Original Article

Efficacy and toxicity in scheduled intravesical gemcitabine versus Bacille Calmette-Guérin for Ta and T1 bladder cancer: a systematic review and meta-analysis

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Background: We conducted a meta-analysis to compare the efficacy and toxicity of scheduled intravesical gemcitabine (GEM) and Bacille Calmette-Guérin (BCG) for Ta and T1 non-muscle invasive bladder cancer (NMIBC).

Methods: The database search was performed in Ovid Medline, Embase, Web of Science, Cochrane Library from the commencement of the database to July 7, 2020. Trials using immediate instillation were excluded and we present the included studies in accordance with the PRISMA 2020 reporting checklist. The data extracted was analyzed using Stata 11.0 software.

Results: Six studies of 466 patients comparing GEM and BCG were finally included. No significant difference was detected between GEM and BCG group in recurrence free survival [hazard ratio (HR) =0.80, 95% confidence interval (95% CI), 0.46–1.37, P=0.410], progression free survival (HR =0.82, 95% CI, 0.38–1.77, P=0.621), and total adverse events [odds ratio (OR) =0.70, 95% CI, 0.38–1.29, P=0.253]. However, patients receiving GEM treatment are less likely to develop urinary adverse events, such as dysuria (OR =0.50, 95% CI, 0.29–0.87) and hematuria (OR =0.40, 95% CI, 0.18–0.91). We performed subgroup analysis and found that the effects of GEM and BCG were similar even on patients with high recurrence risk tumor. Sensitivity analysis showed the robustness of the results.

Discussion: Scheduled intravesical GEM instillation has a similar effect with BCG instillation in preventing NMIBC recurrence and progression, but GEM therapy causes a lower incidence of dysuria and hematuria than BCG. GEM may be an alternative therapy for BCG. However, the results should be treated with caution due to the low to moderate quality of the included studies.

Keywords: Gemcitabine; Bacille Calmette-Guérin (BCG); non-muscle invasive bladder cancer (NMIBC); meta-analysis; tumor recurrence

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Introduction

Intravesical Bacille Calmette-Guérin (BCG) instillation after transurethral resection of bladder tumor (TURBT) has been the standard treatment of intermediate- and high-risk non-muscle invasive bladder cancer (NMIBC) in the last decade (1). However, 35.2–40.4% of patients will relapse in the short term after BCG instillation (2,3). The patients who progress to muscle invasive bladder cancers (MIBCs), accounting for one-third of NMIBC patients receiving BCG treatment, have a much poor prognosis and quality of life (3-5). The high incidence of local and systemic complications of BCG instillation negatively impacts patient's compliance and leads to a high proportion of withdrawal (6,7). After two manufacturers announced the halt or severe reduction of BCG production, BCG strain is under a worldwide shortage (8). The development of alternative treatment with better efficacy and tolerance is imperative.

Gemcitabine (GEM) is an antimetabolite pyrimidine analog with a broad spectrum of antitumor activity. Recent researches investigated its preventive effect on tumor recurrence and progression in NMIBC compared with BCG, but indicating opposite outcomes. A randomized controlled trial (RCT) recruited high risk superficial bladder cancer and found that the recurrence rate was 28.1% for the BCG group and 53.1% for the GEM group (9). Conversely, another phase 2 RCT revealed that intravesical GEM could significantly improve recurrence-free survival (RFS) than BCG in BCG failure patients with high-risk NMIBC (10). A systematic review with qualitative synthesis is required to clarify whether GEM can be an alternative drug for BCG.

A previous meta-analysis included four RCTs and one case-control study, identifying similar efficacy when compared GEM to BCG (11). The study synthesized evidence using risk ratio instead of hazard ratio (HR), which might ignore time effect for RFS and progression-free survival (PFS). Furthermore, a multicenter RCT meeting the selection criteria was not included in this study (10). Therefore, the present work aims to evaluate the efficacy and toxicity of scheduled GEM and BCG in patients with NMIBC using extracted HR. We present the following article in accordance with the PRISMA reporting checklist (12) (available at https://dx.doi.org/10.21037/tcr-21-291).

Methods

Data sources and search strategy

The literature search was conducted by two reviewers (JL Lu and QD Xia). We retrieved four electronic databases (Ovid Medline, Embase, Web of Science, Cochrane Library) from the commencement of the database to July 7, 2020, without language restrictions. Grey literature was searched in the American Society of Clinical Oncology (ASCO) conference abstract, the European Society of Medical Oncology (ESMO) conference abstract, and the National Institute of Health (NIH) website (www.clinicaltrials.gov). The search terms were used in the following strategy: (bladder tumor OR bladder cancer OR urinary bladder neoplasm OR bladder neoplasm OR bladder carcinoma OR urothelium carcinoma OR urothelium tumor) AND (((((non or not) AND (invas* OR invad* OR infiltrat*)) OR noninvas* OR noninvad* OR noninfiltrat*) AND muscle*) OR (cis OR Tis OR Ta OR T1a OR T1b OR superficial)) AND (Bacillus Calmette Guerin OR BCG OR gemcitabine OR GEM). Disagreement during study selection was resolved by consensus with a supervisor (SG Wang).

Inclusion and exclusion criteria

Both prospective study and retrospective study were eligible. The inclusion criteria were as follows: (I) participants were diagnosed as Ta or T1 with/without carcinoma *in situ* NMIBC; (II) intravesical GEM and BCG treatments after TURBT were compared; (III) HRs were available for RFS or PFS. The exclusion criteria were as follows: (I) immediate instillation of GEM; (II) sequential or alternate instillation of intravesical drug; (III) single arm trial. If one research was reported in more than one publication, the most recent study was included.

Data extraction

Two authors (JL Lu and QD Xia) independently extracted data using a predefined form. The primary outcomes of interest were RFS or PFS after instillation of GEM and BCG. Secondary outcomes were overall survival (OS) or the number of deaths, quality of life, and the number of adverse events. Study characteristics (study design, publication year, country of origin, study period, and the number of patients),

patient characteristics (sex and age), tumor characteristics (stage, grade, risk of recurrence, history of treatment, and primary/recurrence), intervention (dosage, schedule, and manufacturer), and outcomes were extracted. HRs for RFS and PFS were calculated under the guidance of previous studies (13,14).

Quality assessment

The quality of RCT was evaluated based on the Cochrane tool for risk of bias assessment (RoB2) (15). The revised RoB2 tool included five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Non-randomized prospective studies were ranked by the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) (16). The quality of the case-control study was assessed using the Newcastle–Ottawa Scale criteria (NOS), which includes three main domains: the selection of patients, comparability between groups, and measurement of exposure (17). Disagreements were resolved by discussion with a third author (SG Wang).

Statistical analysis

The meta-analysis was conducted using Stata 11.0 software. The pooled effect sizes under the random-effect model for RFS and PFS were obtained as HR with 95% confidence interval (CI) of each study, whereas we used odds ratio (OR) with 95% CI to estimate the risk of adverse events in patients treated with GEM and BCG. The methodological and clinical heterogeneity were assessed by Cochrane Q statistic and I^2 statistic. The heterogeneity was considered significant when $P<0.05$ and $I^2>50\%$. Moreover, subgroup analyses were performed in reference to study design, study origin, study center, schedule of therapy, and risk of tumor recurrence. We conducted a sensitivity analysis by omitting the study one by one to assess the robustness of the results.

Results

Study characteristics

From 8,639 publications, six studies with 466 patients are finally included (*Figure 1*) (9,10,18-21). The characteristics of the included studies are summarized in *Table 1*. Four studies are RCT with moderate to high risk of bias. One study is a non-randomized prospective study of serious

risk of bias. One study is a case-control study of high quality. The details of quality assessment can be obtained in supplementary file.

RFS and PFS

All six-studies report recurrence free survival for GEM and BCG (*Figure 2*). The efficacy in preventing tumor recurrence is comparable between GEM and BCG [HR, 0.80 (95% CI, 0.46–1.37), P for effect size, 0.410], showing a high level of heterogeneity (Cochrane Q =17.25, P for heterogeneity =0.004; I^2=71.0%). Four studies report progression free survival (*Figure 2*). The pooled effect also demonstrates a comparative efficacy in progression prophylaxis [GEM *vs.* BCG: HR, 0.82 (95% CI, 0.38–1.77), P for effect size, 0.621] with a low level of heterogeneity (Cochrane Q =3.50, P for heterogeneity =0.321; I^2=14.3%).

Adverse events

The adverse events during GEM or BCG instillation are dysuria, hematuria, fever, neutropenia-thrombocytopenia, dermatitis, nausea-vomiting, urinary frequency, bladder spasms, urge incontinence, itching, skin rash, cystitis, urosepsis, suprapubic discomfort, and systemic BCG infection. The qualitative synthesis is performed when at least two studies report the same outcome (*Figure 3*). The meta-analysis shows that the proportion of patients who develop adverse events is comparable between GEM and BCG group [OR, 0.70 (95% CI, 0.38–1.29), P for effect size, 0.253] with a high level of heterogeneity (Cochrane Q =6.50, P for heterogeneity =0.090; I^2=53.8%). However, patients receiving GEM are less likely to develop dysuria [OR, 0.50 (95% CI, 0.29–0.87), P for effect size, 0.014] or hematuria [OR, 0.40 (95% CI, 0.18–0.91), P for effect size, 0.028]. Fever events are similar between the two groups [OR, 0.46 (95% CI, 0.16–1.34), P for effect size, 0.156].

Subgroup analysis and sensitivity analysis

Subgroup analysis in reference to RFS is conducted to examine the sources of heterogeneity (*Table 2*). Subgroups include study, intervention, and tumor characteristics, such as study design, study origin, study center, schedule, and risk of recurrence. However, the level of heterogeneity for the subgroup is similar to that for the total effect, indicating that the heterogeneity is not originated from these study features. *Figure 4* shows the results of sensitivity analysis
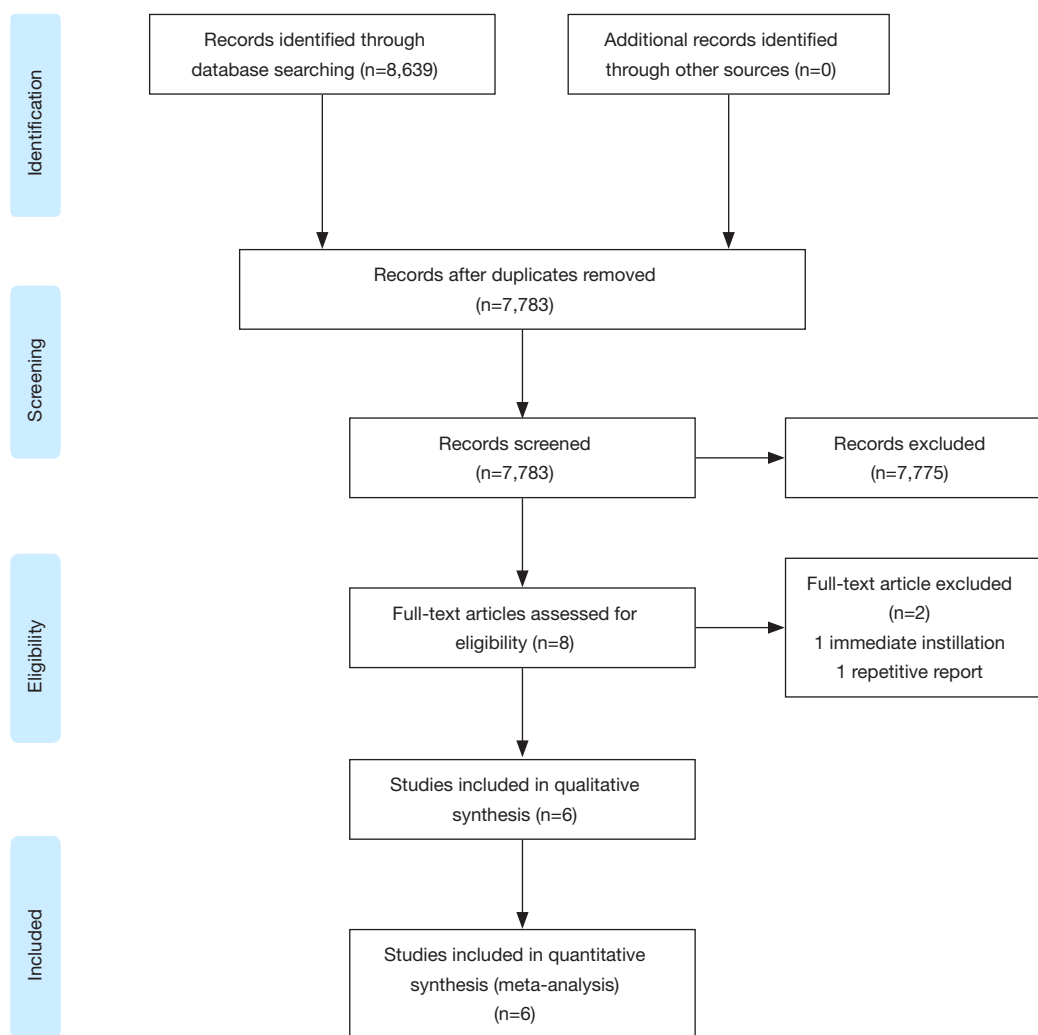
Figure 1 Study selection flowchart.

for both RFS and PFS. All the pooled effect sizes after omitting study are in the 95% CI range of overall effect size, reflecting the robustness of the results.

Discussion

In this study, we carried out a systematic review and meta-analysis to evaluate the efficacy and toxicity of GEM and BCG in patients with NMIBC. The results demonstrated that GEM and BCG had similar effects in preventing tumor recurrence and progression. In a subgroup of patients with high risk of recurrence, the result did not display an advantage in any of the drugs. However, compared with BCG, patients treated with GEM were less likely to develop dysuria and hematuria. Although the number of adverse

events was equal between the two drugs, patients treated with BCG seemed to be more likely to have multiple adverse events at the same time. These results showed that GEM had a favorable efficacy and less toxicity, revealing that it could be used as an alternative to BCG.

Gemcitabine, as a systematic chemotherapeutic agent, has been used to treat many types of tumor, such as bladder cancer, pancreatic adenocarcinoma, non-small cell lung cancer, and breast cancer (22-24). In bladder cancer, GEM combined with a platinum chemotherapeutic drug is the standard treatment of MIBC, which indicating its efficacy in intravenous application (1). In recent years, GEM has also been used to treat NMIBC through intravesical instillation, including immediate instillation and maintenance instillation. Clinical trials of these two instillation strategies

Table 1 Characteristics of the included study

Study	Country	No. of patients	Male	Age (years), Gem/BCG	Tumor characteristics	GEM		BCG		Outcomes	Follow-up
						Dosage	No. of instillations	Dosage	No. of instillations		
Gacci et al. 2006 (18)	Italy	19	78.95%	74/73.6	Recurrent, BCG refractory, pT1G3	2,000 mg/50 mL	21	5×10^8 cfu/50 mL (OncoTICE)	11	RFS; PFS; AE	Gem: 18.4M; BCG: 19.9M
Di Lorenzo et al. 2010 (10)	Italy	80	61.25%	69.3/71.4	BCG failure, high risk	2,000 mg/50 mL	15	81 mg/50 mL (Connaught)	18	RFS; PR; AE	19M
Porena et al. 2010 (9)	Italy	64	84.38%	70.2/68.7	High risk	2,000 mg/50 mL	13	5×10^8 cfu/50 mL (Organon)	13	RFS; AE	44M
Bendary et al. 2011 (19)	Egypt	80	NA	56.2±11.18	Primary Ta-T1	2,000 mg/50 mL	6	6×10^8 cfu/50 mL	6	RFS; AE	10.8±2.7M
Gontero et al. 2013 (20)	Italy	120	85.8%	67.4/67.5	Intermediate risk	2,000 mg/50 mL	18	27 mg/50 mL (Immucyst)	15	RFS; PFS; AE	12M
Prasanna et al. 2017 (21)	Australia	103	83.5%	78/77	Unspecified risk	2,000 mg/50 mL	6(low risk); 6+X (median or high risk)	5×10^8 cfu/50 mL (OncoTICE)	6 (low risk); 6+X (median or high risk)	RFS; PFS; AE	15M

GEM, gemcitabine; BCG, Bacille Calmette-Guérin; CFU, colony forming unit; DFS, disease-free survival; PR, progression rate; rr, recurrence rate; AE, adverse event.
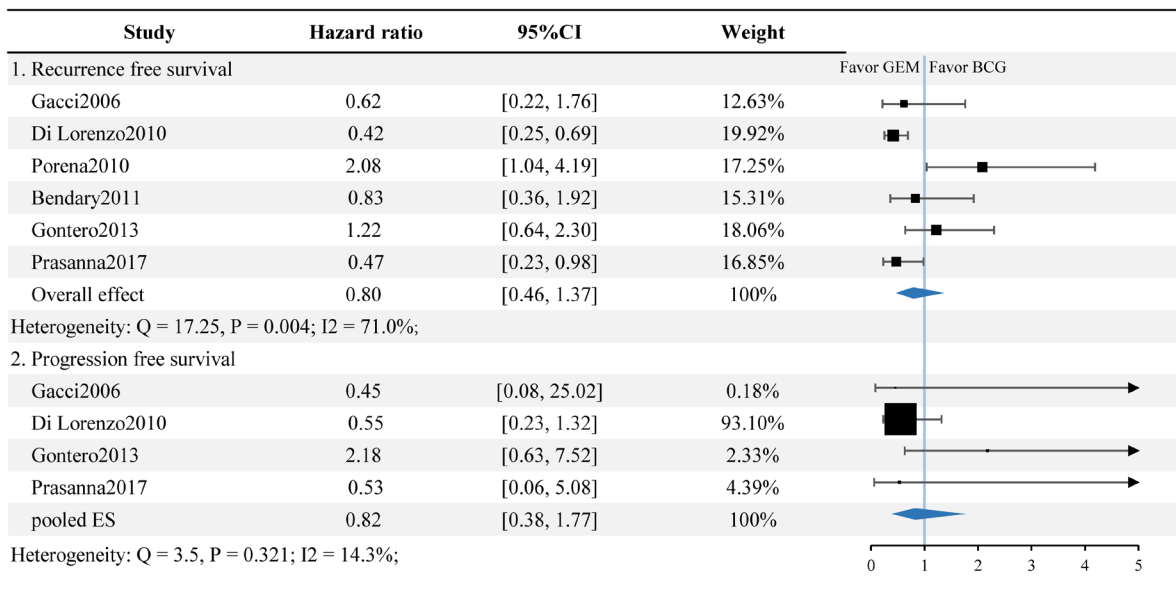

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Study	Hazard ratio	95%CI	Weight	
1. Recurrence free survival				Favor GEM / Favor BCG
Gacci2006	0.62	[0.22, 1.76]	12.63%	
Di Lorenzo2010	0.42	[0.25, 0.69]	19.92%	
Porena2010	2.08	[1.04, 4.19]	17.25%	
Bendary2011	0.83	[0.36, 1.92]	15.31%	
Gontero2013	1.22	[0.64, 2.30]	18.06%	
Prasanna2017	0.47	[0.23, 0.98]	16.85%	
Overall effect	0.80	[0.46, 1.37]	100%	
Heterogeneity: Q = 17.25, P = 0.004; I2 = 71.0%;				
2. Progression free survival				
Gacci2006	0.45	[0.08, 25.02]	0.18%	
Di Lorenzo2010	0.55	[0.23, 1.32]	93.10%	
Gontero2013	2.18	[0.63, 7.52]	2.33%	
Prasanna2017	0.53	[0.06, 5.08]	4.39%	
pooled ES	0.82	[0.38, 1.77]	100%	
Heterogeneity: Q = 3.5, P = 0.321; I2 = 14.3%;				

Figure 2 Forest plot for recurrence free survival and progression free survival.

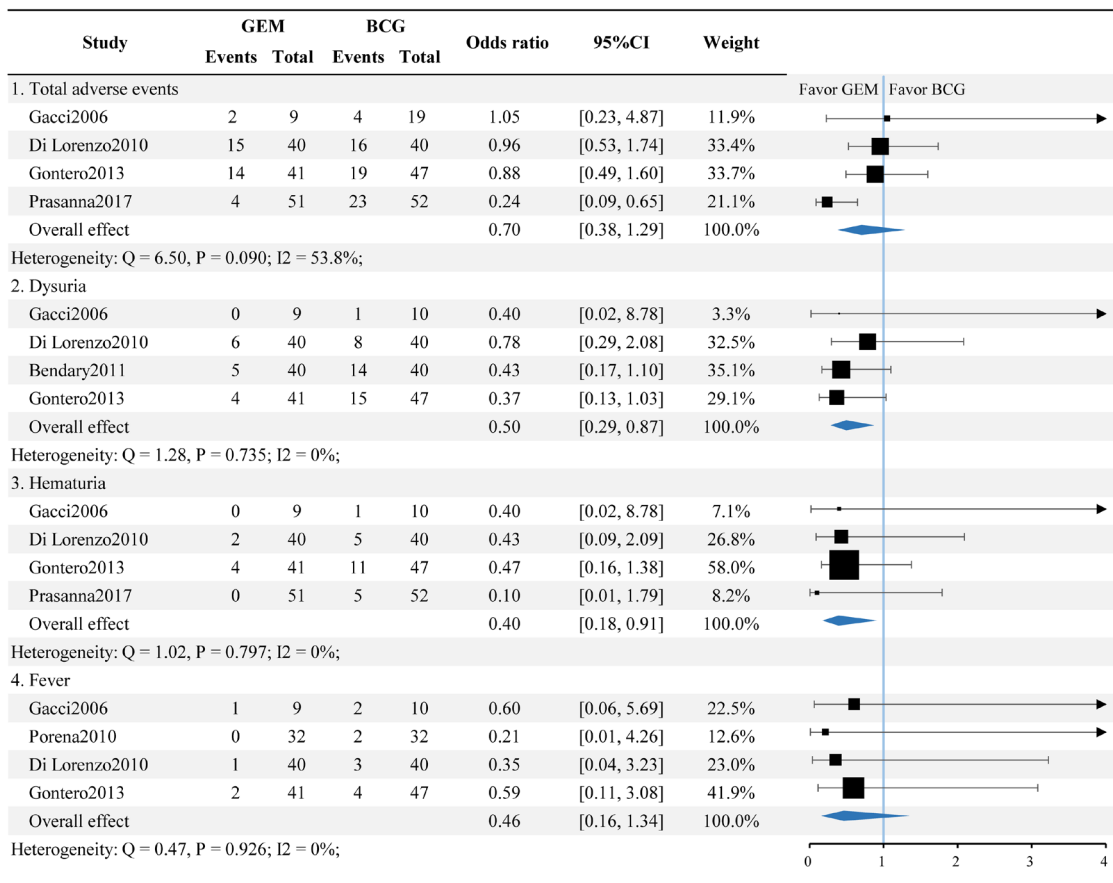| Study	GEM Events	Total	BCG Events	Total	Odds ratio	95%CI	Weight	
1. Total adverse events								Favor GEM / Favor BCG
Gacci2006	2	9	4	19	1.05	[0.23, 4.87]	11.9%	
Di Lorenzo2010	15	40	16	40	0.96	[0.53, 1.74]	33.4%	
Gontero2013	14	41	19	47	0.88	[0.49, 1.60]	33.7%	
Prasanna2017	4	51	23	52	0.24	[0.09, 0.65]	21.1%	
Overall effect					0.70	[0.38, 1.29]	100.0%	
Heterogeneity: Q = 6.50, P = 0.090; I2 = 53.8%;								
2. Dysuria								
Gacci2006	0	9	1	10	0.40	[0.02, 8.78]	3.3%	
Di Lorenzo2010	6	40	8	40	0.78	[0.29, 2.08]	32.5%	
Bendary2011	5	40	14	40	0.43	[0.17, 1.10]	35.1%	
Gontero2013	4	41	15	47	0.37	[0.13, 1.03]	29.1%	
Overall effect					0.50	[0.29, 0.87]	100.0%	
Heterogeneity: Q = 1.28, P = 0.735; I2 = 0%;								
3. Hematuria								
Gacci2006	0	9	1	10	0.40	[0.02, 8.78]	7.1%	
Di Lorenzo2010	2	40	5	40	0.43	[0.09, 2.09]	26.8%	
Gontero2013	4	41	11	47	0.47	[0.16, 1.38]	58.0%	
Prasanna2017	0	51	5	52	0.10	[0.01, 1.79]	8.2%	
Overall effect					0.40	[0.18, 0.91]	100.0%	
Heterogeneity: Q = 1.02, P = 0.797; I2 = 0%;								
4. Fever								
Gacci2006	1	9	2	10	0.60	[0.06, 5.69]	22.5%	
Porena2010	0	32	2	32	0.21	[0.01, 4.26]	12.6%	
Di Lorenzo2010	1	40	3	40	0.35	[0.04, 3.23]	23.0%	
Gontero2013	2	41	4	47	0.59	[0.11, 3.08]	41.9%	
Overall effect					0.46	[0.16, 1.34]	100.0%	
Heterogeneity: Q = 0.47, P = 0.926; I2 = 0%;								

Figure 3 Forest plot for adverse events.

Table 2 Subgroup analysis for recurrence free survival (GEM *vs.* BCG)

Subgroup	No. of study	Hazard ratio	95% CI	Heterogeneity Q	P_h	I^2
Study design						
RCT	4	0.95	[0.46, 1.98]	14.98	0.002	80.0%
Non-randomized prospective study	1	0.62	[0.22, 1.76]	–	–	–
CCS	1	0.47	[0.23, 0.97]	–	–	–
Study origin						
Europe	4	0.90	[0.41, 1.97]	15.30	0.002	80.4%
Africa	1	0.83	[0.36, 1.92]	–	–	–
Oceania	1	0.47	[0.23, 0.97]	–	–	–
Study center						
Multiple	3	0.62	[0.32, 1.21]	7.06	0.029	71.7%
Single	2	1.21	[0.37, 3.96]	3.57	0.059	72.0%
Schedule						
Maintenance	4	0.90	[0.41, 1.97]	15.30	0.002	80.4%
Induction	1	0.83	[0.36, 1.92]	–	–	–
Risk of recurrence						
High risk	3	0.81	[0.28, 2.39]	13.32	0.001	85.0%
Intermediate risk	1	1.22	[0.64, 2.31]	–	–	–
Unspecified risk	2	0.60	[0.35, 1.04]	1.01	0.314	1.30%

RCT, randomized controlled trial; CCS, case-control study; P_h, P for heterogeneity.

demonstrated that GEM could prevent bladder tumor recurrence effectively (10,25). Especially in patients with high risk or BCG failure NMIBC, the effect of GEM was promising.

In the meta-analysis, two studies recruit BCG failure patients. Di Lorenzo *et al.* found that 52.5% of patients developed disease recurrence after GEM treatment, whereas 87.5% of patients relapsed after BCG treatment (10). Another pilot study includes a total of 19 participants with pT1G3 tumor (18). Three in nine patients are recurrence-free after GEM instillation (18). However, in BCG group, only one patient is disease-free, and two patients die (18). A retrospective study with 69 patients analyzed the effect of GEM in different BCG failure types (BCG refractory, BCG resistant, BCG recurrent, and BCG intolerant) (26). The overall recurrence rate is reported as 66.7%, and no difference is detected between BCG refractory and other BCG failure types (26). These results provide a feasible conservative treatment for patients with

BCG failure independent of failure type. In the meta-analysis, we perform a subgroup analysis by different risks of recurrence. All subgroups (high risk, intermediate-risk, and unspecified risk) show comparable efficacies between GEM and BCG. In unspecified risk subgroup, GEM treatment is more effective than BCG treatment but this is not statistically significant [HR =0.60 (0.35–1.04)]. Further studies of GEM treatment for non-high-risk tumor are required.

The total incidence of adverse events is similar between BCG and GEM groups. Patients treated with BCG are more likely to suffer urinary adverse events, such as dysuria, hematuria, cystitis, and even urosepsis (20,21). This may be due to the strong local immune response of urothelial cells to live-attenuated *Mycobacterium Bovis*. Nevertheless, GEM is more likely to cause gastrointestinal tract and skin reactions, such as nausea and dermatitis, even though the incidence is rather low (10,20). Gontero *et al.* measured the quality of life of patients receiving GEM and BCG (20).
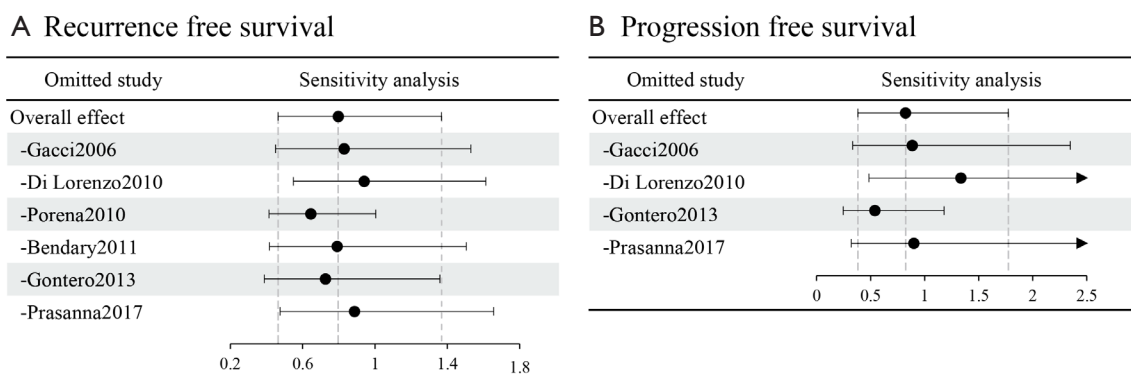
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A Recurrence free survival

B Progression free survival

Figure 4 Sensitivity analysis for (A) recurrence free survival and (B) progression free survival.

The cognitive functioning score is significantly decreased in BCG group than GEM group over time (20). These results conclude that GEM treatment is associated with less toxicity than BCG treatment during regular instillation.

This study combines 6 original studies and provided an alternative intravesical therapy for BCG. The subgroup and sensitivity analysis reveal the robustness of the results. But there are still several limitations. The main limitation is the quality of the included studies. Three studies are of high risk of bias, and two studies are not randomized trials. Considering that different study types are included, we perform subgroup analysis and indicate similar effect sizes between different study designs. Another limitation is the small number of included studies and participants. It disenables the performance of publication bias tests and meta-regression to detect confounding factors. Further well design double-blind RCTs are required to assess the efficacy of scheduled GEM intravesical therapy in patients with NMIBC.

Conclusions

Scheduled intravesical GEM instillation has a similar effect with BCG instillation in preventing NMIBC recurrence and progression, but GEM therapy causes a lower incidence of dysuria and hematuria than BCG. GEM may be an alternative therapy for BCG. However, the results should be treated with caution due to the low to moderate quality of the included studies.

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Footnote

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Table S1 Quality assessment using the Newcastle-Ottawa Scale for case-control study

| Study	Selection				Comparability	Outcomes			Scores
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Prasanna, et al., 2017									8
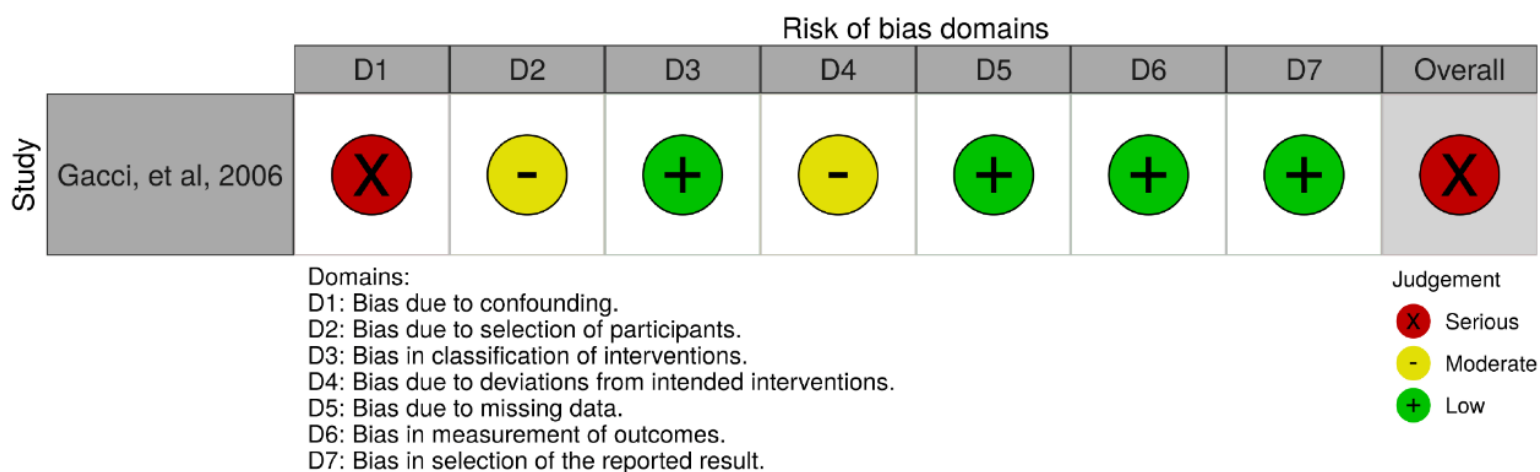
Figure S1 Quality assessment using the Risk Of Bias In Non-randomized Studies of Interventions for prospective intervention study.
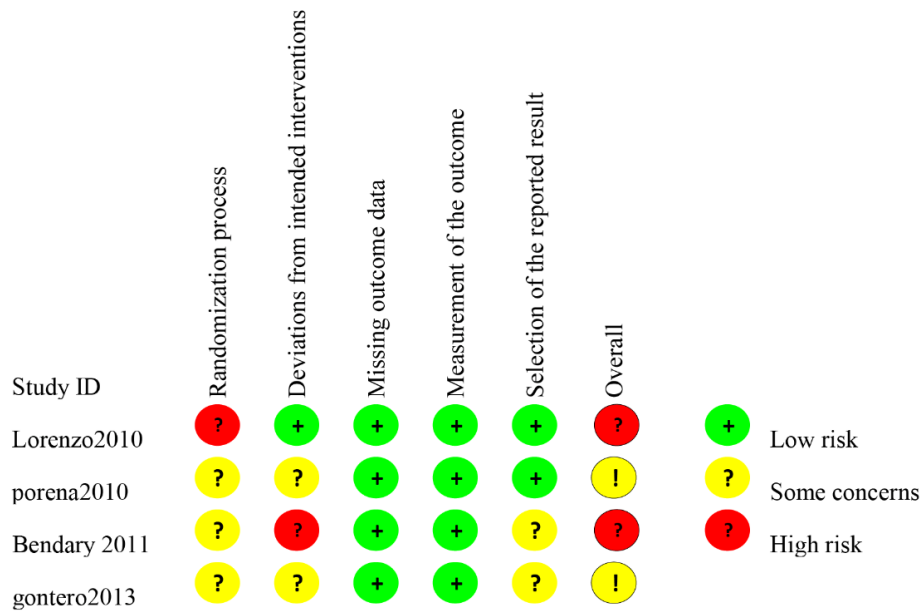
Figure S2 Quality assessment using RoB 2 for randomized controlled study.
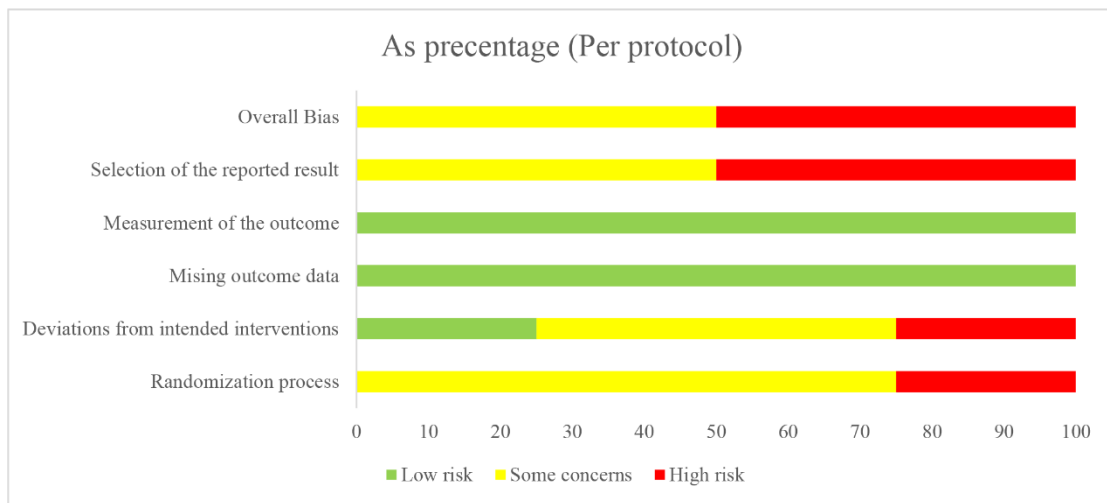

Figure S3 Quality assessment summary using RoB 2 for randomized controlled study.