

Intravesical gemcitabine therapy for non-muscle invasive bladder cancer (NMIBC): a systematic review

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- Intravesical immunotherapy or chemotherapy for non-muscle invasive bladder cancer is a well-established treatment for preventing or delaying tumour recurrence after tumour resection. However, up to 70% of patients may fail and new intravesical agents with improved effectiveness are needed. Gemcitabine is a relatively new anticancer drug that has shown activity against bladder cancer.
- To systematically review the literature on the effectiveness and toxicity of intravesical gemcitabine for non-muscle invasive bladder cancer (NMIBC).
- MEDLINE, EMBASE, CINAHL, the Cochrane database of systematic reviews, LILACS, SCOPUS, BNI, Biomed Central, Web of Science and BIOSIS were searched to identify trials of intravesical gemcitabine for the treatment of NMIBC. Also searched were meeting proceedings, international guidelines and trial registries. Data on authors, study design, patient characteristics, interventions and outcome data relating to tumour recurrence, disease progression, survival and adverse events were extracted from relevant studies.
- Six relevant randomised trials were identified with the number of patients randomised in each trial varying from 30 to 341 (total 704). All trials compared gemcitabine to active controls and varied in the reporting of outcomes.
- The first was a marker lesion study which reported greater tumour response rates when intravesical gemcitabine (2 g) was given as three bi-weekly doses (36%) or six weekly doses (40%) compared with a single dose (9%).
- One study compared a single postoperative instillation of intravesical

What's known on the subject? and What does the study add?

The standard treatment for non-muscle invasive bladder (NMIBC) is transurethral resection followed by intravesical therapy. Intravesical agents, e.g. bacille Calmette-Guérin (BCG) or mitomycin C (MMC), have activity in delaying and reducing the incidence of tumour recurrence after surgery but have significant side-effects and are not effective in all patients. Clinical data suggests that gemcitabine has activity in this disease in terms of tumour response and is less toxic, and warrants further study.

This systematic review comprehensively presents the available clinical evidence on intravesical gemcitabine for NMIBC. The limited data from randomised trials suggest that gemcitabine may have role in intermediate-risk patients, as an alternative to MMC, and in high-risk, BCG-refractory patients. Data from observational studies indicate that minimal systemic absorption occurs with intravesical administration and that gemcitabine is active in reducing tumour recurrence.

gemcitabine with a saline placebo in 341 patients and found no significant difference in the rates of tumour recurrence (28% vs 39%, respectively) or recurrence-free survival (hazard ratio 0.95, 95% confidence interval 0.64–1.39, $P = 0.77$). The rate of progression to invasive disease was greater with gemcitabine (2.4% vs 0.8%).

- A further trial compared gemcitabine with intravesical mitomycin C (MMC) and reported that the rates of recurrence (28% vs 39%) and progression (11% vs 18%) were lower with gemcitabine but did not reach statistical significance. The overall incidence of adverse events was significantly less with gemcitabine (38.8% vs 72.2%, $P = 0.02$).

- Three trials compared gemcitabine with intravesical bacille Calmette-Guérin (BCG) but a meta-analysis was not possible due to clinical heterogeneity.

- In untreated patients at intermediate risk of recurrence (primary Ta–T1, no carcinoma *in situ*) one trial showed that gemcitabine

and BCG were similar with respective recurrence rates of 25% and 30% ($P = 0.92$) and overall progression equal. Dysuria (12.5% vs 45%, $P < 0.05$) and frequency (10% vs 45%, $P < 0.001$) were significantly less with gemcitabine.

- In a second trial of high-risk patients the recurrence rate was significantly greater with gemcitabine compared with BCG (53.1% vs 28.1%, $P = 0.04\%$) and the time to recurrence significantly shorter with gemcitabine (25.5 vs 39.4 months, $P = 0.042$).

- Finally, in a third trial of high-risk patients who had failed previous intravesical BCG therapy, gemcitabine was associated with significantly fewer recurrences (52.5% vs 87.5%, $P = 0.002$) and a longer time to recurrence (3.9 vs 3.1 months, $P = 0.9$) compared with BCG. Progression rates were similar in both groups (33% vs 37.5%, $P = 0.12$) with no significant differences in grade 2 or 3 toxicities.

- The data from several observational studies confirm the pharmacology of

gemcitabine as an intravesical agent whilst others report the activity of gemcitabine in terms of tumour recurrence. However, these studies are inherently biased and these data should be interpreted appropriately.

- In conclusion a single study suggests that in NMIBC multiple doses of intravesical gemcitabine reduce tumour recurrences to a greater extent than a single dose.
- In contrast, a single dose immediately after surgery is ineffective based on one

study. Gemcitabine may be more active than MMC with a lower toxicity profile.

- Compared with intravesical BCG therapy, gemcitabine had similar effects in intermediate-risk patients, less effective in high-risk patients and superior in BCG-refractory patients. However, each randomised trial identified represents a different clinical setting in NMIBC and therefore the evidence base is limited. Consequently these data should be interpreted with caution until

further corroborative evidence becomes available.

- Intravesical gemcitabine is a promising drug that may add to the urologist's options in treating patients with NMIBC.

KEYWORDS

intravesical gemcitabine, non-muscle invasive bladder cancer (NMIBC), systematic review

INTRODUCTION

Bladder cancer is a major clinical problem worldwide and the incidence has increased over the last two decades. The WHO reported 356 557 new cases of bladder cancer globally in 2002 [1]. In 2007, there were ≈67 000 new cases in the USA [2] and in the UK for the year 2006, ≈10 300 new cases were reported [3]. These statistics indicate that bladder cancer is a major problem and represents the fourth most common cancer in men and eighth in women.

At presentation, ≈80% of bladder tumours are classified as non-muscle invasive cancer (NMIBC) confined to the inner lining of the bladder. The typical initial management approach is cystoscopic visualisation, followed by transurethral resection (TUR). NMIBC has a tendency to recur after initial surgery and may progress to muscle-invasive disease, which has a much poorer prognosis. To help prevent or delay tumour recurrence, intravesical therapy with BCG or anti-cancer drugs is frequently used as an adjunctive after TUR. Gemcitabine is a relatively new anti-cancer agent with documented activity against metastatic bladder cancer [4]. Recently, phase I studies

in patients with NMIBC have indicated a good safety profile and the potential for gemcitabine as an intravesical agent for recurrent disease [5]. In phase II studies, intravesical gemcitabine has been administered at a dose of 2 g, achieving a urine concentration of 40 mg/mL and instilled for 1–2 h, generally given once weekly for 6 weeks [6–9]; patients included those with recurrent tumours and BCG-refractory tumours. There were complete tumour responses in 23–56% of patients with a 1-year recurrence-free survival (RFS) of up to 21% [7]. Both systemic and local toxicities generally were not higher than grade 2. These data suggest that intravesical gemcitabine has activity in NMIBC, including in those patients at high risk of recurrence. The favourable toxicity profile of intravesical gemcitabine suggests that dose escalation may be possible.

The activity of gemcitabine for NMIBC and the acceptable safety profile suggest that this agent may have a role in the management of patients with this disease. The objective of this systematic review was to comprehensively present the available clinical data on intravesical gemcitabine for the management of NMIBC, emphasising the evidence from randomised trials. Findings

from observational studies are also presented but we caution against over interpretation of effectiveness due to the lack of randomised controls.

METHODS

Search strategies were developed to identify trials of intravesical gemcitabine for NMIBC in MEDLINE, EMBASE, CINAHL, the Cochrane Database of Systematic Reviews, LILACS, SCOPUS, BNI, Biomed Central and Web of Science. The search was extended to international guidelines on NMIBC, trial registries and recent systematic reviews. The results of the searches were compiled in a bibliographic database (ENDNOTE). Data extraction was carried out from relevant studies by three authors.

RESULTS

The combined searched yielded a total of 521 potential references relevant to this review. After screening the titles and abstracts six randomised trials and 27 observational studies of intravesical gemcitabine were identified. The outcome data for these six randomised trials [10–15] are summarised in Table 1.

TABLE 1 Summary of results from randomised trials of intravesical gemcitabine in NMIBC

Study/patients	Interventions	Study outcomes			
		Complete response of marker lesion, n/N	RFS, %	RFS time, months	Progression rate (over study duration), %
Gardmark <i>et al.</i> 2005 [13]	Gemcitabine				
32 recurrent, multiple Ta G1–2	Single dose	1/11			
	1 dose/week	4/11			
	2 doses/week	4/10			
Bohle <i>et al.</i> 2009 [12]	Gemcitabine		35.5	median 37.2	2.4
355 primary or recurrent Ta–T1, G1–3	vs				
	placebo		36.3	40.2	0.8
Addeo <i>et al.</i> 2010 [10]	Gemcitabine		28	Not reached	11
120 recurrent Ta–T1, G1–3	vs				
	MMC		39	15.0	18
Bendary <i>et al.</i> 2011 [11]	Gemcitabine		25	Not reported	Same for each group ($P = 1.0$)
80 primary Ta–T1 (no CIS)	vs				
	BCG		30		
Porena <i>et al.</i> 2010 [15]	Gemcitabine		53.1	Mean 25.6	0
64 high risk Ta–T1 G1–3 and/or CIS	vs				
	BCG		28.1	39.4	0
Lorenzo <i>et al.</i> 2010 [14]	Gemcitabine		52.5	3.9	33.0
80 BCG-refractory high risk Ta–T1	vs				
	BCG		87.5	3.1	37.5

RFS, recurrence free survival; MMC, mitomycin C; BCG, *Bacillus Calmette-Guerin*.

Intravesical gemcitabine and marker lesion studies

A randomised, multicentre, open-label study was designed to evaluate the response rate of gemcitabine at three different doses levels in 32 patients with recurrent, multiple tumours (14 patients with TaG1 and 16 with TaG2) recruited from five Swedish centres [13]. This was a marker lesion study, where a well-defined tumour was left in place after TUR and used to assess the effectiveness of gemcitabine. Generally patients with Ta NMIBC are considered at low to intermediate risk of progression and for this reason were the patient group chosen in case the treatment protocol was ineffective.

A central randomisation scheme was used to allocate patients to one of three schedules of intravesical gemcitabine, although there was no 'blinding' reported. Gemcitabine 2000 mg/100 mL saline was instilled for 60 min either as a single dose (11 patients), twice weekly for 3 weeks (11), or once per week for 6 weeks (10).

Of the 32 patients recruited, two were excluded because of protocol violations and none were lost to follow-up. This trial was designed as a feasibility study with 20 patients planned for each group; however, due to recruitment problems the trial was stopped early. This trial was assessed as low to intermediate risk of bias.

The results of this study indicated that a single dose of gemcitabine (2 g) induced a complete response in one of 11 patients (complete disappearance of the marker lesion with no new ones), no response in four of 11 patients and progressive tumour development in five of 11 patients. When gemcitabine was administered twice weekly for 3 weeks or once per week for 6 weeks, there were complete responses in four of 10 patients and four of 11 patients, respectively. There was no statistical analysis of these data but they suggest that a single dose is suboptimal and multiple doses are more effective. Eight of the 32 patients reported toxicity, mainly in the multiple dose groups consisting of nausea, anaemia, thrombocytopenia and fever.

As shown in Table 2 [6,8,16–18], several published observation studies have reported tumour response data for marker lesions in patients with NMIBC. At a dose of 2 g gemcitabine given weekly for 6–8 weeks the response rates were between 14% and 69%. Disease progression was either not observed or low. Generally these gemcitabine schedules were reported as well tolerated.

Single agent gemcitabine studies

A single postoperative instillation of gemcitabine was compared with a saline placebo in a multi-centre, double-blind, randomised study recruiting 355 patients with primary or recurrent Ta–T1 G1–3 TCC [12]. The instillations of gemcitabine 2000 mg/100 mL saline were given between 30 and 40 min of TUR, followed by continuous saline irrigation for at least 20 h. Patients were stratified by primary or recurrent disease and centre. The primary endpoint was RFS with secondary objectives of type of recurrence, progression and adverse events. A second TUR with no instillation, and adjuvant BCG instillations

TABLE 2 Marker lesion studies of intravesical gemcitabine in NMIBC

Study	Participants	Gemcitabine schedule	Study outcomes
Gontero <i>et al.</i> 2004 [6]	39 intermediate risk	2 g weekly × 6	CR: 56% No progression in 17 NR. No toxicity above grade 1.
De Berardinis <i>et al.</i> 2004 [16]	18 recurrent, multiple Ta–T1, G1–2	2 g weekly × 6	CR: 50% at 2 months PR: 27%, NR: 22%. No progression observed. Minimal toxicity.
Serretta <i>et al.</i> 2005 [8]	27 Ta–T1, 3 doses, 9 in each group	0.5 g, 1 g, and 2 g All weekly × 6	CR: overall 23% (1 patient at 0.5g, 2 at 1g, 3 at 2g). 4 patients DF at 22 months
Calais da Silva and Calais da Silva 2005 [17]	42 multiple Ta–T1	2 g weekly × 8	CR: 69% NR: 33%. No evidence of progression. Haematuria in 2, dysuria in 4.
Brausi <i>et al.</i> 2007 [18]	14 primary, low-risk, single tumour <2 cm	2 g weekly × 6	CR: 2 (14%) Failure: 11 (79%). 1 patient progressed (7%). 4 grade 1 and 1 grade 2 toxicity (pollakiuria)

CR, complete response – generally defined as negative cystoscopy, cytology and biopsy; PR, partial response; NR, no response; DF, disease free.

were permissible. However, the method for randomisation was not stated and the number of patients lost before intravesical therapy was reported as 7.3% in the gemcitabine arm and 8.0% in the placebo arm. This trial was therefore considered at low risk of bias.

With follow-up cystoscopies at 3 and 6 months and then 6 monthly, an immediate instillation after TUR of gemcitabine was associated with a median RFS of 37.2 months compared with 40.2 months in the saline placebo arm ($P = 0.78$) [12]. The RFS rates from a Kaplan–Meier analysis at 12 and 24 months were also similar for gemcitabine (77.7% and 64%) and placebo (75.3% and 60.7%). The overall recurrence rates were 35.5% and 36.3%, respectively. In a subgroup analysis, the RFS was not significantly associated with risk (high vs low), primary or recurrent disease, primary or secondary TUR, concomitant BCG therapy or the number of lesions. The number of patients who had disease progression was small in each group (gemcitabine three [2.4%], placebo one [0.8%]). In this study, there were fewer events than expected (87 recurrences and seven deaths) and the trial

was stopped early. These data indicate that with this trial design, a single instillation of gemcitabine was no better than placebo for tumour recurrence.

Several observational studies [9,19–23] have evaluated the efficacy and tolerability of intravesical gemcitabine for NMIBC including immediate single-dose gemcitabine (Table 3). A dose of 2 g gemcitabine was consistently given but the dissolution volume, dwell time and frequency of administration varied. The treatment appears to be active with between 46% and 92% of patients diagnosed as recurrence-free after gemcitabine. Using these schedules gemcitabine was reported to be well tolerated with little or no toxicities above grade 1, which resulted in high patient compliance.

Intravesical gemcitabine compared with other intravesical agents

Several randomised trials have compared intravesical gemcitabine with either mitomycin C (MMC) or BCG. In a prospective, randomised trial Addeo *et al.* [10] compared intravesical gemcitabine with

MMC in 109 previously treated, recurrent patients who had progressed or failed BCG therapy. The schedules were gemcitabine 2000 mg/50 mL saline instilled for 1 h given weekly for 6 weeks (54 patients) or MMC 40 mg/50 mL instilled for 1 h within 2 days of TUR then weekly for 4 weeks (55). The 'responders' in each group had 10 monthly treatments. The primary endpoints of this study were disease-free interval (date of randomisation to first positive cytology), relative risk of tumour recurrence and the recurrence rate. Progression rates and toxicity were also assessed. Patients were stratified by age, stage (T1 or Ta) and grade (1–2 or 3) before randomisation to ensure these variables were equally distributed between patient groups. The method of randomisation was not reported, nor was there any blinding of treatment or outcome assessment. The 11 patients excluded from the initial 120 recruited were described as follows: 'three not meeting the study inclusion criteria, four refused to participate and four for other reasons'. This study was considered low to intermediate risk of bias.

At a median follow-up of 36 months, the percentage of patients with tumour recurrence was 28% for gemcitabine and 39% for MMC (no P value given). The mean time to recurrence was longer for gemcitabine than MMC. The relative risk of recurrence (0.72 vs 0.94, $P = 0.29$) and the recurrence rate per 100 patient-months (1.26 vs 1.71, $P = 0.31$) were higher for the MMC group. The rate of disease progression by stage was also greater for MMC (11% vs 18%, $P = 0.14$). The overall incidence of adverse events was 38.8% for gemcitabine and 72.2% for MMC. These data suggest that intravesical gemcitabine has a more favourable efficacy and toxicity profile than MMC and may be potentially useful in BCG-refractory patients.

Three randomised trials compared the efficacy and tolerability of intravesical gemcitabine with intravesical BCG [11,14,15]. However, pooling of these data and meta-analysis was considered inappropriate because of considerable clinical heterogeneity.

An Egyptian randomised trial compared the efficacy and safety of gemcitabine with BCG and was presented in abstract form at the AUA meeting in 2011 [11]. Between June 2006 and June 2008, this study randomised

TABLE 3 Observational studies of gemcitabine in NMIBC

Study	Participants	Gemcitabine schedule	Study outcomes
Buettner <i>et al.</i> 2004 [19]	23 with complete resection of NMIBC. Feasibility study.	2 g in 100 mL buffer for 30 min within 1 h of resection, then saline irrigation.	Nine tumour-free, one progression. No toxicity exceeded grade 2. Grade 1: bleeding – 1, haematuria – 1, dysuria – 4. Grade 2: haematuria – 3, incontinence 1. Median follow-up 8.5 months. 81% recurrence-free. Median DF interval 11.8 months. Dysuria 48%, frequency 10%, haematuria 5%, nausea 5%.
Iannelli <i>et al.</i> 2004 [20]	21 pTa–T1, G1–2. Multifocal in 19%.	2 g in 50 mL saline for 1 h weekly × 6 then monthly × 12.	CR: 89%. Non-responders progressed. Side-effects did not exceed grade 1. Follow-up 26 months. 92% recurrence-free, 8% relapsed. Toxicities only grade 1: irritative bladder 5%, asthenia 3%, hot flashes 2%, nausea and vomiting 2%, anaemia 7%, leukopenia 5%.
De Cataldis <i>et al.</i> 2005 [21]	34 pTa–T1 G1–3	2 g in 50 mL saline for 2 h weekly × 6	CR: 46%. NR: 54%. Median (range) TTR 9.1 (2.9–26.5) months. Local or systemic toxicities 26%. 75% recurrence-free at 1 year. Urgency 14%, dizziness 5%, pain 1%, bladder ulcers 1%. 82% no toxicities.
Bounedjar <i>et al.</i> 2005 [22]	60 (nine CIS, 51 pT1)	2 g in 100 mL saline weekly × 6	
Maffezzini <i>et al.</i> 2007 [23]	28 recurrent, low- or intermediate-risk NMIBC	2 g in 50 mL weekly × 4	
Bartoletti <i>et al.</i> 2005 [9]	116 intermediate- or high-risk NMIBC	2 g weekly × 6	

CR, complete response – generally defined as negative cystoscopy, cytology and biopsy; NR, no response; TTR, time to recurrence.

80 patients with intermediate risk, primary Ta–T1 NMIBC without carcinoma *in situ* (CIS) to either agent.

All patients underwent complete TUR, after which they were randomised to six weekly instillations of either BCG 6×10^8 colony-forming units in 50 mL saline or 2000 mg gemcitabine in 50 mL saline. The main study endpoint was either completing a period of 18 months follow-up without relapse, or the appearance of recurrence or progression during the study period. All patients received the treatment to which they were randomised. However, they did not report the method used for the randomisation procedure. In addition, there was no 'blinding' of either the intervention received or outcome assessment. This study was reported as a meeting abstract and consequently was not subject to the same peer-review process as journal articles. For these reasons this study was categorised as having an intermediate risk of bias.

At a mean (SD, range) follow-up of 10.8 (2.7, 3–18) months, the percentage of patients with tumour recurrence was similar in each group (25% gemcitabine, 30% BCG, $P = 0.61$). The results were also similar when expressed according to Ta stage (22% gemcitabine, 26% BCG, $P = 0.92$) and T1 stage (27% gemcitabine, 33% BCG, $P = 0.66$). Overall progression rates were also similar between gemcitabine and BCG ($P = 1.0$), although no individual values were reported. When analysed according to stage, one patient in each group with Ta disease progressed, whilst those with T1 had a 9.1% progression rate for gemcitabine and 9.5% for BCG ($P = 1.0$). Dysuria was significantly more common in patients receiving BCG (12.5% vs 35%, $P = 0.05$) as was urinary frequency (10% vs 45%, $P = 0.001$). These data suggest that in patients at intermediate risk of recurrence or progression, gemcitabine appears equivalent to BCG but with less side-effects.

An Italian, single centre, prospective randomised trial compared intravesical BCG with gemcitabine in patients with high-risk NMIBC [15]. Patients who had received prior chemotherapy within the previous 3 months or immunotherapy within 6 months were excluded. This study reported on the comparative rates for recurrence and disease progression, and tolerability for both BCG and gemcitabine. All patients underwent TUR, and then 4 weeks later a 'second-look' TUR was performed. Patients were randomised to either six weekly instillations of BCG 5×10^8 colony-forming units in 50 mL saline for 2 h (32 patients) or six weekly instillations of gemcitabine 2000 mg in 50 mL saline for 2 h (32). The maintenance therapy for patients that did not have recurrence in each group was at 3, 6, 12, 18, 24, 30 and 36 months. Randomisation was performed using a random number generator and permuted block design. There was no 'blinding' of the interventions or outcome assessments. In all,

10 patients were excluded after recruitment: eight did not meet the inclusion criteria and two refused to participate. This trial was rated as low to intermediate risk of bias.

At 3 months after TUR, all patients underwent cytology, cystoscopy and cold-cup biopsy. At a mean follow-up of 44 months the recurrence rate was significantly less with BCG (28.1% vs 53.1%, $P = 0.037$). The mean recurrence-free interval was also significantly longer with BCG (39.4 vs 25.6 months, $P = 0.042$). No patient in either group developed disease progression. There was no significant difference in local toxicity, e.g. cystitis (BCG 12.5%, Gemcitabine 9.3%) or systemic toxicity, e.g. fever (BCG 6.2%, Gemcitabine 0%). The results from this study suggested that gemcitabine was inferior to BCG in preventing or delaying tumour recurrence but that the favourable toxicity profile indicated that gemcitabine could be a treatment option for patients unsuitable for BCG therapy.

The third randomised trial comparing gemcitabine with BCG was a multicentre, prospective phase II study, recruiting 80 high-risk patients who were refractory to BCG therapy and had refused or were not suitable for cystectomy [14]. The primary endpoint was the recurrence rate at 1 year with secondary endpoints of RFS, disease progression and toxicity. Patients were randomised to gemcitabine (40 patients), 2000 mg/50 mL for 6 weeks then weekly for 3 weeks at 3, 6 and 12 months or BCG (Connaught) 8 mg/50 mL (same schedule as gemcitabine; 40 patients). Both treatments were started 4–6 weeks after the last TUR. A central computer randomisation method was used to allocate treatment options. This was an open-label study, so there was no 'blinding' of treatments or outcomes. In all, 12 patients were excluded from the 92 recruited patients and the reasons documented were: eight not meeting the inclusion criteria, three refused to participate and one for other reasons. This trial was assessed as low risk of bias.

BCG-refractory, high-risk patients had a recurrence rate of 52.5% (21/40) after intravesical gemcitabine compared with 87.5% (35/40) for intravesical BCG. This difference was statistically different ($P = 0.002$). The recurrence rates at 2 years extrapolated from the Kaplan–Meier

analysis, confirmed the significant difference (19% gemcitabine, 3% BCG; hazard ratio 0.15, 95% CI 0.1–0.3, $P < 0.008$). However, there was no significant difference in the RFS (hazard ratio 1.1, 95% CI 0.8–1.2, $P = 0.9$). Progression rates were also similar between groups: gemcitabine 33% and BCG 37.5% ($P = 0.12$). It appears that intravesical gemcitabine is significantly more active than BCG in reducing and delaying tumour recurrence in patients who have failed prior BCG therapy. Gemcitabine may therefore be an effective option as a second-line treatment for this difficult group of patients where cystectomy is refused or not suitable.

Observational studies of gemcitabine in refractory patients

Table 4 [5,24–30] presents published observational studies that have reported on the administration of intravesical gemcitabine in patients previously treated with intravesical immunotherapy or chemotherapy and have consequently failed treatment [5,24–30]. These data indicate that gemcitabine at a dose of 2 g with varying schedules may induced a recurrence-free status in some patients (46–60%), although a substantial number develop disease progression. Most report that the treatment is well tolerated. The combination of gemcitabine with intravesical MMC is also active in refractory patients. However, these studies designs are inherently biased and therefore these data should be treated with caution. The role of intravesical gemcitabine in refractory patients is at present unclear.

Suitability of gemcitabine as an intravesical agent

Gemcitabine has several pharmacological properties that are conducive for its use as an intravesical agent in the management of NMIBC. The low molecular weight and the high lipid solubility allow sufficient uptake into malignant urothelial cells for cytotoxicity *in vivo*. Our literature search identified eight studies investigating the pharmacokinetics of intravesical gemcitabine [31–38]. These studies (Table 5) have shown a high plasma clearance for gemcitabine, indicating that any drug distributed to the systemic circulation after intravesical administration, will be quickly eliminated, reducing the risk of systemic toxicity. Minimal amounts of intravesical gemcitabine

reach the systemic circulation with plasma levels ranging from undetectable to a maximum of 2.5 µg/mL (0.83 µM) for the parent drug. As much as 100% of the instilled dose of gemcitabine has been reported to remain within the bladder, which is an ideal pharmacological characteristic for an intravesical agent. One study showed that the pH of the instilled gemcitabine, the urine concentration achieved and the dwell time are important for maximum tumour drug penetration [38].

DISCUSSION

This review aimed to determine the role of intravesical gemcitabine in NMIBC emphasising the evidence from published randomised trials. However, an extensive search of the literature resulted in identifying only six relevant randomised studies. The first study showed that tumour response rates were higher when gemcitabine was given in multiple doses rather than a single dose [13]. An additional trial compared a single dose of gemcitabine with a placebo immediately after surgery and found no significant difference in the rate of tumour recurrence or RFS [12]. Another study compared intravesical gemcitabine with intravesical MMC and reported that more patients remained recurrence-free with gemcitabine and had less chemical cystitis [10]. Three trials compared gemcitabine with intravesical BCG [11,14,15]. The first trial enrolled patients with intermediate risk of recurrence and reported gemcitabine was as effective as BCG in preventing tumour recurrence and disease progression but with fewer side-effects. The second trial enrolled untreated patients with a high risk of recurrence and found gemcitabine to be inferior to BCG in preventing recurrence but again was less toxic than BCG. The third trial recruited BCG-refractory patients and showed that gemcitabine was better than BCG in reducing the rate of tumour recurrence. These few trials suggest that intravesical gemcitabine has activity in delaying tumour recurrence.

The dose-finding study of Gardmark *et al.* [13] used a residual tumour (marker lesion concept) to assess responses to intravesical gemcitabine in low-risk patients. This type of study allows rapid identification of the ablative activity of gemcitabine. Multiple

TABLE 4 Observational studies of intravesical gemcitabine for refractory NMIBC

Study	Participants	Gemcitabine schedule	Study outcomes
Raj and Dalbagni 2010 [5]	30 BCG refractory	2 g bi-weekly × 6 1 week break then repeat	Median follow-up 19 months. 46% CR (21% RF at 1 year). 13% progressed. 37% had cystectomy.
Gunelli <i>et al.</i> 2007 [24]	40 TaG3–T1G3 BCG refractory	2 g days 1 and 3 for 6 weeks	Median follow-up 28 months. 95% cystoscopy/cytology negative at 6 months. 35% recurred. Toxicity very mild.
Mohanty <i>et al.</i> 2008 [25]	35 BCG failures	2 g 2 weeks after TUR for 6 weeks	60% RF. 31% recurred (superficial). 9% progressed. Adverse events mild.
Morabito <i>et al.</i> 2006 [26]	61 pre-treated, multiple recurrence	2 g per week × 8 (reported tolerability)	87% completed the cycle. 4 severe systemic toxicities, 4 severe local toxicities.
Perdona <i>et al.</i> 2010 [27]	20 high risk BCG refractory	2 g weekly × 6 then weekly × 6 at 3, 6 and 12 months	Median follow-up 15.2 months. 55% recurred. 25% progressed. Treatment well tolerated – urinary symptoms mainly.
Breyer <i>et al.</i> 2010 [28]	10 BCG refractory	1 g gemcitabine plus 40 mg MMC weekly × 6 then monthly × 12	Median follow-up 26.5 months. 6 recurrence-free. 4 biopsy-proven recurrence. Therapy well tolerated.
Maymi <i>et al.</i> 2006 [29]	39 chemotherapy and BCG refractory	Gemcitabine 1 g × 6–8 weeks (12 patients) or gemcitabine + MMC 40 mg (27 patients)	Median follow-up 5 months. Gemcitabine alone – all 12 failed. With MMC 56% disease-free.
Gacci <i>et al.</i> 2006 [30]	19 previously treated T1G3	Compared gemcitabine (nine patients) with BCG (10 patients)	Both well tolerated No adverse events reported. Gemcitabine – 3 RF, 7 intact bladder. BCG – 1 RF, 6 intact bladder.

CR, complete response – generally defined as negative cystoscopy, cytology and biopsy; RF, recurrence free.

doses of gemcitabine (2 g) given twice per week for 3 weeks or every week for 6 weeks, were active in inducing complete responses. However, a single dose was clearly suboptimal, which may reflect the larger instillation volume (100 mL) used and thus the lower concentration of intravesical gemcitabine achieved in this study compared with the standard volume of 50 mL.

When a single dose of gemcitabine (2000 mg/100 mL) was given immediately after surgery, no effect on tumour RFS was found compared with a saline placebo [12]. However, this study differs from the single dose in the previous lesion marker study in several ways including: the timing of the instillation, the type of patients recruited and the measure of effectiveness. The reported lack of activity for gemcitabine contrasts with data from published

randomised studies of other cytotoxic agents given intravesically as a single dose immediately after tumour resection [39]. Importantly, the Bohle *et al.* [12] 2010 study, used continuous bladder irrigation after instillation for at least 20 h and a short dwell time of 30–40 min, which may have contributed to the lack of effectiveness compared with placebo. Possibly gemcitabine may require a longer exposure time for optimum activity, as it acts as a phase-specific agent. The authors also emphasised that the RFS was exceptionally high in both groups. For example at 12 months the RFS rates were 77.7% for gemcitabine and 75.3% for the placebo group, making it difficult to demonstrate a difference statistically. However, these trial data do not support the use of a single-dose intravesical gemcitabine immediately after resection for NMIBC using this drug schedule.

In contrast to the single dose results for gemcitabine, a six weekly induction course in patients previously treated with BCG or epirubicin and with recurrent Ta–T1 disease, induced encouraging results when compared with intravesical MMC [10]. MMC is an established intravesical agent with proven activity in NMIBC [40]. At a median follow-up of 36 months, 72% of patients randomised to gemcitabine remained recurrence-free compared with 61% for those receiving MMC. In addition, the toxicity associated with gemcitabine, in particular chemical cystitis, was also significantly less compared with MMC. The results of this study suggest that gemcitabine may have a role in patients who have failed intravesical therapy and refuse or are not suitable for cystectomy. However, the data are limited to this one study of 109 assessable patients and warrants further confirmation in randomised studies.

TABLE 5 Pharmacokinetic studies of intravesical gemcitabine in NMIBC

Study	Participants	Gemcitabine schedule	Study outcomes
Laufer <i>et al.</i> 2003 [31]	15 recurrent and refractory	0.5–2 g in 50 mL or 100 mL saline for 2 h weekly × 6	Plasma gemcitabine $\leq 1 \mu\text{g/mL}$ at 2 g dose, undetectable at $<1.5 \text{ g}$ dose. 60–100% of instilled dose in voided urine. 0.5–5.5% of dose absorbed.
Palou <i>et al.</i> 2004 [32]	10 Ta–T1	1.5–2 g in 100 mL saline for 1 h. Singles doses immediately after TUR	Mean plasma gemcitabine level $1.81 \mu\text{g/mL}$, AUC $1.58 \mu\text{g/mL}\cdot\text{min}$.
Witjes <i>et al.</i> 2004 [33]	10 pTa–T1	1–2 g in 50 mL saline for 1 h weekly × 6	Gemcitabine plasma level undetectable or low peaking at 30–60 min. Maximum dFdU $5 \mu\text{M}$
Mattioli <i>et al.</i> 2005 [34]	9 with NMIBC	2 g in 50 mL saline for 1 h weekly × 4 before TUR then × 4 after TUR	Maximum gemcitabine plasma level before TUR $1 \mu\text{g/mL}$ and after TUR $0.35 \mu\text{g/mL}$. Plasma dFdU > gemcitabine.
Bassi <i>et al.</i> 2005 [35]	9 with CIS refractory to BCG	1–1.5 g in 50 mL saline for 1 h	52–100% of gemcitabine dose in voided urine. Gemcitabine only detectable in serum of 1 patient at a dose of 1.5 g.
Codacci-Pisanelli <i>et al.</i> 2005 [36]	No data given	0.5–2 g weekly × 6	Plasma gemcitabine not detectable in a phase I study. At 2 g dose in a separate phase II study, maximum plasma gemcitabine was $0.60 \mu\text{M}$ and the median level of dFdU was $2.07 \mu\text{M}$.
Maffezzini <i>et al.</i> 2008 [37]	15 recurrent, low/intermediate risk NMIBC undergoing small or large tumour resection	2 g in 50 mL saline for 1 h immediately after TUR	Maximum mean plasma gemcitabine in small resection $1.38 \mu\text{g/mL}$ and $2.47 \mu\text{g/mL}$ for large. Plasma gemcitabine at 15 min after TUR proportional to extent of surgery but not for dFdU.
Gontero <i>et al.</i> 2010 [38]	18 NMIBC	2g – six-arm study varying pH (3.5 or 5.5), volume (50 or 100 mL) and dwell time (1 or 2 h)	Maximum plasma gemcitabine $1.42 \mu\text{M}$ and dFdU $7.5 \mu\text{M}$. Greatest tumour penetration of gemcitabine at pH 5.5 in 50 mL for 2 h ($18.5 \mu\text{g/mg}$ protein)

dFdU, difluorodeoxyuridine.

Intravesical BCG is probably the most commonly used intravesical agent for the treatment of NMIBC and has superior efficacy compared with surgical excision alone [41]. It is therefore not surprising that several randomised trials have compared the relatively new agent, gemcitabine, with BCG therapy in this disease. Three randomised trials relevant to this review made this comparison [11,14,15]. They all used gemcitabine at a dose of 2000 mg/50 mL administered over 6 weeks and similar BCG schedules with or without maintenance. However, they differed in the type of patients they recruited and their risk of tumour recurrence and progression. Bendary *et al.* [11] recruited intermediate-risk patients with primary Ta–T1 and no CIS, and reported that gemcitabine was as effective as BCG in preventing tumour recurrence and

progression but with a better safety profile. Intravesical gemcitabine may therefore be a treatment option for low-risk patients. The Porena *et al.* [15] 2010 study enrolled patients with primary high-risk disease according to European Association of Urology guidelines and showed that gemcitabine was significantly inferior to BCG in this patient group although it was less toxic. Gemcitabine therefore may have some clinical use in these patients who are not suitable for BCG therapy. In the third randomised study [14], high-risk patients were included who had previously received BCG therapy and had failed to respond. Gemcitabine in this patient group was significantly more effective than BCG in reducing recurrence rates and may therefore be a suitable second-line option in BCG-refractory patients.

A large number of published observational studies provide data on intravesical gemcitabine for the management of NMIBC in terms of activity, tolerance and pharmacology (Tables 2–5). The pharmacokinetic studies report low plasma gemcitabine levels during intravesical administration, which is one of the key properties required when developing new intravesical agents. Other observational studies, confirm the ablative effect of gemcitabine using marker lesions and the activity of gemcitabine in reducing or delaying tumour recurrence in untreated patients, and in those with refractory disease. However, observational studies only provide low level evidence because of the lack of a control, the inherent bias in patient selection and the few recruited patients. Therefore the results of the observational

studies should be interpreted considering these limitations.

This systematic review has identified that the clinical data on intravesical gemcitabine are limited in quality and consistency and do not typically assess the impact on mortality. This suggests that further research is needed in several areas. Additional randomised trials are needed to add to the data already published to allow treatment decision-making to be more informed. It is unclear how effective intravesical gemcitabine is in preventing or delaying disease progression and ultimately overall survival. Long-term trials are needed to clarify the influence of gemcitabine on these important outcomes measures. Additionally, randomised trials should aim to determine the optimum dosing schedule for intravesical gemcitabine. Parameters that require addressing include the volume and pH of the fluid in which gemcitabine is instilled and therefore the urine concentration of gemcitabine achieved, the dwell time, whether irrigation after instillation is beneficial, the frequency of instillations and the role of maintenance therapy with gemcitabine. It is also important to identify those patients who may benefit most from intravesical gemcitabine. A recent study [42] reported that a pathological complete response of a marker lesion to gemcitabine occurred in patients whose tumours expressed equilibrative nucleoside transporter gene. This, and other biomarker research, warrants further exploration.

It is not possible to make a generalised statement concerning the role of gemcitabine in NMIBC because all of the reviewed randomised studies were undertaken in different clinical settings with respect to the patients recruited and trial objectives and design. In addition, some of the trials recruited very few patients. The available evidence suggests that intravesical gemcitabine may have a role in the management of intermediate-risk patients, as an alternate choice to MMC in previously treated patients with recurrent disease and in high-risk, BGC-refractory patients with NMIBC. However, until further data are available, these conclusions should be interpreted with caution.

The aim of intravesical therapy in NMIBC is to prevent tumour recurrence and

progression and to avoid the morbidity associated with cystectomy. Intravesical gemcitabine is a promising drug that may add to the urologist's options in achieving this goal.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: NMIBC, non-muscle invasive bladder cancer; RFS, recurrence-free survival; TUR, transurethral resection; MMC, mitomycin C; CIS, carcinoma *in situ*.