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Comparative study between intravesical gemcitabine *versus* bacillus Calmette–Guérin in high risk superficial bladder cancer

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Objectives. To study the efficacy and safety of intravesical gemcitabine (GEM) in comparison to intravesical bacillus Calmette–Guérin (BCG) for patients with high risk non-muscle invasive tumors.
Methods. 100 patients with histologically confirmed non-muscle invasive bladder cancer (carcinoma *in situ*, Ta, T1), in the high-risk group of urothelial carcinoma, treated in the outpatient clinic of the Urology between 2021 and 2023 who received adjuvant intravesical therapy were simply randomized to group A (BCG group) and group B (GEM group) following single postoperative intravesical instillation of (GEM) chemotherapy after transurethral resection of bladder tumor, each group contained 50 patients were evaluated.
Results. All patients were evaluated for a follow-up of 24 months after treatment. There is no significant statistical difference in clinical and pathological characteristics between the groups. There was no statistically significant difference in the recurrence rate and progression rate of the disease in each group respectively ($p = 0.2, 0.06$) also overall disease-free rate ($p = 0.128$). Regarding safety, free cases of any adverse events were clinically and statistically significant between both groups ($p = 0.002$). There were statistically significant differences between groups A and B in grade II (hematuria, fever) and grade III (allergy, BCGosis) adverse effects respectively ($p = 0.001, 0.003$). Although grade I complications were more in the BCG arm, but it was not statistically significant.
Conclusion. The adjuvant intravesical GEM chemotherapy has equal efficacy for BCG immuno-therapy in the treatment of high-risk superficial bladder cancer patients following transurethral resection of bladder tumor. In addition, GEM is associated with reduced local and systemic toxicity compared with BCG.

Keywords: gemcitabine, bacillus Calmette–Guérin, non-muscle invasive bladder cancer, transurethral resection of bladder tumor, urothelial carcinoma

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Сравнительное исследование внутрипузырного введения гемцитабина и бациллы Кальметта–Герена для лечения поверхностного рака мочевого пузыря высокого риска

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Цель. Изучить эффективность и безопасность внутрипузырного введения гемцитабина (GEM) в сравнении с внутрипузырным введением бациллы Кальметта–Герена (BCG) у пациентов с немышечно-инвазивным раком мочевого пузыря высокого риска.
Методы. В исследовании 100 пациентов с гистологически подтвержденным немышечно-инвазивным раком мочевого пузыря (карцинома *in situ*, Ta, T1) и уротелиальной карциномой высокого риска, получавшие амбулаторное лечение в клинике урологии в период с 2021 по 2023 г., были рандомизированы в группу A (группа BCG) и группу B (группа GEM) после трансуретральной резекции опухоли мочевого пузыря и единственной послеоперационной внутрипузырной дозы (GEM) химиотерапии. В каждой группе было по 50 пациентов.

Результаты. Срок наблюдения за всеми пациентами после лечения составил 24 мес. Статистически значимых различий в клинических и патологических характеристиках между группами не обнаружено. Также не было значимых различий в частоте рецидивов и прогрессирования заболевания (p = 0,2; 0,06) и общей безрецидивной выживаемости (p = 0,128). В отношении безопасности между группами наблюдались клинически и статистически значимые различия по количеству нежелательных явлений (p = 0,002). Между группами A и B выявлены значимые различия по количеству нежелательных явлений II (гематурия, лихорадка) и III (аллергия, диссеминированная BCG-инфекция) степеней тяжести (p = 0,001; 0,003, соответственно). Осложнения I степени тяжести встречались чаще в группе BCG, но различия не были статистически значимыми.
Заключение. Адъювантная внутрипузырная химиотерапия GEM по эффективности близка к иммунотерапии BCG у пациентов с поверхностным раком мочевого пузыря высокого риска после трансуретральной резекции опухоли. Более того, химиотерапия GEM обладает меньшей локальной и системной токсичностью, чем BCG.

Ключевые слова: гемцитабин, бацилла Кальметта–Герена, немышечно-инвазивный рак мочевого пузыря, трансуретральная резекция опухоли мочевого пузыря, уротелиальная карцинома

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Introduction

In terms of global cancer incidence, bladder cancer is ninth, with men and women developing it at rates of fourth and seventeen, respectively [1]. Older people are more likely to develop bladder urothelial carcinoma, with patients 55 years of age and above accounting for more than 90 % of cases [1].

About 70 % of bladder cancers at first presentation are non-muscle invasive bladder cancer (NMIBC), which include the entities of carcinoma *in situ* (CIS) and papillary carcinomas of stage Ta and T1 [2, 3]. Only 20 % of recurrences in NMIBC cancer lead to muscle-invasive disease, while 70 % of recurrences do not progress to muscle invasive bladder cancer (MIBC) [3].

Transurethral resection of bladder tumor (TURBT) is the main treatment for bladder cancer that NMIBC [4]. After TURBT, intravesical chemotherapy or immunotherapy are frequently used as local treatments [3, 4]. Although intravesical bacillus Calmette–Guérin (BCG) has been the gold standard for post-TURBT treatment, over 30 % of patients still experience recurrence. After BCG injection, several local toxicities, including cystitis and, more crucially, systemic BCG infection, may occur [3]. Furthermore, there is still disagreement about how long maintenance therapy should last after a 6-week induction cycle, whether it be using the SWOG (South West Oncology Group) technique or monthly doses [5].

Many intravesical chemotherapeutic agents like mitomycin C (MMC), gemcitabine (GEM), and epirubicin have been used as adjuvant therapy post-TURBT as an alternative to BCG or as second-line therapy. A randomized controlled study found GEM to be superior to MMC in efficacy and less toxic compared to MMC [3]. Intravesical GEM has been investigated as a potential treatment for NMIBC [6].

Gemcitabine is a novel chemotherapeutic agent for non-muscle invasive transitional cell carcinoma of the urinary bladder, which has activity in the treatment of metastatic bladder cancer [7]. GEM is a deoxycytidine analog that inhibits DNA synthesis [8]. GEM can easily penetrate the bladder mucosa with beneficial effects on non-muscle-invasive transitional cell carcinoma of the urinary bladder [9]. At the same time, its molecular weight is high enough to prevent significant systemic absorption in an intact bladder. GEM has been proven effective as intravesical therapy and well tolerated as single-agent therapy for non-muscle invasive transitional cell carcinoma of the urinary bladder [10].

GEM had comparable efficacy to BCG at least in the intermediate risk group and superior in BCG refractory patients, according to numerous small trials [11–13] that demonstrated good responses in NMIBC [14]. Despite the existence of numerous single-arm studies and a solitary phase 2 trial comparing GEM to BCG [15], no head-to-head randomized phase 3 trials are currently available.

Therefore, we aimed to compare oncological outcomes and safety profiles between patients treated with adjuvant intravesical BCG *vs* GEM for high-risk treatment naive NMIBC at our institution between 2021 and 2023 in a prospective randomized comparative study.

Materials and methods

The aim of the study was to compare [1] the efficacy, as indicated by disease recurrence, progression and [2] toxicity, of intravesical BCG immunotherapy with intravesical GEM chemotherapy in the treatment of patients with high risk NMIBC.

This prospective study was conducted in 100 patients with histologically confirmed NMIBC (CIS, Ta, T1) of the urinary

bladder, in the high risk group urothelial carcinoma according to European Association of Urology (EAU) guidelines, treated in the outpatient clinic of the Urology between 2021 and 2023.

There were 84 men and 16 women with age mean (67.84, 64.02) and SD (13.12, 12.54) in both groups respectively. A histopathological diagnosis, before study entry, was made after TURBT.

All patients were assessed according to guidelines (full history taking, general and local examinations, laboratory studies and radiological investigations).

Under cystourethroscopy, complete TURBT was done until the muscle fibers were visible. Biopsies were taken from the tumor base and from all bladder walls and prostatic urethra, processed and examined separately. The tumor location, number, diameter was documented.

Following TURBT, the stage and the grade of the tumor were determined using the TNM staging system (2009 system, American Joint Commission on Cancer in combination with the International Union Cancer Consortium). The EAU risk stratification scoring system [16] was used to stratify into three groups: low [1–4], intermediate [5–9], and high risk [10–17].

Recurrence was defined as histology proven tumor recurrence (any grade) or appearance of CIS. It may occur with or without progression. Progression in tumor stage defined by the depth of bladder muscle invasion (T2).

If the tumor recurred during treatment, TURBT was repeated and the patient with non-muscle invasive recurrence was retained in the same group, along with a second course of induction therapy.

Serial No. 32-2021 R was the approval number given by the institutional ethics committee for the study. Before every dose, each patient signed a paper outlining all potential side effects in order to facilitate early diagnosis.

Sample size. Sample size of 100 patients (Fig. 1) with high risk NMIBC divided into two groups by simple randomization methods (one by one) one group treated with BCG intravesical installation & the other group treated with GEM intravesical installation.

Group A: 50 patients were treated by BCG intravesical installation.

Group B: 50 patients were treated by GEM intravesical installation.

Calculation of sample size: Group sample sizes is 50 in group one and 50 in group two achieve 81 % power to detect

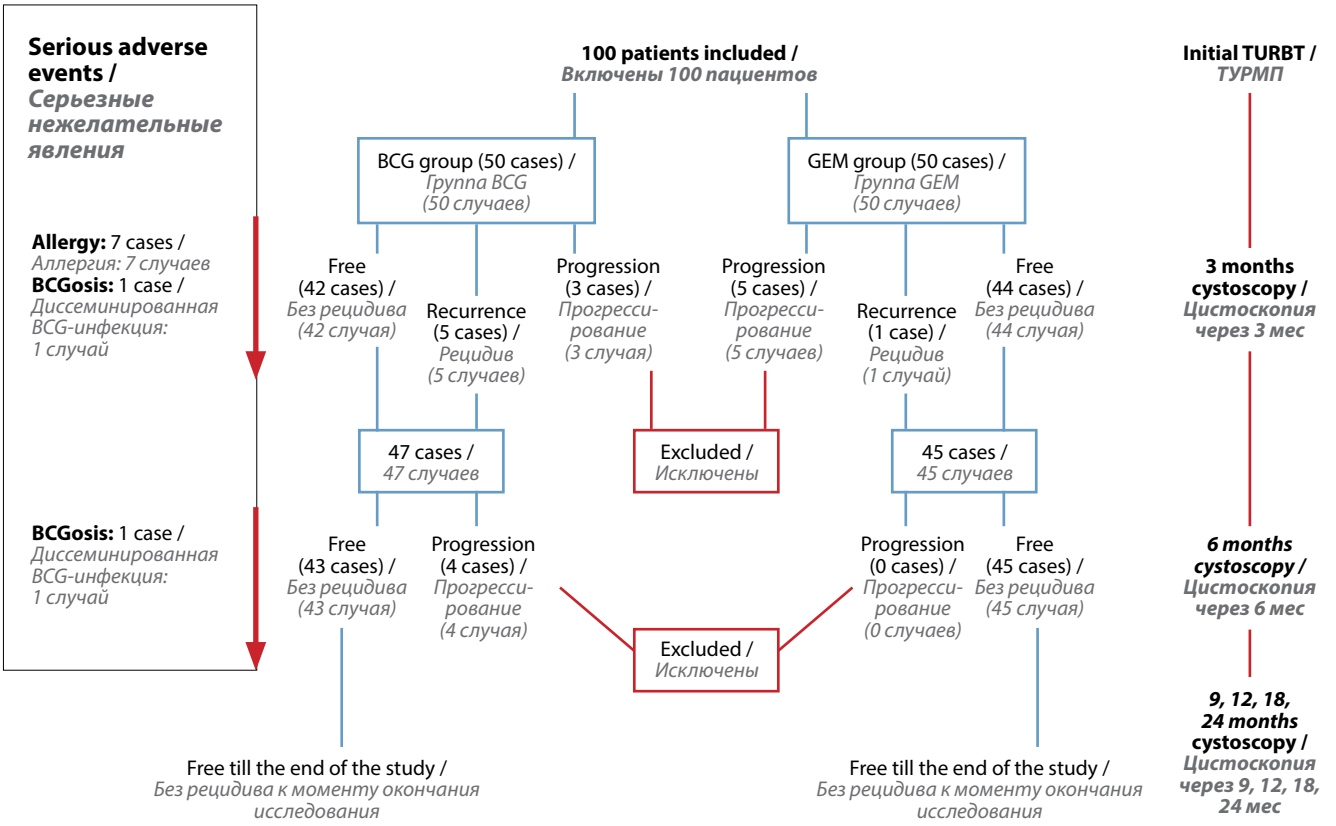

Fig. 1. *CONSORT flow chart of the patients through the study from enrollment till the end of study. TURBT – transurethral resection of bladder tumor; BCG – bacillus Calmette–Guérin; GEM – gemcitabine*

Рис. 1. *Блок-схема CONSORT, демонстрирующая ведение пациентов от включения в исследование до окончания исследования. ТУРМП – трансуретральная резекция опухоли мочевого пузыря; BCG – бацилла Кальметта–Герена; GEM – гемцитабин*

a difference between the group proportions of –0.27. The proportion in group one (the treatment group) is assumed to be 0.36 under the null hypothesis and 0.09 under the alternative hypothesis.

Inclusion criteria: high-risk non- muscle-invasive transitional cell carcinoma of the bladder (Ta, T1, CIS).

Exclusion criteria:

- low and intermediate risk non-muscle-invasive bladder cancer;
- rcurrent TCC of the bladder;
- other bladder tumors (e.g. adenocarcinoma, squamous cell carcinoma);
- upper urinary tract affection (hydronephrosis);
- pregnancy (in females);
- others immune-compromised status as, human immunodeficiency virus, cancer, organ transplant patients who are taking immunosuppressive drugs).

Procedure and steps. All study participants will be subjected to the following:

First step (clinical trial details and follow up period):

Group A:

Single postoperative instillation of GEM within 6–24 hours after TURBT (GEM vial 1000 mg/25 cc normal saline for 1–2 hours).

- 6 weekly induction cycle of BCG vial after 2 weeks of TURBT (BCG dose is 1 vial 3 ml (90 mg)/50 ml normal saline);
- maintenance cycle of BCG: one intravesical installation each week for 3 weeks at 3, 6 and 12 months after the BCG induction cycle, and then every 6 months thereafter for a total of 2 years.

Group B:

Single postoperative instillation of GEM within 6–24 hours after TURBT (GEM vial 1000 mg/25 cc normal saline for 1–2 hours).

- 8 weekly induction cycle of GEM vial after 2 weeks of TURBT: one intravesical installation weekly for 8 weeks of 1000 mg gemcitabine vial;
- maintenance cycle of GEM: after the induction cycle one instillation of 1000 mg vial every month for 10 months.

Second step (assessment of outcome among studied groups):

- Follow-up cystoscopy every 3 months (from the date of TURBT) in the first year and every 6 months in the second year.
- Upper urinary tract radiology (U/S, CT) every 6 months in the first 2 years.

Check and stop points:

- Check points: complete blood picture (twice/month), liver & renal functions (twice/month (during induction cycle), monthly (during maintenance cycle)). Pregnancy test for married female patients.
- Stop points:
  - local side effects: dysuria, hematuria frequency, urgency (according to Cleveland clinic approach of toxicity) [17].
  - systemic side effects: thrombocytopenia, liver or renal dysfunction (according to common toxicity criteria) (CTC) 2017 version 5 [18].

Follow up points:

Primary objective: the efficacy of intravesical treatment is the primary goal. If the tumor recurrence while the patient was receiving treatment, TURBT was repeated, and the patient with non-muscle invasive recurrence was retained in the same group with close follow-up following a second course of induction therapy. Recurrence was defined as the development of CIS or histologically confirmed tumor recurrence (any grade). It could happen either with or without progression. The degree of bladder muscle invasion defines the progression in tumor stage. Low [1–4], intermediate [5–9], and high risk [10–17] were identified using the EAU risk stratification scoring system [16]. Histology and cystoscopy guided biopsies both verified the advancement of all recurrences.

Secondary objective: the toxicity profile is the secondary goal. All adverse events were documented and assessed using the BCG Cleveland clinic scale.

End points:

- progression to muscle invasive disease (stage >T1);
- development of grade IV or severe grade III adverse events.

Statistical analysis. Data was analyzed using SPSS (statistical package for social sciences) version 24. Qualitative data was presented as number and percent, Quantitative data was described as mean and standard deviation for normally distributed data and median and range for non-normally distributed. The appropriate statistical test was applied according to the data type with the following suggested tests: Chi-Square for the categorical variables. Survival rate was determined, Kaplan–Meier curve was used. And when p <0.05, it was statistically significant.

Results

Comparison of general conditions between the two groups of patients (Table 1). There was no significant difference between the two groups on general conditions (including age, gender, risk factors, tumor size, tumor grade, tumor number, tumor stage) (p >0.05).

Efficacy analysis (Table 2). The two groups were followed up by outpatient visits, and Kaplan–Meier survival analysis was used. The results were shown in Fig. 2: the median tumor recurrence-free survival time of GEM group was 88 %; While the median tumor recurrence-free survival time of BCG group was 76 %. After the recurrence occurs without progression and reinduction of the adjuvant therapy in both groups, complete response in GEM group single case but in BCG group recurrence with progression in 5 patients. Recurrence with stage progression to MIBC

Table 1. *General patients and tumour characteristics*

Таблица 1. *Общие характеристики пациентов и опухолей*

Characteristic **Характеристика**	**BCG group** **Группа BCG**	**GEM group** **Группа GEM**	***p***
Mean age, years Средний возраст, лет	67.9	64	0.59
Sex, *n* (%): Пол, *n* (%): male мужской female женский	 41 (82) 9 (18)	 43 (86) 7 (14)	0.14
Risk factors, *n* (%): Факторы риска, *n* (%): smoking курение occupation профессия	 39 (78) 3 (6)	 38 (76) 2 (4)	0.87
Size, *n* (%): Размер, *n* (%): <3 cm <3 см >3 cm >3 см	 13 (26) 37 (74)	 13 (26) 37 (74)	1.00
Grade, *n* (%): Степень злокачественности опухоли, *n* (%): 1 2 3	 2 (4.3) 23 (48.9) 22 (46.8)	 1 (2.1) 15 (31.9) 31 (66)	0.17
Number of tumor foci, *n* (%): Число опухолевых очагов, *n* (%): single единственный multiple множественные	 27 (54) 23 (46)	 29 (58) 21 (42)	0.69
Stage of tumor, *n* (%): Стадия опухоли, *n* (%): Ta T1 carcinoma *in situ* карцинома *in situ*	 20 (40) 27 (54) 3 (6)	 16 (32) 31 (62) 3 (6)	0.69

Note. *Here and in tables 2, 3: BCG – bacillus Calmette–Guérin; GEM – gemcitabine.*
Примечание. *Здесь и в табл. 2, 3: BCG – бацилла Кальметта–Герена; GEM – гемцитабин.*

Table 2. *Efficacy analysis*

Таблица 2. *Анализ эффективности*

Outcome **Исход**	**BCG group, *n* (%)** **Группа BCG, *n* (%)**	**GEM group, *n* (%)** **Группа GEM, *n* (%)**	**Total, *n* (%)** **Всего, *n* (%)**	***p***
Disease free Без рецидива	38 (76)	44 (88)	82 (82)	0.128
Recurrence Рецидив	5 (10)	1 (2)	6 (6)	0.2
Progression Прогрессирование	7 (14)	5 (10)	17 (34)	0.06
Total *Всего*	50	50	100	

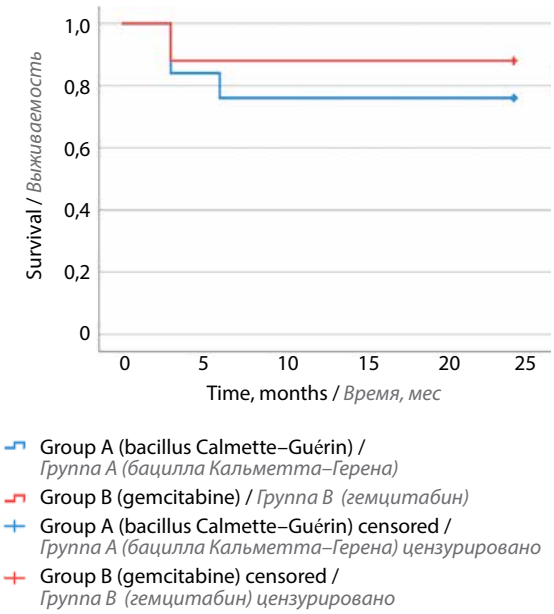

Fig. 2. *Kaplan–Meier survival curve: the median tumor recurrence-free survival time of gemcitabine group was 88 %; while the median tumor recurrence-free survival time of BCG group was 76 %. The mean (SE: 95 % confidence interval) survival time was 20.34 (0.78; 18.8–21.8) months*
Рис. 2. *Кривая выживаемости Каплана–Майера: медиана числа пациентов без рецидива в группе гемцитабина к концу исследования составила 88 %, в группе BCG – 76 %. Средняя выживаемость (СО; 95 % доверительный интервал) составила 20,34 (0,78; 18,8–21,8) мес*

in 5 patients with GEM but 7 with BCG (2 cases after first induction cycle). Considering possible confounding factors, the patients' age, gender, tumor number, tumor diameter, tumor stage, tumor grade and bladder perfusion scheme were included.

Comparison of main adverse reactions and side-effects between the two groups (Table 3). No toxicity (side effects) of both drugs reported in 21 patients in GEM group (42 %) but only in 5 patients in BCG group (10 %). The adverse reactions of the two groups were mainly dysuria, gross hematuria, fever, nausea and vomiting. The most common grade I side effect was dysuria reported in 25 patients in group A (50 %) and in 20 patients in group B (40 %). The incidence of fever and gross hematuria (grade II adverse events) in BCG group was significantly higher than those in GEM group (p <0.05) but grade III adverse events occur only in BCG group. There was no significant difference on the other side-effects (frequency, bladder irritability) between the two groups (p >0.05).

Discussion

Intravesical BCG has been used in the treatment of superficial bladder cancer for more than 30 years, with effectiveness demonstrated in randomized trials. Four meta-analyses have confirmed its efficacy after TURBT [19–22]. However, at least 40–45 % of patients have residual tumors after initial treatment and 20 % of these are truly refractory [23]. Multiple studies have investigated various intravesical options including MMC, and GEM. The MMC infusions have shown a response rate of 40–50 %, though found to be slightly less efficacious than BCG and less well tolerated with more chemical cystitis and allergic reactions with MMC [24–26]. Though epirubicin was shown to be more beneficial than TURBT alone, it was inferior to adjuvant BCG therapy in the post-TURBT setting [27]. GEM is generally not used as first-line therapy intravesical due to the lack of clinical trial evidence comparing GEM with BCG. Nation-wide shortage of BCG resulted in the widespread use of intravesical GEM in first-line settings. In our present study, we analyzed prospective data to compare the efficacy and toxicity of BCG and GEM. We noted a trend toward better DFS in the GEM group with fewer side effects. Eighty-eight percent of patients remained disease free in the GEM group, compared with 76 % in the BCG group at the end of two years (Table 2). In the GEM group, recurrence occurs without progression but in the BCG group recurrence with progression in 5 patients. Stage progression without recurrence to MIBC in 5 patients with GEM but 7 with BCG. Though numerically more patients benefited from intravesical GEM in our study population including those with high-grade NMIBC. The EAU risk groups and the grade of the tumor were dependently associated with recurrence. This study suggests that GEM could be a potentially important therapeutic option for NMIBC, in the first-line setting. It supports the results of a phase 2 randomized controlled study comparing BCG and GEM by Di Lorenzo et al., which showed significant improvement in DFS and lower recurrence rate with GEM [15] in those who failed initial BCG therapy. A randomized controlled phase 3 trial in the first line setting with a larger number is required to clarify the place of GEM therapy.

In terms of toxicity, intravesical GEM has a favorable toxicity profile that is consistent with earlier research [3]. Five patients in the BCG group (ten percent) and 21 patients in the GEM group (twenty-one percent) did not experience any toxicity (side effects) from either treatment (p = 0.002). Overall, patients responded well to GEM, experiencing fewer grade I side effects (dysuria) than with BCG without static significance; however grade II and grade III side effects statistically significant (p = 0.01, 0.03; Table 3) respectively, patients experienced less grade II (gross hematuria, fever) with GEM than with BCG and grade III (allergy, BCGosis) side effects only in BCG group rather than GEM (18 % and 0 %) respectively. Those who had BCG were more likely to use antibiotics and interrupt their treatments, two patients experienced systemic BCG infection, necessitating systemic antituberculosis therapy.

Table 3. *Side effects analysis*
Таблица 3. *Анализ побочных явлений*

Adverse event Нежелательное явление		BCG group, *n* (%) Группа BCG, *n* (%)	GEM group, *n* (%) Группа GEM, *n* (%)	*p*
None Нет		5 (10)	21 (42)	0.002
Grade I Степень I	Dysuria Дизурия	25 (50)	20 (40)	0.32
Grade II Степень II	Fever Лихорадка	9 (18)	0	0.001
	Hematuria Гематурия	13 (26)	9 (18)	
Grade III Степень III	Allergic reaction Аллергическая реакция	7 (14)	0	0.003
	Systemic BCG infection Системная BCG-инфекция	2 (4)	0	
Total *Всего*		50	50	

Conclusion

In summary, when compared to BCG, GEM had a clinically significantly better toxicity profile and a similar (with a trend towards greater) DFS. Although intravesical BCG is still the preferred first-line adjuvant therapy, GEM may be a viable alternative for individuals who are not candidates for intravesical BCG therapy or who have experienced a BCG relapse. Due to its improved tolerability and lower incidence of adverse effects, GEM may also be used as a first-line treatment for older patients as well as for individuals who are at a high risk of contracting systemic BCG infection, such as those with immune system disorders or recurrent hematuria. Our results should support and inspire a potential alternative to BCG shortage.

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Authors' contributions
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