Intravesical gemcitabine vs. intravesical Bacillus-Calmette-Guérin for non-muscle invasive bladder cancer: A systematic review and meta-analysis

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Abstract. Non-muscle invasive bladder cancer (NMIBC) remains a major disease burden worldwide. Although Bacillus Calmette-Guérin (BCG) immunotherapy is among the first-line treatments for NMIBC, it is associated with a high rate of adverse events. The present systematic review aimed to compare the efficacy and safety of intravesical gemcitabine and BCG immunotherapy in patients with NMIBC. For this purpose, a literature search was conducted using the PubMed, Cochrane, ProQuest and EBSCOhost databases, accompanied by citation searching. Eligible articles were critically appraised, assessed for risk of bias and analyzed using random-effects meta-analysis. In total, five studies comprising 447 patients were included. From four randomized controlled trials, gemcitabine was shown to be non-inferior to BCG in terms of preventing recurrence [relative risk (RR), 0.97; 95% confidence interval (CI), 0.58-1.60; high heterogeneity (I^2=72.9%, P=0.011) and progression, 1.02 (0.54-1.93); and low heterogeneity (I^2=0.0%, P=0.766)]. The overall risk of adverse events (RR, 0.78; 95% CI, 0.53-1.13; I^2=11.8%, P=0.322) and severe adverse events were similar between the groups (RR, 0.67; 95% CI, 0.25-1.77; I^2=0.0%, P=0.402). However, gemcitabine was associated with a lower risk of developing dysuria (four studies; RR, 0.59; 95% CI, 0.39-0.89); I^2=0.0%, P=0.674) and fever (three studies; RR, 0.17; 95% CI, 0.04-0.76; I^2=0.0%, P=0.569), and urinary frequency (one study; RR, 0.22; 95% CI, 0.13-0.37) and itching (one study; RR, 0.34; 95% CI, 0.18-0.64) were lower in patients receiving gemcitabine. Stratified analyses yielded consistent results in patients both at high-risk and low-to-intermediate risk. On the whole, the present study demonstrates that intravesical gemcitabine was non-inferior to BCG immunotherapy in preventing the recurrence and progression of NMIBC. Although the overall adverse event rates were similar, gemcitabine was less frequently associated with dysuria, fever, urinary frequency and itching.

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Introduction

Bladder cancer is a common malignancy that ranks as the 9th most frequently diagnosed malignancy worldwide. This type of cancer is also ranked 13th in terms of mortality rates, with developing countries having higher mortality rates than developed countries (1). Non-muscle invasive bladder cancer (NMIBC) is a subset of bladder cancer that comprises tumors of stage Ta, T1 and carcinoma *in situ* (CIS). It is estimated that NMIBC accounts for 70-75% of all diagnosed cases of bladder cancer (2,3).

NMIBC is known to have a high recurrence and progression rate that depends on the tumor risk profile with the chance of recurrence at 1 year ranging between 15-61% and 31-78% at 5 years. Progression rates also vary significantly, with the 1-year progression rate into muscle invasive metastatic bladder cancer (MIBC) ranging from 0.2-17%, and increasing to 0.8-45% at 5 years (2). Mortality rates associated with NMIBC are relatively lower than those associated with MIBC, and increases with higher-risk tumor features. In patients with low-grade Ta tumors, the 15-year progression-free survival is 95% with no cancer-specific mortality. This decreases to 61% in Ta high-grade Ta tumors, with a disease-specific mortality of 26%. Patients with T1 tumors have a progression-free survival rate of 44%, with a disease-specific mortality reaching 38% (4). When progression to MIBC occurs, patients are expected to have a poor prognosis, with a 5-year mortality rate of 50-70% even following radical cystectomy (5).

Bladder cancer is among the types of cancer affecting the elderly with the highest treatment costs, with an estimated economic burden of approximately US $4 billion per year. This high cost is attributed to the need for lifelong cystoscopic surveillance and multiple treatment modalities (6). Transurethral resection of bladder tumor (TURBT) is the initial treatment of choice, where the tumor is resected using a resectoscope inserted via the urethra. In this procedure, it is recommended that all visible tumors be resected along with

the underlying detrusor muscle (7). It is known that the risk of upstaging NMIBC (≥T2) increases up to 49% in the case that the detrusor muscle is not obtained during resection (8). TURBT is also associated with a high recurrence rate, with a 5-year recurrence reaching 42% for T1 tumors (9). To mitigate this risk, clinicians usually recommend a second TURBT and adjuvant therapy. The instillation of intravesical chemotherapy is recommended by the European Association of Urologist (EAU) to reduce the recurrence rate (10). A previous meta-analysis demonstrated that immediate post-operative intravesical chemotherapy reduced recurrence to 37% compared to 48% with TURBT alone (11). Several agents, such as mitomycin C, epirubicin, doxorubicin and gemcitabine are used for this purpose. Mitomycin C is the most commonly studied drug; however, it is currently not available in Indonesia (12).

Immunotherapy using bacillus Calmette-Guérin (BCG) is a widely-recognized first line agent for managing high-risk NMIBC, according to the European Organization for Research and Treatment of Cancer (EORTC) risk calculator (13,14). Currently, The EAU Guidelines suggest that BCG following TURBT is more effective in preventing recurrence than TURBT alone or TURBT with intravesical chemotherapy (10). Despite its efficacy, BCG is associated with a greater number of side-effects than chemotherapy (15).

Given the high economic burden associated with NMIBC, the careful and evidence-based selection of treatment modalities is essential for optimizing outcomes and efficiency. There is a need to compare intravesical chemotherapy agents other than mitomycin C with first-line BCG immunotherapy in the Indonesian setting. The present study aimed to investigate the efficacy and safety of gemcitabine-based intravesical chemotherapy vs. BCG immunotherapy in order to provide a clearer perspective on which treatment provides a better prognostic value for patients with NMIBC.

Data and methods

Eligibility criteria. The present systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines. The inclusion criteria were randomized controlled trials (RCTs) and observational studies of patients diagnosed with NMIBC comparing the efficacy of and safety between gemcitabine and BCG immunotherapy following TURBT. Only English-language articles with available full-texts were included. No date restrictions were applied. Editorials, commentaries, case reports and review articles were excluded. The selected studies were then critically appraised for validity, importance and applicability using the checklist from Oxford's Centre of Evidence Based Medicine (CEBM) (https://www.cebm.ox.ac.uk/resources/ebm-tools/critical-appraisal-tools).

Search strategy. A database search was conducted using various databases, including PubMed, Cochrane, ProQuest and EBSCOhost with the search strategies detailed in Table S1. Citation searching was performed in eligible studies and prior systematic reviews to identify relevant literature not captured through the database search. An author (FZN) screened both the records and full-text articles.

Risk of bias assessment and data extraction. The included studies were assessed using the Cochrane risk-of-bias tool for randomized control studies (RoB 2.0) (https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials) for RCTs or Risk of Bias in the Non-randomized Studies of Interventions (ROBINS-I) tool for observational studies (https://methods.cochrane.org/bias/risk-bias-non-randomized-studies-interventions). The following data were extracted: The name of the first author and year of publication, study design, patient risk group and classification system, details of intervention and comparison including dosage and BCG strain, and outcomes related to efficacy and safety. Efficacy outcomes included, but not limited to. recurrence, progression, mortality rates and recurrence-free survival. Safety outcomes included any adverse events (AEs), severe AEs (defined as grade ≥3 AEs resulting in treatment modification) and the type of AE. Data extraction and risk of bias assessment were performed by one of the authors (FZN), as previously described (16).

Statistical analysis. The extracted data were tabulated and described narratively. Where feasible (≥2 studies reporting the same outcome), data were pooled using inverse-variance random-effects meta-analysis with risk ratios (RR) as the effect measure. Random-effects weighting was applied due to variations in patient risk groups and classifications, intervention types and doses, and follow-up durations. Given inherent differences in study design and procedures, analyses and syntheses were prioritized for RCTs. Heterogeneity was assessed using the Chi-squared test (with $P<0.10$ indicating statistical heterogeneity) and the I^2 statistic, categorized as low (0-25%), moderate (26-50%), high (51-75%), or very high (>75%). Galbraith plots were produced to identify outliers and visualize heterogeneity. For primary efficacy (recurrence and progression) and safety outcomes (any and severe AEs), analyses were further stratified by patient risk group. However, stratification by risk group classification system, BCG dose and strain, and follow-up duration was not possible due to heterogeneous distributions and limited data. Subgroup analysis by overall risk of bias was also not conducted, as all included studies were judged to have moderate-to-high risk of bias. As <10 articles were included, funnel plots were not generated.

Results

Characteristics of the included studies. A total of 501 records were retrieved from the search (Fig. 1). Following screening, five studies were included: Four RCTs (16-19) and one prospective cohort study (20). All studies were deemed valid following critical appraisal using the Oxford's CEBM checklists (Table SII). Across the five studies, a total of 447 patients with NMIBC were included, with 224 (50.1%) patients receiving gemcitabine and 223 (49.9%) patients receiving BCG. All patients in the gemcitabine group received either a weekly or twice-weekly dose of 2,000 mg gemcitabine in 50 ml normal saline for 6 weeks (induction phase), followed by maintenance for 12 months in two studies (16,18), 36 months in one study (17) and an unspecified duration in two studies (19,20). By contrast, BCG dosing and strain varied by study: Two studies used the

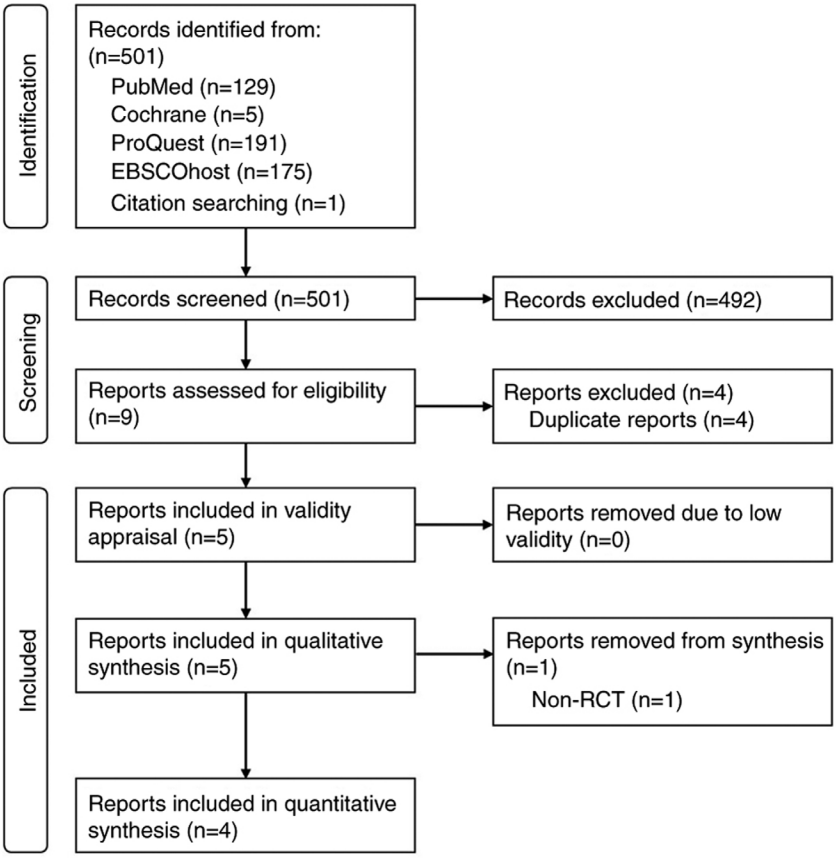

Figure 1. PRISMA flow chart.

Connaught strain administered weekly for 6 weeks (induction phase) with a 3-week maintenance schedule (16,18), two studies used Tice strains administered weekly for 6 weeks (17,20), and one study did not report a strain or dosing interval (19). Patient risk classification was high-risk in two studies (17,18), low-to-intermediate risk in two studies (16,19), and mixed in one study (20). The EAU classification system was used in three studies (16,17,20), EORTC in one study (18), and was unspecified in one study (19). The duration of follow-up ranged from 3 to 60 months (Table I).

Risk of bias assessment. Risk of bias assessment revealed a moderate overall risk in four studies (16,18-20) and low risk in only one study (17). Specifically, all four RCTs had some concerns regarding the risks of deviation from intended intervention (16-19), and three RCTs had some concerns from measurement of the outcome (16,18,19). Moreover, the study by Prasanna *et al* (20) had a moderate risk from selection and attrition bias and a serious risk from confounding effects (Fig. 2).

Efficacy outcomes. A total of four studies and 344 patients were included in the meta-analysis of efficacy outcomes. Intravesical gemcitabine was non-inferior to gemcitabine in terms of recurrence [relative risk (RR), 0.97; 95% confidence interval (CI), 0.58-1.60; high heterogeneity (I^2=72.9%, P=0.011); and progression (RR, 1.02; 95% CI, 0.54-1.93); low heterogeneity (I^2=0.0%, P=0.766; Fig. 3]. Recurrence and progression rates were similar between the groups both in patients with high-risk NMIBC (RR, 1.03; 95% CI, 0.33-3.15; I^2=89.8%, P=0.001; and RR, 0.90; 95% CI, 0.43-1.89) and in those with a low-to-intermediate risk (RR, 0.98; 95% CI, 0.61-1.57; I^2=0.0%, P=0.559; and RR, 1.46; 95% CI, 0.42-5.04; I^2=0.0%, P=0.760) (Fig. S1). Galbraith plots did not identify any outlier, although the wide spread of estimates suggests apparent heterogeneity (Fig. S1A and B).

Recurrence-free survival was shorter in the gemcitabine group in one study (mean, 25.6 vs. 39.4 months, P=0.042) (17), similar in another (10.6 vs. 10.4 months, P=0.66) (16), and longer in one study (3.9; 95% CI, 3.0-7.0 vs. 3.1 months 95% CI, 2.2-6.0; P=0.008) (18). Additionally, Di Lorenzo *et al* (18) reported a significantly higher 2-year recurrence-free survival in patients with NMIBC receiving gemcitabine compared to those receiving BCG [hazard ratio (HR), 0.15; 95% CI, 0.10-0.30; P<0.008]. Progression-free survival, as reported in the study by Gontero *et al* (16), was similar between gemcitabine and BCG (both mean 11.6 months, P=0.500). Mortality was reported by only one study, with one death in the BCG group and none in the gemcitabine group, although the difference was not statistically significant (P=0.120) (18). Similarly, Porena *et al* (17) reported that the rates of persistent high-risk disease and regression were similar in both groups (44.4 vs. 41.1% and 55.5 vs. 52.9%, respectively; both P-values non-significant) (Table I).

Safety outcomes. A total of four studies comprising a total of 337 patients were included in the meta-analysis of safety outcomes. The overall risk of AEs was similar between the

Table I. Details of studies included in the qualitative synthesis.

First author, year of publication	Study design	Chemotherapeutic agent	Population characteristics	Intervention	Outcomes	(Refs.)
Porena, 2009	RCT	Gemcitabine and BCG	• 64 High-risk superficial bladder cancer patients based on EAU Guideline • Patients randomized into two groups; Gemcitabine group (n=32) with mean age 70.2±5.5 and BCG group (n=32) mean age, 68.7±10.2 years	• All patients underwent first TURBT and bladder mapping to determine the presence of CIS; 4 weeks later the second TURBT was conducted without prior instillation of chemotherapeutic agents • Gemcitabine group: 14 days after the second TURBT, the patients received 6 weekly installations of Gemcitabine with a dose of 2,000 mg diluted in 50 ml saline held in bladder for 2 h and received maintenance therapy at 3 ,6, 12, 18, 24, 30 and 36 months after TURBT • BCG group: 14 days after the second TURBT, the patients received 6 weekly installations of Tice-strain BCG with a dose of $5x10^8$ CFU diluted in 50 ml saline held in the bladder for 2 h and received maintenance therapy at 3, 6, 12, 18, 24, 30 and 36 months after TURBT • Outcome measured consists of recurrence and progression rates detected with cystoscopy and TURBT, tolerability and safety	• Recurrence rate ◦ BCG group: 28,1% ◦ Gemcitabine group: 53,1% ◦ P=0.037 • Mean recurrence-free survival time ◦ Gemcitabine group: 25.6 months ◦ BCG group: 39.4 months ◦ P=0.042 • Local toxicity (urinary tract infection, cystitis, dysuria) ◦ BCG group: 12.5% ◦ Gemcitabine group: 9.4% ◦ P>0.05 • Systemic toxicity (fever) ◦ BCG group: 6.25% ◦ Gemcitabine group: 12.5% ◦ P>0.05 • Rates of persistent high-risk disease ◦ BCG group: 44.4% ◦ Gemcitabine group: 41.1% ◦ P>0.05 • Rates of regression ◦ BCG group: 55.5% ◦ Gemcitabine group: 59.2% ◦ P>0.05	(17)
Di Lorenzo, 2010	RCT	Gemcitabine and BCG	• 80 High-risk NMIBC patients based on the EORTC scoring system Patients randomized into two groups; gemcitabine group (n=40) with mean age 69.3±8.4 and BCG group (n=40) mean age, 71.4±7.9 years	• Gemcitabine group: 4-6 weeks after the last TURBT 0performed after the failure of the first treatment with BCG, the patients received twice weekly intravesical gemcitabine with a dose of 2,000 mg/50 ml for 6 weeks and maintenance at 2, 6 and 12 months.	• Recurrence rate ◦ Gemcitabine group: 52.5%, ◦ BCG group: 87.5% ◦ P=0.002 • Time to first recurrence ◦ Gemcitabine group: 3.9 months	(18)

Table I. Continued.

First author, year of publication	Study design	Chemotherapeutic agent	Population characteristics	Intervention	Outcomes	(Refs.)
			• Patients had a history of treatment failure with BCG	• BCG group: 4-6 weeks after the last TURBT performed after the failure of the first treatment with BCG, the patients received Connaught strain BCG (81 mg/50 ml) over a 6-week induction course and the maintenance at 3, 6 and 12 months • Outcome measured consist of recurrence and progression rates detected with cystoscopy and TURBT, and toxicity assessed with toxicity criteria 3.0	◦ BCG group 3.1 months ◦ P=0.09 • 2-year recurrence-free survival ◦ Gemcitabine group: 19% ◦ BCG group: 3% ◦ P<0.008 • Toxicity rate (dysuria, hematuria, fever, dermatitis, nausea-vomiting) ◦ Gemcitabine group: 37.5% ◦ BCG group: 40% ◦ P>0,05 • Mortality incidence ◦ Gemcitabine group: none ◦ BCG group: 1 ◦ P=0.120	
Bendary, 2011	RCT	Gemcitabine and BCG	• 80 Patients diagnosed with primary stage of Ta-T1 without CIS with mean age 56.2±11.18 years • All patients are randomized into two groups, 40 each, to receive either gemcitabine or BCG. Each group had a subgroup of Ta and T1 tumors	• Gemcitabine group received a 6 weekly intravesical instillation after 2 weeks from resection with a dose of 2,000 mg/50 ml of saline. • BCG group received a 6 weekly intravesical instillation after 2 weeks from resection with a dose of $6x10^8$ CU in 50 ml saline. • Follow-up period range from 3-18 months (mean, 10.8±2.7 months) • Outcome measured were recurrence rate and progression rate	• Recurrence rate in Ta patient ◦ BCG group: 26.31% ◦ Gemcitabine group: 22.22% ◦ P=0.92 • Recurrence rate in T1 patient ◦ BCG group: 33.33% ◦ Gemcitabine group: 27.27% ◦ P=0.66 • Overall Recurrence rate ◦ BCG group: 30% ◦ Gemcitabine group: 25% ◦ P=0.61 • Progression rate ◦ BCG group: 9.5% ◦ Gemcitabine group: 9.1% ◦ P=1.0	(19)

Table I. Continued.

First author, year of publication	Study design	Chemotherapeutic agent	Population characteristics	Intervention	Outcomes	(Refs.)
					• Toxicity rate: dysuria ◦ BCG group: 35% ◦ Gemcitabine group: 12.5% ◦ P<0.05 • Toxicity rate: urinary frequency ◦ BCG group: 45% ◦ Gemcitabine group: 10% ◦ P<0.01	
Gontero, 2013	RCT	Gemcitabine and BCG	• 120 Intermediate-risk NMIBC patients based on EAU risk stratification • Patients are randomized into two groups, Gemcitabine (n=61) and BCG (nS59) • All patients are BCG naïve and had no prior intravesical chemotherapy in the last 3 months	• BCG group: 7-15 weeks after previous TURBT, patients received 6 weekly inductions of Connaught strain BCG 1/3 dose (27 mg) in 50 ml saline and maintenance of 3 weekly instillations at 3, 6 and 12 months • Gemcitabine group: 7-15 weeks after previous TURBT, patients received 6 weekly induction of 2000 mg/50 ml saline of gemcitabine with maintenance of monthly instillations up to 1 year • Secondary outcome are recurrence and progression at 1 year and assessment of toxicity	• 1-year recurrence rate BCG group: 23.7% ◦ Gemcitabine group: 26.2% ◦ P=0.83 • Recurrence-free survival ◦ BCG group: 10.4 months ◦ Gemcitabine group: 10.6 months ◦ P=0.66 • 1-year disease progression rate ◦ BCG group: 11.6 months ◦ Gemcitabine group: 11.6 months ◦ P=0.5 • Both local and systemic side effects are more common in BCG group compared to Gemcitabine group after first induction (56.1% vs 35.7%; P=0.03), but not significant after second induction (40.4 vs. 34.1%; P=0.66)	(16)

Table I. Continued.

First author, year of publication	Study design	Chemotherapeutic agent	Population characteristics	Intervention	Outcomes	(Refs.)
Prasanna, 2017	Retrospective cohort	Gemcitabine and BCG	• 103 Patients; gemcitabine group (n=51) and BCG group (n=52) • Patients consisted of all three different risk group with no significant different in distribution in each group	• BCG treatment: initial weekly instillation of Oncotice BCG with a dose of $5x10^8$ CFU with 2 h of retention time for 6 weeks • Gemcitabine: Weekly instillation of 2,000 mg Gemcitabine for 6 weeks Patients were administered maintenance treatment based on their recurrence risk profile • Primary outcome is disease-free survival (DFS) with recurrences confirmed by cystoscopic guided biopsy and histology • Secondary outcomes include toxicity examination	• Median follow-up, 15 months • Mean disease-free survival time ◦ BCG group: 19.6 months ◦ Gemcitabine group: Not reached, significantly longer ◦ Unadjusted HR of 0.47 (95% CI, 0.23-0.98, P=0.04) in favour of gemcitabine • 2-year disease-free survival rate ◦ BCG group: 48.0% ◦ Gemcitabine group: 55.1% ◦ P 0.32 • Adverse event rate ◦ BCG group: 44% ◦ Gemcitabine group: 7% ◦ P<0.05	(20)

RCT, randomized controlled trial; BCG, Bacillus Calmette-Guérin; TURBT, transurethral resection of bladder tumor.

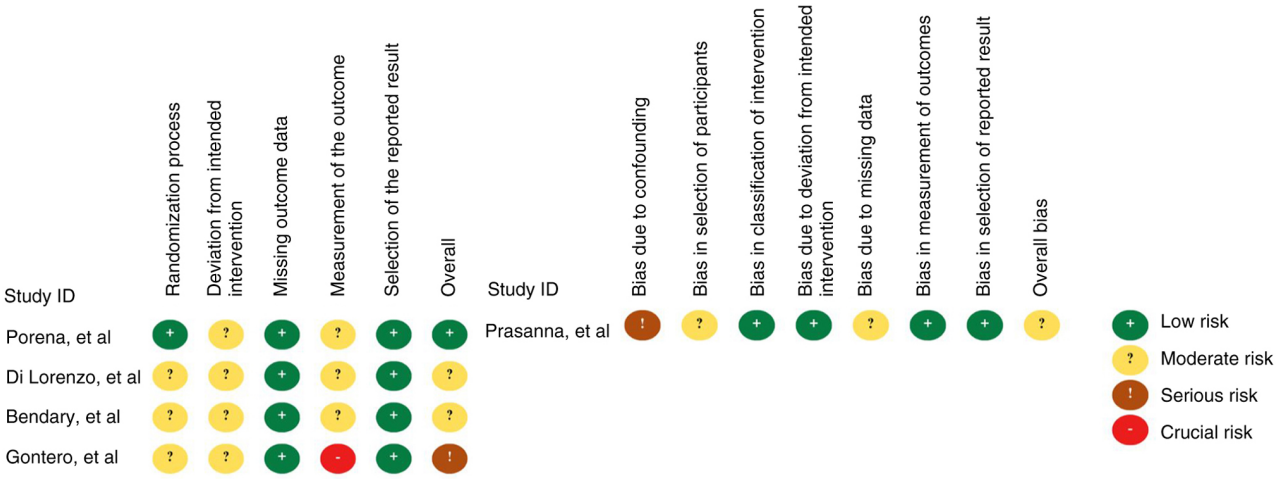

Figure 2. Risk of bias assessment using the Cochrane risk-of-bias tool for randomized control studies (RoB 2.0) for RCTs and Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool for observational studies checklists. The studies included were the following: Porena *et al* (17), Di Lorenzo *et al* (18), Bendary *et al* (19), Gontero *et al* (16) and Prasanna *et al* (20).

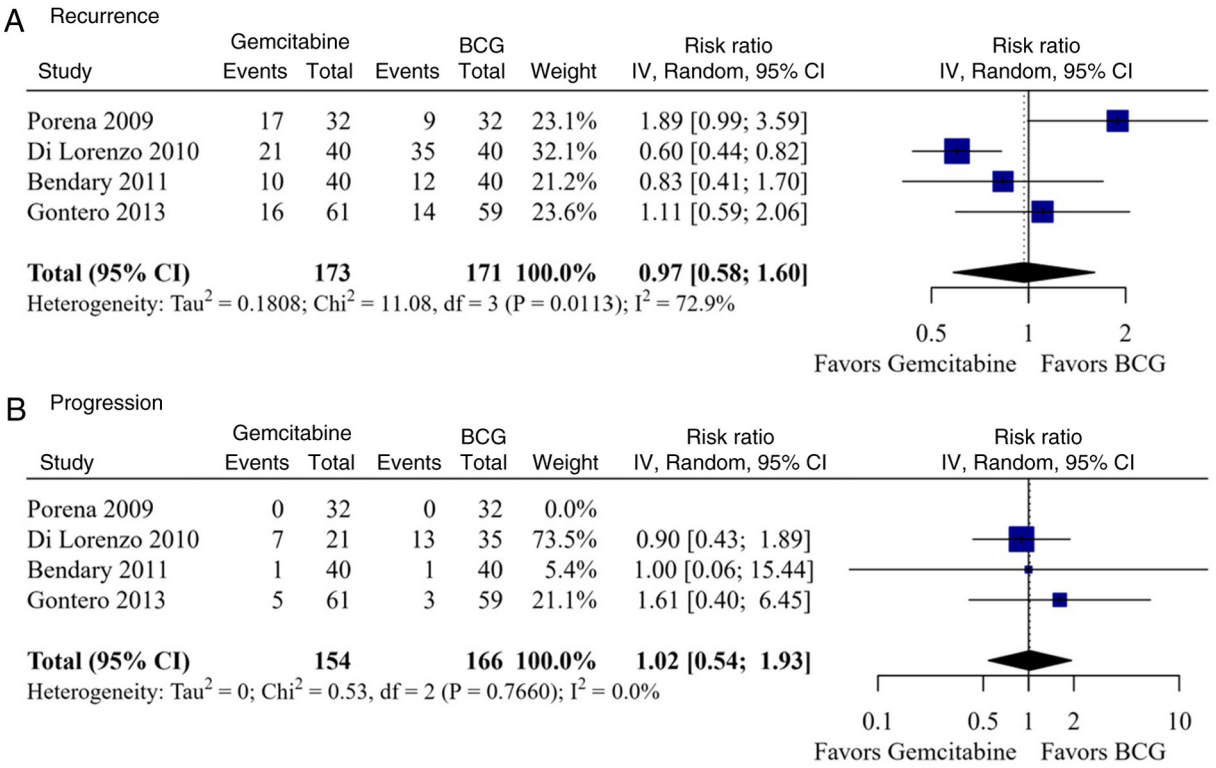

Figure 3. Comparison of (A) recurrence and (B) progression rates between intravesical gemcitabine and BCG immunotherapy in non-muscle invasive bladder cancer. BCG, Bacillus Calmette-Guérin.

gemcitabine and BCG groups (RR, 0.78; 95% CI, 0.53-1.13; I^2=11.8%; P=0.322) (Fig. 4A), as well as among patients with high-risk disease (RR, 0.99; 95% CI, 0.61-1.60; I^2=0.0%; P=0.702) and low-to-intermediate risk disease (RR, 0.62; 95% CI, 0.41-0.93) (Table II). Similarly, the rate of severe AEs, defined as grade ≥3 AEs requiring treatment modifications, did not differ significantly between the groups overall (RR, 0.67; 95% CI, 0.25-1.77; I^2=0.0%; P=0.402) (Fig. 4B), or when stratified by patient risk classification (high-risk: RR, 0.37; 95% CI, 0.03-4.28; I^2=58.8%; P=0.119; low-to-intermediate risk: RR, 0.81; 95% CI, 0.20-3.25; I^2=0.0%; P=0.549) (Table II). Galbraith plots identified no outlier, although the limited data may constrain further interpretation (Fig. S1C-H).

According to the type of AE, patients receiving gemcitabine had significantly lower risks of dysuria (four studies; RR, 0.59; 95% CI, 0.39-0.89; I^2=0.0%; P=0.674), fever (three studies; RR, 0.17; 95% CI, 0.04-0.76; I^2=0.0%; P=0.569), urinary frequency (one study; RR, 0.22; 95% CI, 0.13-0.37) and itching (one study; RR, 0.34; 95% CI, 0.18-0.64); whereas the risk was similar for other local (hematuria: RR, 0.21; 95% CI, 0.03-1.32; I^2=32.7%; P=0.223; bladder spasms: RR, 3.05; 95%

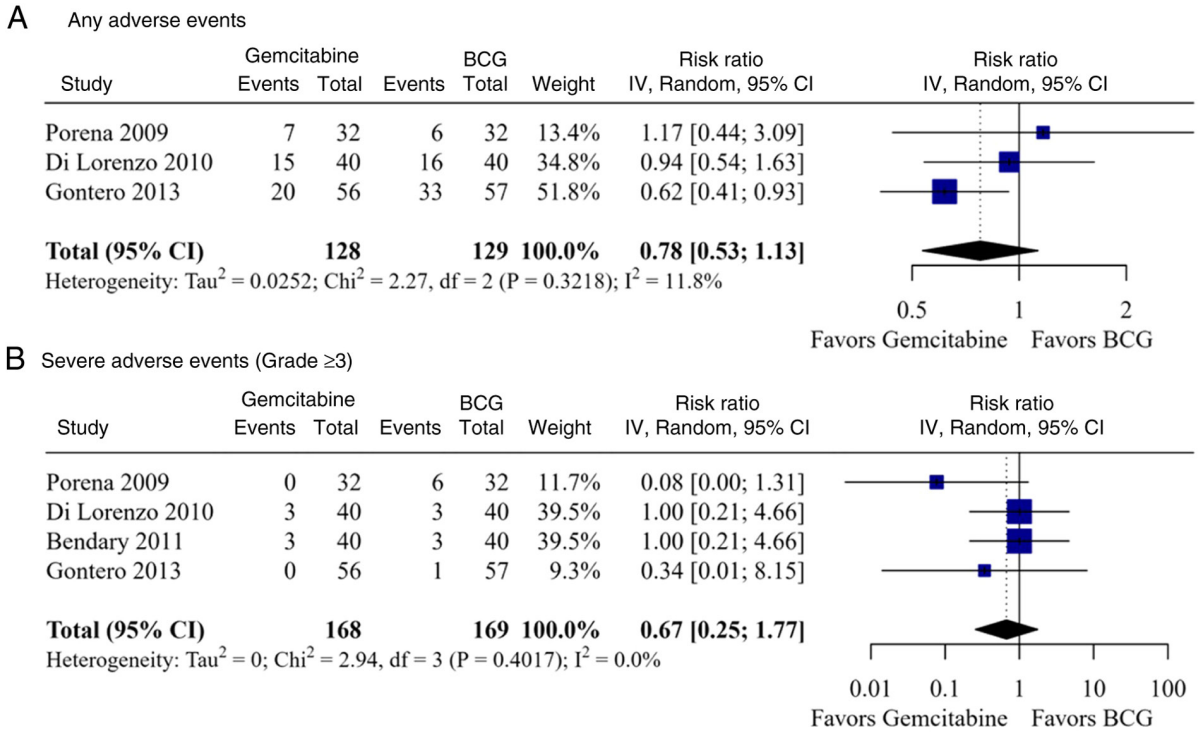

Figure 4. Comparison of (A) any adverse events and (B) severe adverse events (grade ≥3) between intravesical gemcitabine and BCG immunotherapy in non-muscle invasive bladder cancer. BCG, Bacillus Calmette-Guérin.

CI, 0.98-9.54; dermatitis: RR, 5.00; 95% CI, 0.25-100.93; skin rash: RR, 1.02; 95% CI, 0.25-4.13; and urge incontinence: RR, 0.51; 95% CI, 0.26-1.01) and systemic (nausea and vomiting: RR, 5.94; 95% CI, 0.73-48.31; I^2=0.0%; P=0.875; asthenia: RR, 3.00; 95% CI, 0.13-70.96; and neutropenia and thrombocytopenia) AEs (Table II).

Discussion

The present systematic review and meta-analysis included four RCTs comprising 344 patients and one retrospective cohort study with 103 patients. The earliest RCT was conducted by Porena *et al* (17) in 2010 among high-risk superficial bladder cancer patients based on the EAU risk classification system. BCG was administered as a 6-weekly instillation of $5x10^8$ CFU of Tice strain BCG retained intravesically for 2 h (17). Gemcitabine was administered as a 6-weekly instillation of 2,000 mg, also retained for 2 h. In that study, BCG was associated with a lower recurrence rate (28.1 vs. 53.1%) and a longer recurrence-free survival than gemcitabine (17). These findings are in contrast to those of the other three RCTs included in the present study.

Di Lorenzo *et al* (18) compared these treatments in patients with high-risk NMIBC (per EORTC scoring system) who had previously failed BCG therapy. In their study, BCG (Connaught strain, 81 mg/50 ml) was administered 4-6 weeks after the first treatment failure, over a 6-week induction followed by maintenance at 3, 6 and 12 months. The gemcitabine group received 2,000 mg/50 ml over a period of 6 weeks and similar maintenance at 2, 6 and 12 months (18). In contrast to the study by Porena *et al* (17), the study by Di Lorenzo *et al* (18) found lower recurrence rates and a higher 2-year recurrence-free survival in the gemcitabine group, with no significant differences in time-to-recurrence or progression. This was the only study to include BCG-refractory patients, which may explain the divergent findings from that of Porena *et al* (17).

In their study, Bendary *et al* (19) included patients with primary Ta-T1 tumors without CIS and reported no significant differences in recurrence or progression rates between BCG and gemcitabine. In that study, BCG was administered at $6x10^8$ CFU (strain unspecified) and gemcitabine at 2,000 mg in 50 ml saline, both over 6 weekly 2-h instillations (19). Similarly, Gontero *et al* (16) found no significant difference in recurrence, recurrence-free survival, or progression in intermediate-risk patients with NMIBC. Their BCG regimen used one-third dose (27 mg) of Connaught strain over a 6-week induction period. Gemcitabine was administered identically across studies (2,000 mg/50 ml, 6-week induction) (16).

Prasanna *et al* (20) conducted a retrospective cohort study on patients with CIS, pTa and pT1 tumors, stratified into EAU-defined risk groups. BCG (Oncotice strain, $5x10^8$ CFU) and gemcitabine (2,000 mg) were administered as 6 weekly instillations. Despite baseline differences in risk-group distribution, adjusted multivariate analysis revealed no difference in disease-free survival between the groups (20). All studies agreed that gemcitabine had a more favorable safety profile, with fewer local and systemic adverse events, leading to better tolerability and quality of life.

The variability in the findings across these five studies is largely attributable to clinical and methodological heterogeneity. Porena *et al* (17) included only high-risk patients per EAU criteria, which included patients with NMIBC with CIS, all T1 tumors without CIS, Ta LG/G2 without CIS with three risk factors, Ta HG/G3 without CIS and with two risk

Table II. Summary of meta-analysis results for efficacy and safety outcomes from the included randomized controlled trials

Outcome	No. of studies	No. of patients; event/no.		RR (95% CI)	Heterogeneity	
		Gemcitabine	BCG		I^2	P-value
A, Primary outcomes						
Efficacy						
Recurrence						
Overall	4	64/173	70/171	0.97 (0.58-1.60)	72.9%	0.011
High-risk	2	38/72	44/72	1.03 (0.33-3.15)	89.8%	0.001
Low-to-intermediate risk	2	26/101	26/99	0.98 (0.61-1.57)	0.0%	0.559
Progression						
Overall	3	13/122	17/134	1.02 (0.54-1.93)	0.0%	0.766
High-risk	1	7/21	13/35	0.90 (0.43-1.89)	NA	NA
Low-to-intermediate risk	2	6/101	4/99	1.46 (0.42-5.04)	0.0%	0.760
Safety						
Any AE						
Overall	3	42/128	65/129	0.78 (0.53-1.13)	11.8%	0.322
High-risk	2	22/72	32/72	0.99 (0.61-1.60)	0.0%	0.702
Low-to-intermediate risk	1	20/56	33/57	0.62 (0.41-0.93)	NA	NA
Severe AE (grade ≥3)						
Overall	4	6/168	13/169	0.67 (0.25-1.77)	0.0%	0.402
High-risk	2	3/72	9/72	0.37 (0.03-4.28)	58.8%	0.119
Low-to-intermediate risk	2	3/96	4/97	0.81 (0.20-3.25)	0.0%	0.549
B, Secondary outcomes						
Efficacy						
Mortality	1	0/21	1/35	0.55 (0.02-12.92)	NA	NA
Persistence of high-risk disease	1	13/32	14/32	0.93 (0.69-1.24)	NA	NA
Regression	1	17/32	18/32	0.94 (0.75-1.19)	NA	NA
Safety						
Local AEs						
Dysuria	4	27/168	4/169	0.59 (0.39-0.89)	0.0%	0.674
Hematuria	2	2/96	14/97	0.21 (0.03-1.32)	32.7%	0.223
Dermatitis	1	2/40	0/40	5.00 (0.25-100.93)	NA	NA
Urinary frequency	1	4/40	18/40	0.22 (0.13-0.37)	NA	NA
Bladder spasm	1	3/56	1/57	3.05 (0.98-9.54)	NA	NA
Urge incontinence	1	3/56	6/57	0.51 (0.26-1.01)	NA	NA
Itching	1	3/56	9/57	0.34 (0.18-0.64)	NA	NA
Skin rash	1	1/56	1/57	1.02 (0.25-4.13)	NA	NA
Systemic AEs						
Fever	3	1/128	15/129	0.17 (0.04-0.76)	0.0%	0.569
Nausea and vomiting	2	5/72	0/72	5.94 (0.73-48.31)	0.0%	0.875
Asthenia	1	1/32	0/32	3.00 (0.13-70.96)	NA	NA
Neutropenia and thrombocytopenia	1	2/40	0/40	5.00 (0.25-100.93)	NA	NA

AE, adverse event; CI, confidence interval; NA, not available; RR, risk ratio.

factors, and T1 G2 without CIS and with one risk factor (10). Conversely, Gontero *et al* (16) focused on intermediate-risk NMIBC, and accordingly reported no difference in outcomes between gemcitabine and BCG. Di Lorenzo *et al* (18) used the EORTC scoring system to define high risk (recurrence score >9 and/or progression score >13). Although EORTC

risk classification may slightly outperform EAU in predicting recurrence (c-index 0.64 vs. 0.62; P=0.035), the key distinguishing feature in the study by Di Lorenzo *et al* (18) was the inclusion of BCG-refractory patients, not the risk model used.

Bendary *et al* (19) and Prasanna *et al* (20) included broader and less well-defined populations. In the study by Bendary *et al* (19), the inclusion of all Ta-T1 tumors without CIS spanned a wide risk spectrum but lacked proper risk stratification. By contrast, Prasanna *et al* (20) used similarly broad criteria but stratified patients into EAU risk groups, strengthening the interpretation of findings. BCG regimens also varied. Although strain and dose differences existed, a previous meta-analysis of 65 trials involving >12,000 patients concluded that no strain demonstrated clear superiority (21). Gontero *et al* (16) used a one-third dose of the Connaught strain in intermediate-risk patients to reduce toxicity without sacrificing efficacy. Gemcitabine regimens were consistent across studies. Only Di Lorenzo *et al* (18) included patients with prior BCG failure, and only in this context did gemcitabine demonstrate superior efficacy.

The findings presented herein align with those of prior reviews. Shelley *et al* (22) reported that gemcitabine was comparable to BCG in intermediate-risk patients, inferior in high-risk, and superior in BCG-refractory NMIBC. However, the present systematic review included more representative populations from Bendary *et al* (19) and Prasanna *et al* (20), both demonstrating no efficacy difference across wider risk groups. Similarly, the Cochrane review by Jones *et al* (23) found gemcitabine less effective in high-risk NMIBC, comparable in intermediate-risk, and more effective in BCG-refractory patients. A separate meta-analysis also revealed no significant difference in recurrence (HR, 1.04; 95% CI, 0.38-2.89) or progression (HR, 0.01; 95% CI, -0.75 to 0.77) between the two agents (24).

Overall, the findings of the present systematic review and meta-analysis suggest that intravesical gemcitabine was non-inferior to BCG immunotherapy in terms of efficacy, while it resulted in lower rates of dysuria, fever, urinary frequency and itching. However, intravesical gemcitabine appears particularly useful for patients with BCG-refractory NMIBC. In this population, the EAU recommends radical cystectomy (11), although it remains an invasive procedure with significant morbidity and mortality, and entails major lifestyle changes (25). Intravesical gemcitabine may therefore serve as a non-invasive alternative for NMIBC patients unresponsive to BCG immunotherapy.

The superiority of gemcitabine over BCG in BCG-refractory NMIBC may be explained by several factors. BCG, as with other immunotherapies, relies on an intact immune system to activate innate immunity and initiate BCG-specific and tumor-specific T-cell responses. Although the exact mechanisms remain unclear, BCG failure is considered to result from complex interactions between host immunity and tumor microenvironment, leading to immune dysregulation and inadequate immune activation. Specifically, non-responders have been shown to be associated with increased levels of $CD25^+$ regulatory T-cells and tumor-associated macrophage, enrichment of exhausted $CD8^+$PDL-1(+) T-cells, and reduced levels of Th2-predominant $CD4^+$ T-cells within the tumor microenvironment (26). By contrast, gemcitabine inhibits tumor DNA synthesis, leading to apoptosis, and is therefore less dependent on host immune function (23). Its lower risk of adverse events may be attributed to its immune-selective cytotoxicity and high plasma clearance, allowing any drug that enters systemic circulation to be rapidly eliminated (23). Furthermore, BCG is a live-attenuated strain of *Mycobacterium bovis* that activates a strong immune response and induces inflammation following urothelial invasion (27), which contributes to a higher incidence of local and systemic side-effects (27,28).

In conclusion, the present systematic review and meta-analysis demonstrated that intravesical gemcitabine was non-inferior to BCG immunotherapy in the treatment of patients with NMIBC and may serve as a viable option for those unresponsive to BCG. Although the overall risk of AEs was comparable, gemcitabine was associated with lower rates of dysuria, fever, urinary frequency and itching. Further high-quality RCTs with larger sample sizes, standardized dosing, treatment intervals, and follow-up durations are warranted to confirm these findings.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

FZN and ARAHH were involved in the study conception and design. FZN was involved in the acquisition of data and in the drafting of the manuscript. FZN, ARAHH, CAM and FR were involved in the analysis and interpretation of data. ARAHH and CAM critically revised the manuscript for important intellectual content. FZN and FR performed the statistical analysis. ARAHH and CAM provided administrative, technical and material support (data analysis coaching) and supervised the study as required. All authors have read and approved the final manuscript. All authors confirm the authenticity of all the raw data

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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