publications of the article's theme;
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S.A. Berzin, A.V. Zyryanov: developing the research design, obtaining data for analysis.

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The study protocol was approved by the biomedical ethics committee of Sverdlvsk Region Clinical Hospital No 1.
All patients gave written informed consent to participate in the study.

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