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Intravesical gemcitabine for non-muscle invasive bladder cancer: An abridged Cochrane Review

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Purpose: To assess the comparative effectiveness and toxicity of intravesical gemcitabine instillation for non-muscle invasive bladder cancer (NMIBC).

Materials and Methods: We performed a comprehensive literature search on 11 September 2020. We included RCTs in which participants received intravesical gemcitabine for primary or recurrent NMIBC. Two review authors independently assessed the included studies and extracted data for the primary outcomes (time to recurrence, time to progression, grade III to V adverse events) and the secondary outcomes (time to death from bladder cancer, time to death from any cause, grade I or II adverse events, and disease-specific quality of life). We performed statistical analyses using a random-effects model and rated the certainty of the evidence using GRADE.

Results: We found seven studies with 1,222 participants. Gemcitabine may reduce the risk of recurrence over time, but may have a similar effect on progression and grade III to V adverse events compared to saline. Gemcitabine may reduce recurrence and progression compared to mitomycin. We are uncertain about the effect of gemcitabine on the grade III to V adverse events compared to mitomycin. Gemcitabine may reduce recurrence and progression compared to giving BCG again in recurrent high-risk NMIBC after BCG treatment.

Conclusions: Based on the findings of this review, gemcitabine may have a favorable impact on recurrence and progression-free survival than saline and mitomycin but we are uncertain about how major adverse events compare. The same is true when comparing gemcitabine to BCG in individuals with high-risk diseases who have previously failed BCG.

Keywords: Administration, intravesical; Gemcitabine; Systematic review; Urinary bladder neoplasms

INTRODUCTION

The initial management of non-muscle invasive bladder cancer (NMIBC) is transurethral resection (TUR) to remove all visible tumors, and depth includes the muscularis propria. After the initial transurethral surgery, 50% to 70% of tumors have recurred [1], and 10% to 30% of tumors are progressing (grade and stage progression) within five years [2].

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Factors associated with recurrence and progression include high stage, high grade, large tumor size, multifocality, high number of the previous recurrence, presence of concomitant CIS (carcinoma *in situ*), lymphovascular invasion, and histologic variants [3]. To overcome the problem of tumor recurrence, anti-tumor agents may be instilled into the bladder for a short time to bathe the tumor cells. This is called intravesical therapy and is frequently used as an adjunctive following TUR. The objective is to eradicate residual tumor cells missed in the original resection and to prevent or delay tumors from recurring or progressing to more invasive disease [4,5]. Therefore, intravesical therapy has an essential role in the management of NMIBC. Gemcitabine can be used as an intravesical therapeutic agent however, the effects are somewhat uncertain compared to other agents such as mitomycin or Bacillus Calmette–Guérin (BCG). Therefore, we updated a previously published Cochrane Review to assess the comparative effectiveness and toxicity of intravesical gemcitabine instillation for NMIBC. This is an abridged version of Cochrane Review [6].

MATERIALS AND METHODS

1. Search strategy and selection criteria

We performed comprehensive searches (CENTRAL, MEDLINE, EMBASE, Web of Science, Scopus, LILACS, ClinicalTrials. gov, World Health Organization International Clinical Trials Registry Platform), applying no restrictions on the language of publication or publication status. All searches were from inception to 11 September 2020. See Supplementary Table 1 for the full search strategies.

2. Types of participants

We included studies that used participants with NMIBC (Stage 0a, Stage 0is, and Stage I) [4,7], with any tumor grade [8,9] as determined via cross-sectional imaging, cystoscopic appearance, or biopsy. We included studies irrespective of intravesical therapy dose or schedule. Participants who received prior intravesical therapy and failed to respond, such as BCG-refractory participants, were also eligible. We excluded participants with previous or concurrent upper urinary tract or prostatic urethral urothelial cancer, cancers other than bladder, and previous systemic treatment or radiation therapy for any cancer.

3. Data collection, extraction, and summary of findings table

We included randomized controlled trials (RCTs) comparing gemcitabine to other intravesical therapy for the treatment of NMIBC. Two independent reviewers screened identified references, extracted data, and assessed the risk of bias according to Cochrane's methodological recommendations [10]. We performed meta-analyses using the random effects model and assessed the heterogeneity between studies with the I^2 statistic. All analyses were conducted with Review Manager 5 software [11].

Review outcomes were as follows: (1) Primary outcomes: time to recurrence, time to progression, grade III to V adverse events. (2) Secondary outcomes: time to death from bladder cancer, time to death from any cause, grade I or II adverse events and disease-specific quality of life. We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to rate the certainty of the evidence for each predefined outcome [12].

RESULTS

1. Search results

We identified 1,002 records through electronic database searching and four records in existing systematic review. We included seven studies in the review [13-19]. The flow of literature through the assessment process is shown in the PRISMA flowchart (Supplementary Fig. 1).

2. Included studies

Detailed characteristics of included studies are summarized in Supplementary Table 2. We included 1,222 randomized participants (gemcitabine 611, mitomycin 55, BCG 171, saline 385), of which 644 completed the trials (gemcitabine 310, mitomycin 55, BCG 119, saline 160). However, one study that compared gemcitabine to BCG did not report the number of participants who completed the trial in each group [14]. All studies included men and women. Excluded studies are not reported here but described in the original review [6].

3. Risk of bias in included studies

Further details on the assessment of Risk of Bias were stated in the review published in Cochrane Library. Assessments of risk of bias are summarized in Supplementary Fig. 2.

4. Summary of findings tables and effect of the intervention

This abridged version focuses on the primary outcomes of the three most clinically relevant comparisons. Please refer to the original review for whole outcomes [6].

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1) Gemcitabine versus saline

Two studies compared gemcitabine versus saline for primary and recurrent NMIBC (Table 1) [15,18].

(1) Time to recurrence

Gemcitabine may reduce the risk of recurrence over time compared to saline (hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.54–1.09; studies=2, participants=734; I^2=49%; low-certainty evidence), but the CI included the possibility of no effect.

(2) Time to progression

Gemcitabine may result in little to no difference in the risk of progression over time compared to saline (HR 0.96, 95% CI 0.19–4.71; studies=2, participants=654; I^2=53%; low-certainty evidence).

(3) Grade III to V adverse events

Gemcitabine may result in little to no difference in the Common Terminology Criteria for Adverse Events (CTCAE) grade III to V adverse events compared to saline (risk ratio [RR] 1.26, 95% CI 0.58–2.75; studies=2, participants=668; I^2=24%; low-certainty evidence).

2) Gemcitabine versus mitomycin

One study compared gemcitabine versus mitomycin for recurrent NMIBC (Table 2) [13]. There was no data available for gemcitabine versus mitomycin for primary NMIBC.

(1) Time to recurrence

Gemcitabine may reducethe risk of recurrence over time compared to mitomycin (HR 0.36, 95% CI 0.19–0.69; studies=1, participants=109; low-certainty evidence).

(2) Time to progression

Gemcitabine may reduce the risk of progression over time compared to mitomycin (HR 0.57, 95% CI 0.32–1.01; studies=1, participants=109; low-certainty evidence), but the CI included the possibility of no effect.

(3) Grade III to V adverse events

We are very uncertain about the effect of gemcitabine on the grade III to V adverse events compared to mitomycin (RR 0.51, 95% CI 0.13–1.93; studies=1, participants=109; very low certainty evidence).

3) Gemcitabine versus BCG for recurrent (one-course BCG failure) high-risk NMIBC

One study compared gemcitabine versus BCG for recurrent high-risk NMIBC in participants who had previously undergone one course of BCG treatment and recurred (Table 3) [16].

(1) Time to recurrence

Gemcitabine may reduce the risk of recurrence over time compare to BCG (HR 0.15, 95% CI 0.09–0.26; studies=1, participants=80; low-certainty evidence).

(2) Time to progression

Gemcitabine may reduce the risk of progression over time compared to BCG (HR 0.45, 95% CI 0.27–0.76; studies=1, participants=80; low-certainty evidence).

(3) Grade III to V adverse events

We are very uncertain about the effect of gemcitabine on the grade III to V adverse events compared to BCG (RR 1.00, 95% CI 0.21–4.66; studies=1, participants=80; very low-certainty evidence).

DISCUSSION

The findings of this review were based on fairly narrow evidence base on seven unique trials. Only one or two trials informed each of the five comparisons and all trials were conducted in Europe (four studies from Italy) or the US. Similar studies performed by other investigators in other countries would be valuable in validating these findings. Based on current evidence-based guidelines [4], after TUR of bladder tumor, people should undergo immediate postoperative instillation of mitomycin C followed by an induction course of anti-tumor agents, namely BCG, with or without maintenance therapy according to their risk of recurrence. As none of the included studies used this comparison, which is considered the standard of care, these issues limit clinical applicability.

We found only two systematic reviews that investigated the effect of gemcitabine compared to BCG [20] and mitomycin [21]. Ye et al. [20] included 365 participants from five trials, both randomized and non-randomized, and concluded that intravesical gemcitabine may have a similar effect on the recurrence (RR 1.17, 95% CI 0.83–1.67), progression (RR 1.02, 95% CI 0.42–2.56), and any adverse events (RR 0.55, 95% CI 0.25–1.20) compared to BCG. However, this review did not consider clinical heterogeneity of included studies (i.e., meta-analysis with regard to primary high-risk and intermediate-risk bladder cancer) and used RR for time to event outcomes, thereby questioning the appropriateness of pooling. Moreover, it provided no information of a priori registered protocol and risk of bias of included studies. Li et al. [21] reported that gemcitabine was more effective than mitomycin in terms of recurrence and adverse events. Although, the author explicitly mentioned that they included RCTs only, some studies were not RCTs. With regard to analysis, they did not consider clinical heterogeneity between included studies [21]. Recently, two systematic reviews which included participants with NMIBC not responsive to intravesical BCG were published [22,23]. They included all

Table 1. Gemcitabine compared to saline

Outcomes	Number of participants (studies)	Certainty of the evidence (GRADE[a])	Relative effect[b] (95% CI)	Anticipated absolute effects	
				Risk with saline	Risk difference with Gemcitabine
Time to recurrence (absolute effect size estimates based on recurrence rate at 4 years) Follow-up: range 2–4 years MCID: 5% absolute difference	734 [15,18]	⨁⨁◯◯ LOW[c,d,e]	HR 0.77 (0.54 to 1.09)	470 per 1,000[f]	Moderate 83 fewer per 1,000 (180 fewer to 29 more)
Time to progression (absolute effect size estimates based on recurrence rate at 4 years) Follow-up: range 2–4 years MCID: 5% absolute difference	654 [15,18]	⨁⨁◯◯ LOW[c,d,e]	HR 0.96 (0.19 to 4.71)	48 per 1,000[f]	Low 2 fewer per 1,000 (39 fewer to 159 more)
Grade III–V adverse events assessed with: 1 study: measured as serious adverse events; 1 study: CTCAE version 3.0 and version 4.0 Follow-up: range 1–3 months MCID: 5% absolute difference	668 [15,18]	⨁⨁◯◯ LOW[c,e]	RR 1.26 (0.58 to 2.75)	47 per 1,000	Study population 12 more per 1,000 (20 fewer to 83 more)

Patient or population: participants with non-muscle invasive bladder cancer (607 men, 127 women). Country: Germany, Turkey, and the US. Setting: multicenter, likely inpatients. Intervention: gemcitabine. Comparison: saline.

GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; CI, confidence interval; MCID, minimal clinically important difference; HR, hazard ratio; RR, risk ratio; CTCAE, Common Terminology Criteria for Adverse Events.

[a]:GRADE Working Group grades of evidence: (1) High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. (2) Moderate certainty: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. (3) Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. (4) Very low certainty: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

[b]:The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[c]:Downgraded by one level for study limitations: high risk of selective reporting and other bias.

[d]:Not downgraded further for moderate inconsistency; this contributed to the decision to downgrade twice overall.

[e]:Downgraded by one level for imprecision: CI crosses a clinical important threshold and no effect.

[f]:Baseline risk for recurrence, progression, and death from any cause came from [18].

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Table 2. Gemcitabine compared to mitomycin

Outcomes	Number of participants (studies)	Certainty of the evidence (GRADE[a])	Relative effect[b] (95% CI)	Anticipated absolute effects	
				Risk with mitomycin	Risk difference with Gemcitabine
Time to recurrence Follow-up: 3 years MCID: 5% absolute difference	109 [13]	⊕⊕◯◯ LOW[c,d]	HR 0.36 (0.19 to 0.69)	Study population 400 per 1,000	232 fewer per 1,000 (308 fewer to 103 fewer)
Time to progression Follow-up: 3 years MCID: 5% absolute difference	109 [13]	⊕⊕◯◯ LOW[c,e]	HR 0.57 (0.32 to 1.01)	Study population 182 per 1,000	74 fewer per 1,000 (120 fewer to 2 more)
Grade III–V adverse events (local adverse events which result in delay intravesical treatment were regarded as Grade III-V complications.) Follow-up: 3 years MCID: 5% absolute difference	109 [13]	⊕◯◯◯ VERY LOW[c,f]	RR 0.51 (0.13 to 1.93)	Study population 109 per 1,000	53 fewer per 1,000 (95 fewer to 101 more)

Patient or population: participants with non-muscle invasive bladder cancer[g] (93 men, 16 women). Country: Italy. Setting: single center, likely inpatients. Intervention: gemcitabine. Comparison: mitomycin.

GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; CI, confidence interval; MCID, minimal clinically important difference; HR, hazard ratio; RR, risk ratio.

[a]:GRADE Working Group grades of evidence: (1) High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. (2) Moderate certainty: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. (3) Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. (4) Very low certainty: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

[b]:The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[c]:Downgraded one level for study limitations: unclear or high risk of bias on one or more domains.

[d]:Downgraded one level for imprecision: outcome based on only a single study of a small number of participants.

[e]:Downgraded one level for imprecision: CIs crossed a clinically important threshold and no effect.

[f]:Downgraded two levels for imprecision: CIs crossed a clinically important threshold and no effect; wide CIs.

[g]:The analysis was only based on participants with recurrent non-muscle invasive bladder cancer; the only included trial did not include participants with primary (untreated) disease.

Table 3. Gemcitabine compared to BCG for recurrent (one-course BCG failure) non-muscle invasive bladder cancer

Outcomes	Number of participants (studies)	Certainty of the evidence (GRADE[a])	Relative effect[b] (95% CI)	Anticipated absolute effects	
				Risk with BCG	Risk difference with Gemcitabine
Time to recurrence Follow-up: range 6–22 months MCID: 5% absolute difference	80 [16]	⊕⊕◯◯ LOW[c,d]	HR 0.15 (0.09 to 0.26)	Study population 970 per 1,000	561 fewer per 1,000 (699 fewer to 372 fewer)
Time to progression Follow-up: range 6–22 months MCID: 5% absolute difference	80 [16]	⊕⊕◯◯ LOW[c,d]	HR 0.45 (0.27 to 0.76)	Study population 325 per 1,000	163 fewer per 1,000 (224 fewer to 67 fewer)
Grade III–V adverse events assessed with: CTCAE version 3.0 Follow-up: range 6–22 months MCID: 5% absolute difference	80 [16]	⊕◯◯◯ VERY LOW[c,e]	RR 1.00 (0.21 to 4.66)	Study population 75 per 1,000	0 fewer per 1,000 (59 fewer to 275 more)

Patient or population: participants with recurrent (1-course BCG failure) high-risk non-muscle invasive bladder cancer (49 men, 31 women). Country: Italy. Setting: multicenter, likely inpatients. Intervention: Gemcitabine. Comparison: BCG.
BCG, Bacillus Calmette–Guérin; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; CI, confidence interval; MCID, minimal clinically important difference; HR, hazard ratio; CTCAE, Common Terminology Criteria for Adverse Events; RR, risk ratio.
[a]:GRADE Working Group grades of evidence: (1) High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. (2) Moderate certainty: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. (3) Low certainty: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. (4) Very low certainty: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.
[b]:The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[c]:Downgraded one level for study limitations: high risk of bias on one or more domains.
[d]:Downgraded one level for imprecision: outcome based on only a single study of a small number of participants.
[e]:Downgraded by two levels for imprecision: CI crossed a clinically important threshold and no effect; wide CIs.

studies regardless of the study design; however, they found no additional RCTs to the ones that we included. These two reviews can help the reader understand the current best body of evidence; however, our confidence must be very low about the results from study designs other than RCTs given the inherent study limitations of nonrandomized studies. This updated Cochrane Review used rigorous methodology, exhaustive literature search, and assessment of the certainty of the evidence using GRADE, thereby providing the most reliable evidence summary.

CONCLUSIONS

Based on findings of this review, gemcitabine may have a favorable impact on recurrence and progression-free survival than saline and mitomycin but we are uncertain about how major adverse events compare. The same is true when comparing gemcitabine to BCG in individuals with high risk disease who have previously failed BCG.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and the CDSR should be consulted for the most recent version of the review.

AUTHORS' CONTRIBUTIONS

Research conception and design: Eu Chang Hwang and Philipp Dahm. Data acquisition: Mi Ah Han, Philipp Maisch, Jae Hung Jung, and Jun Eul Hwang. Statistical analysis: Eu Chang Hwang and Vikram Narayan. Data analysis and interpretation: Eu Chang Hwang and Jun Eul Hwang. Drafting of the manuscript: Mi Ah Han and Eu Chang Hwang. Critical revision of the manuscript: Philipp Dahm and Jun Eul Hwang. Administrative, technical, or material support: Anne Cleves. Supervision: Philipp Dahm. Approval of the final manuscript: Mi Ah Han, Philipp Maisch, Jae Hung Jung, Jun Eul Hwang, Vikram Narayan, Anne Cleves, Eu Chang Hwang, and Philipp Dahm.

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SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4111/icu.20210265.

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