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Intravesical gemcitabine for non-muscle invasive bladder cancer (Review)

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[Intervention Review]

Intravesical gemcitabine for non-muscle invasive bladder cancer

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ABSTRACT

Background

Intravesical immunotherapy or chemotherapy for non-muscle invasive bladder cancer is a well established treatment for preventing or delaying tumour recurrence following 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.

Objectives

To evaluate the effectiveness and toxicity of intravesical gemcitabine in preventing tumour recurrence and progression in non-muscle invasive bladder cancer (NMIBC).

Search methods

A search strategy was developed for MEDLINE to identify randomised trials of intravesical gemcitabine for the treatment of non-muscle invasive bladder cancer. The searches were from 1947 to May 2011. Other databases searched included EMBASE, CINAHL, the Cochrane Central Register of Controlled Trials, LILACS, SCOPUS, BNI, Biomed Central, Web of Science and BIOSIS. Handsearching of meeting proceedings, international guidelines and trial registries was also carried out.

Selection criteria

The titles and abstracts of the combined electronic and handsearching were manually screened by three authors independently to determine if they met the inclusion criteria for this review. Studies were selected if they were randomised, controlled trials or quasi-randomised clinical trials that included intravesical gemcitabine in at least one arm of a comparative study.

Data collection and analysis

Data extraction was carried out by three reviewers. The information retrieved included the author's details, the study design, the characteristics of the recruited patients, details of the interventions and data relating to the primary, and secondary outcome measures.

Main results

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. One study compared a single post-operative instillation of intravesical gemcitabine with a saline placebo in 341 patients and found no significant difference in the rates of tumour recurrence (28% versus 39%, respectively) or recurrence-free survival (HR (hazard ratio) 0.95, 95% CI 0.64 to1.39, P = 0.77). The rate of progression to invasive disease was greater with gemcitabine (2.4% versus 0.8%). A further trial compared gemcitabine with intravesical mitomycin C and demonstrated that the rates of recurrence (28% versus 39%) and progression (11% versus 18%) were lower with gemcitabine but did not reach statistical significance. The global incidence of adverse events was significantly less with gemcitabine (38.8% versus 72.2%, P = 0.02).

Three trials compared gemcitabine with intravesical BCG but a meta-analysis was not possible due to clinical heterogeneity. In untreated patients at intermediate risk of recurrence (primary Ta-T1 no CIS) one trial showed that gemcitabine and BCG were similar with respective recurrence rates of 25% and 30% (P = 0.92) and overall progression equal (P = 1.0). Dysuria (12.5% versus 45%, P < 0.05) and frequency (10% versus 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 to BCG (53.1% and 28.1%, P = 0.04) and the time to recurrence significantly shorter with gemcitabine (25.5 versus 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% versus 87.5%, P = 0.002) and a longer time to recurrence (3.9 versus 3.1 months, P = 0.9) compared to BCG. Progression rates were similar in both groups (33% versus 37.5%, P = 0.12) with no significant differences in grade 2 or 3 toxicities.

The final trial was a marker lesion study which reported greater response rates when intravesical gemcitabine (2 g) was given as three bi-weekly doses (36%) or six weekly doses (40%) compared to a single dose (9%).

Authors' conclusions

A single dose immediately following surgery is ineffective based on one study. Gemcitabine may be more active than mitomycin C with a lower toxicity profile. Compared to intravesical BCG therapy, gemcitabine had similar effects in intermediate risk patients, less effective in high risk patient 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. 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.

PLAIN LANGUAGE SUMMARY

Intravesical gemcitabine for early stage bladder cancer

When bladder cancer is confined to the lining of the bladder it is treated surgically to remove the tumours. However, the tumours may recur and so another type of treatment is often used following surgery called intravesical therapy, whereby agents are instilled directly into the bladder to prevent tumour recurrence. These agents, such as Bacillus Calmette-Guérin (BCG) may stimulate the body's immune system to kill any residual cancer cells, or they may be anticancer drugs that act directly on the tumour cells. A relatively new drug used in this situation is gemcitabine. We searched the published literature for randomised clinical trials that evaluated intravesical gemcitabine in bladder cancer patients and found six trials. The first trial compared a single dose of gemcitabine with a placebo immediately following surgery and found no difference in the rate of tumour recurrence, although there was some concern over the trial methodology. Another study compared gemcitabine with the established anticancer drug mitomycin C and showed that gemcitabine was more active and less toxic. Three trials compared gemcitabine with intravesical BCG. The first 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 patients who had previously received BCG but had not responded and this study showed that gemcitabine was superior to BCG in reducing the rate of tumour recurrence. These small numbers of trials indicate that intravesical gemcitabine has activity in delaying tumour recurrence and may have a role in patients who are not suitable for, or who have failed, BCG therapy. The final study suggested that multiple doses of gemcitabine gave better tumour responses compared to a single dose, although the clinical significance of this is unclear.

BACKGROUND

Description of the condition

Bladder cancer is a major clinical problem worldwide and the incidence has increased over the last two decades. The World Health Organisation reported 356,557 new cases of bladder cancer globally in 2002 (Parkin 2008). In 2007, there were about 67,000 new cases in the USA (Jemal 2007) and in the UK for the year 2006, approximately 10,300 new cases were reported (CRUK 2011). These statistics indicate that bladder cancer is a common cancer and represents the fourth most common cancer in men and eighth in women.

At presentation, approximately 80% of bladder tumours are classified as nonmuscle invasive tumours which are confined to the inner lining of the bladder and have not invaded the deeper muscle layer. Nonmuscle invasive tumours can be either papillary or non-papillary. Those papillary tumours that are confined to the outermost layer of the bladder (urothelium) are designated Ta tumours, whilst those that have invaded the basement membrane beneath this layer, the lamina propria; are designated T1 tumours. The majority of tumours diagnosed are Ta tumours (70%) (Donat 2003). Patients who present with T1 are at higher risk due to the greater propensity of these tumours to recur and progress. Non-papillary tumours include carcinoma in situ (CIS), a flat, high grade transitional cell carcinoma which commonly presents concurrently with papillary tumours and has a high risk of progression (Millan-Rodriguez 2000).

The typical initial management approach for patients suspected of having nonmuscle invasive disease is cystoscopic visualization, followed by transurethral resection (TUR) to elucidate the nature of the tumour. TUR is advocated, with the inclusion of the muscularis propria (the muscle layer surrounding the bladder) in the biopsy specimen, to allow accurate staging and grading of the tumour. Then, if possible, total endoscopic resection of the visible tumour is undertaken. This modality is particularly beneficial for primary, solitary tumours and is the standard treatment for single low grade superficial Ta, T1 and CIS.

A major problem in the treatment of non-muscle invasive cancer is the recurrence of tumours following transurethral resection which occurs in up to 90% of patients (Herr 2000). Up to a third of tumours may go undetected using cystoscopy with consequent failure to resect the tumour in its entirety (Zaak 2001). As a result of this, microscopic lesions may produce recurrent tumours. Tumour recurrence may also occur by the re-implantation of "freed" cells released during TUR, which accounts for as many as 50% of recurrences at the time of initial resection; this is supported by the finding that a large proportion of synchronous and metachronous lesions have similar clonal origins (Takahashi 1998). Data derived from multivariate analysis indicate that the number of tumours, their size and the prior recurrence rate, are the most important prognostic factors for predicting tumour recurrence (Sylvester 2006).

In roughly 15% of patients with recurrence the tumours progress to invade the muscularis propria, and the increased risk of metastasis results in a poorer prognosis for the patient. Frequent cystoscopic surveillance is then required which not only impacts on the patient's quality of life but also has considerable implications for healthcare in terms of cost.

Description of the intervention

To overcome the problem of tumour recurrence, anti-tumour agents may be instilled into the bladder for a short time to bathe the tumour cells. This is called intravesical therapy and is frequently used as an adjunctive following transurethral resection. The objective is to eradicate residual tumour cells missed in the original resection and to prevent or delay tumours from recurring or progressing to more invasive disease. The most commonly used intravesical agent is bacillus Calmette-Guérin (BCG) and is considered by most urologists to be the standard of care for NMIBC. Intravesical BCG is generally given as an induction course of 6 weekly instillations followed by maintenance therapy for up to 3 years (Shelley 2010). This schedule is associated with a significant reduction in the incidence of tumour recurrence and disease progression in patients with NMIBC and, importantly, in T1G3 tumours which are at high risk of recurrence and progression. However, BCG immunotherpy is associated with local toxicities such cystitis, which may occur in up to 90% of patients, and haematuria in approximately 45% of patients. Systemic toxicities are less frequent but include fever and possibly BCG sepsis.

Intravesical chemotherapy is an alternative to intravesical BCG immunotherapy and the most commomly used drugs include mitomycin C, Adriamycin and epirubicin. Gemcitabine is a relatively new anti-cancer agent with documented activity against metastatic bladder cancer (Shelley 2011). Recently, phase I studies in patients with nonmuscle invasive bladder cancer have indicated a good safety profile and the potential for gemcitabine as an intravesical agent for recurrent disease (Raj 2010). In phase II studies, intravesical gemcitabine has been administered at a dose of 2 g (grams), achieving a urine concentration of 40 mg/mL (milligrams per millilitre) and instilled for 1 to 2 hours, generally given once weekly for 6 weeks (Gontero 2004; Dalbagni 2006; Seretta 2005; Bartoletti 2005). Patients included those with recurrent tumours and BCG-refractory tumours. Complete tumour responses were seen in 23% to 56% of patients with a 1 year recurrence-free survival of up to 21% (Dalbagni 2006). Both systemic and local toxicities generally were not higher than grade 2. These data suggest that intravesical gemcitabine has activity in nonmuscle invasive disease including those patients at high risk of recurrence. The favourable toxicity profile of intravesical gemcitabine suggests that dose escalation may be possible.

How the intervention might work

Gemcitabine is an anti-cancer drug categorised as an anti-metabolite. It has a similar structure to cytidine, one of the pyrimidine molecules of DNA. On entering the tumour cell, gemcitabine undergoes phosphorylation by nucleoside kinases to form the active metabolites gemcitabine di-phosphate and gemcitabine tri-phosphate. These metabolites are responsible for the cytotoxic action of gemcitabine by blocking DNA synthesis and leading to programmed cell death or apoptosis (Mini 2006).

Gemcitabine has a number of pharmacological properties that are conducive for its use as an intravesical agent in the management of nonmuscle invasive bladder cancer. Firstly, gemcitabine has demonstrated activity in killing cultured bladder cancer cells in vitro (Kilani 2002). Secondly, the low molecular weight and the high lipid solubility allow sufficient uptake into malignant urothelial cells for cytotoxicity in vivo. And thirdly, gemcitabine has a high plasma clearance so that any drug that does enter the systemic circulation after intravesical administration, will be quickly eliminated, reducing the risk of systemic toxicity (Laufer 2003).

Why it is important to do this review

Nonmuscle invasive bladder cancer has a tendency to recur following initial surgery and may progress to muscle-invasive disease which has a much poorer prognosis. Any intervention that can prevent or delay tumour recurrence and progression would be of important clinical benefit for this patient group. Intravesical gemcitabine has shown encouraging activity in phase I and II studies in patients with this disease and may have a significant role in the treatment of nonmuscle invasive bladder cancer. It is therefore important to review the clinical data on intravesical gemcitabine to determine the effectiveness and toxicities of this agent. There is also a need to establish the optimum schedule of intravesical gemcitabine and whether it is active as a first line therapy and in those patients who become refractory to established intravesical therapies. This information would be of value to patients with this disease, clinicians and policymakers when making decisions concerning treatment.

OBJECTIVES

The activity of gemcitabine for non-muscle invasive bladder cancer 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 review is to assess the comparative effectiveness and toxicity of intravesical gemcitabine compared to placebo or any other treatment option for non-muscle invasive bladder.

METHODS

Criteria for considering studies for this review

Types of studies

This review was restricted to published and unpublished prospective, randomised, controlled trials evaluating the clinical benefit and harms of intravesical gemcitabine in patients with non-muscle invasive bladder cancer. Randomisation was considered to have been performed if the authors state this in the manuscript of a relevant clinical study. Quasi-randomised trials that allocate treatments by alternation, such as date of birth, were also potential studies for inclusion in this review. The comparative arm of the randomised study may include a placebo, surgery, or other intravesical agents used for treating non-muscle invasive bladder cancer. Randomised trials that have more than two patients groups but include intravesical gemcitabine as one of them were considered for review. Relevant randomised trials should have adequate cystoscopic follow up following intravesical gemcitabine. Trials published in full or in abstract form were included for review.

Types of participants

Studies were eligible if they had enrolled adult patients of any gender, with histologically confirmed Ta or T1 transitional cell carcinoma of the bladder, with or without carcinoma in situ (CIS). Patients were included if they were of low, medium or high risk for tumour recurrence and/or disease progression as defined by Hall 1994 and Kurth 1995, respectively. Studies reporting on patients with CIS alone were also be eligible. Bladder tumour lesions may be solitary or multiple and of any grade. Patients who have received prior intravesical therapy and failed to respond, such as BGC refractory patients, were also be eligible for review.

Types of interventions

The main intervention of interest was intravesical gemcitabine, either as a single agent or in combination with other treatments, as the first-line or second-line therapy for non-muscle invasive bladder cancer. Schedules of intravesical gemcitabine administered immediately post-operative to TUR or as a weekly regime were relevant. In addition, intravesical gemcitabine evaluated in randomised marker lesion studies, where a small defined tumour is left in situ following resection to assess the effectiveness of the treatment, were included. Intravesical gemcitabine administered at varying doses and schedules and randomised dose finding studies were considered for review.

Types of outcome measures

Primary outcomes

The primary outcome of interest was treatment efficacy as measured by the effect of intravesical gemcitabine on tumour recurrence. Outcome data presented as the time to first recurrence, recurrence-free survival or the incidence of tumour recurrence at 12 and 24 months following treatment were relevant.

Secondary outcomes

Secondary outcomes included measures of disease progression, overall survival, disease-specific survival, and quality of life. For marker lesion studies the outcome of interest was tumour response at cystoscopy. Response was as defined by the authors of any relevant randomised study. In addition, local side-effects such as drug-induced cystitis and haematuria, and systemic side-effects were also assessed.

Search methods for identification of studies

A number of electronic databases were searched for published randomised trials that included intravesical gemcitabine for the treatment of non-muscle invasive bladder cancer. There were no language or location restrictions. A search strategy was developed for MEDLINE and searched from 1947 to May 2011 to identify relevant trials. The strategy was then modified to search other electronic databases including EMBASE, CINAHL, the Cochrane Central Register of Controlled Trials, LILACS, SCOPUS, BNI, Biomed Central and Web of Science® Appendix 1.

Electronic searches

The search strategy was developed for MEDLINE using text words and subject headings for gemcitabine and non-muscle invasive bladder cancer and incorporating the Cochrane filter for randomised trials.

Searching other resources

The reference lists from publications identified as potentially relevant to this review were scrutinised for additional randomised studies that were of relevance. Handsearching of the Proceedings of major national and international cancer meetings was undertaken, including the American Society for Clinical Oncology, the European Society for Therapeutic, Radiology and Oncology, and The European Organisation for Research and Treatment of Cancer.

Clinical colleagues and experts in the field of bladder cancer were asked to identify any additional studies that could be potentially useful for this review. Recent relevant systematic reviews and international urological guidelines were also searched.

Data collection and analysis

Selection of studies

Study selection was undertaken by three authors independently (GJ, AC and MS). The titles and abstracts of the combined electronic and handsearching were manually screened to determine if they met the inclusion criteria of this review. When doubt existed the full paper was examined for a more detailed assessment. All potentially relevant trials were listed in EndNote®, a bibliographical software. Those studies that did not meet this review's inclusion criteria were excluded with the appropriate reasons for exclusion listed.

Data extraction and management

Three authors (GJ, AC and MS) each independently evaluated all studies and extracted relevant data. Conflicts between reviewers on issues of data extraction and study selection were resolved by mutual discussion.The information retrieved included:

- authors names and institutions, title of article, full publication details and language;
- details of the study design including the number of patients randomised, the method of randomisation and the length of follow up;
- the characteristics of the recruited patients including gender, age, tumour characteristics, performance status, previous therapies;
- details of the interventions used including the drug doses and schedules, and the drug sequence in combination regimes;
- data relating to primary and secondary outcomes including the number of patients in each group experiencing the event of interest, statistics for time-to-event outcomes such as hazard ratios and 95% CI test for significance, and P values.

Where there was more than one report of the same study, only the reference with the most complete data was used. Where possible, data based on an 'intention-to-treat' basis was extracted as well as on the 'treatment received' basis.

Assessment of risk of bias in included studies

When assessing the risk of bias of studies included in this review, the Cochrane Collaboration's method was used as described in Chapter 8 of the *Cochrane Handbook* (Higgins 2008). The following questions were addressed.

- Was the sequence of intervention allocation adequately generated, e.g. using a random number generator?
- Was the allocation sequence adequately concealed from the participants and investigators, e.g. by using central allocation?

- Was knowledge of the allocated interventions adequately prevented (blinding) throughout the duration of the study?

- Were the problems of incomplete outcome data adequately addressed?

- Was the data analysis carried out on an intention-to-treat basis?

- Was the trial free of other breaches of internal validity that could be potential sources of bias, e.g. the trial was stopped early, or does the trial have external validity?

Following the Cochrane guidelines, the answers to these questions was either 'low risk', 'unclear' or 'high risk' of bias.

RESULTS

Description of studies

Results of the search

The electronic searches of MEDLINE, EMBASE, CINAHL, LILACS, Web of Science® SCOPUS, BNI,Biomed Central, BIOSIS and the Cochrane Central Register of Controlled Trials plus handsearching of relevant journals and guidelines yielded a total of 521 potential references relevant to this review. These were compiled in a bibliographic database (ENDNOTE). After screening the titles and abstracts 23 studies were considered potentially relevant to this study and selected for further reading. Seventeen of the 23 studies were considered irrelevant and are described in the 'Characteristics of excluded studies' with reasons for exclusion. The six remaining randomised trials of intravesical gemcitabine were considered suitable for inclusion in this review (Addeo 2010; Bendary 2011; Bohle 2009a; Gardmark 2005a; Lorenzo 2010; Porena 2010). The details of these trials are given in the table 'Characteristics of included studies' and the results summaries in 'Table 1'.

Included studies

A single post-operative instillation of gemcitabine was compared to a placebo in a multi-centre randomised study recruiting 355 patients with primary or recurrent Ta-T1 G1-3 transitional cell carcinoma (Bohle 2009a)**.** The instillations were given between 30 and 40 minutes after TUR followed by continuous saline irrigation for 20 hours. Patients were stratified by primary or recurrent disease and centre. The primary endpoint was recurrence-free survival with secondary objectives of type of recurrence, progression and adverse events. A second TUR with no instillation, and adjuvant BCG instillations were permissible.

Addeo 2010 compared 6 week schedule of intravesical gemcitabine with a 4 week schedule of intravesical mitomycin C in 109 previously treated, recurrent patients who had progressed or failed BCG therapy. Responders in each group received 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.

The results of an Egyptian randomised trial comparing intravesical gemcitabine and intravesical BCG was presented in abstract form at the American Urological Association in 2011 (Bendary 2011). Between June 2006 and June 2008, this study randomised 80 patients with primary Ta-T1 NMIBC without CIS to either agent. The main study endpoint was either completing a period of 18 months follow-up without recurrence or progression, or the appearance of recurrence or progression during the study period.

An Italian randomised trial compared intravesical BCG against gemcitabine in patients with high risk NMIBC (Porena 2010). 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.

In a multicentre, prospective randomised phase II trial, intravesical gemcitabine was compared to BCG in high-risk patients who had failed previous BCG therapy and had refused or were not suitable for cystectomy (Lorenzo 2010). The primary endpoint was the recurrence rate at 1 year with secondary endpoints of recurrence-free survival, disease progression and toxicity.

A randomised study was designed to evaluate the response rate of gemcitabine at 3 different doses levels in stage Ta urothelial cell cancer (Gardmark 2005a). 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. The definition of response is given in the 'Characteristics of included studies' table. 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.

Excluded studies

Sixteen potential published studies for this review were rejected (see table of excluded studies). The most common reason for exclusion was that the report was a repeat publication of an accepted study. Some papers describing comparative studies were considered unacceptable because they were not randomised studies.

Risk of bias in included studies

An immediate, post-TUR, single instillation of gemcitabine was compared to a saline placebo in a prospective, multi-centre, double blind, randomised study (Bohle 2009a). However the method for randomisation was not stated. The number of patients lost before intravesical therapy was described - 7.3% in the gemcitabine arm and 8.0% in the placebo arm. This trial was considered at low risk of bias.

Patients in the Addeo 2010 study 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: 3 not meeting the study inclusion criteria, 4 refused to participate and 4 for other reasons. This study was considered low to intermediate risk of bias.

In the randomised trial reported by Bendary et al (Bendary 2011) comparing gemcitabine with BCG, 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 and 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.

High risk patients with NMIBC were randomised to intravesical BCG or gemcitabine using a random number generator and permuted block design (Porena 2010). There was no blinding of the interventions or outcome assessments. There were 10 patients who were excluded following recruitment: 8 did not meet the inclusion criteria and 2 refused to participate. This trial was rated as low to intermediate risk of bias.

The trial comparing gemcitabine with BCG in 80 BCG-refractory high-risk patients used a central computer randomisation method to allocate treatment options (Lorenzo 2010). This was an open-label study so there was no blinding of treatments or outcomes. Twelve patients were excluded from the 92 recruited patients and the reasons documented: 8 not meeting the inclusion criteria, 3 refused to participate and 1 for other reasons. This trial was assessed as low risk of bias.

The lesion marker study by Gardmark and colleagues (Gardmark 2005a) was a multicentre, open label randomised trial. A central randomisation scheme was used to allocate patients to one of three schedules of intravesical gemcitabine, although there was no blinding reported. Of the 32 patients recruited, 2 were excluded because of protocol violations and none were lost to follow-up. This trial was designed as a feasibility study with 20 patients in 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.

Effects of interventions

'Table 1' summarises the included studies participants, interventions and outcomes.

An immediate post-TUR instillation of gemcitabine was associated with a median recurrence-free survival of 37.2 months compared to a saline placebo of 40.2 months (P = 0.78) (Bohle 2009a). The recurrence-free rates from a Kaplan-Meier analysis at 12 and 24 months were also similar for gemcitabine (77.7% and 64%) and placebo (73.3% and 60.7%). The overall recurrence rates were 35.5% and 36.3%, respectively. In a subgroup analysis, the recurrence-free survival was not significantly associated with risk (high versus low), primary or recurrent disease, primary or secondary TUR, concomitant BCG therapy or the number of lesions. The number of patients who suffered disease progression was small in each group (gemcitabine n = 3 (2.4%), placebo n = 1 (0.8%)). In this study there were fewer events than expected (87 recurrences and 7 deaths) and the trial was stopped early. The data indicated that with this trial design, a single instillation of gemcitabine was not superior to placebo in terms of tumour recurrence.

The Addeo 2010 study reported that at a median follow up of 36 months the percentage of patients with tumour recurrence was 28% for gemcitabine and 39% for mitomycin C (no P value given). The mean time to recurrence was longer for gemcitabine than mitomycin C. The relative risk of recurrence (0.72 versus 0.94, P = 0.29) and the recurrence rate per 100 patient-months (1.26 versus 1.71, P = 0.31) were higher for the mitomycin C group. The rate of disease progression by stage was also greater for mitomycin (11% versus 18%, P = 0.14). The global incidence of adverse events was 38.8% for gemcitabine and 72.2% for mitomycin C. These data suggest that intravesical gemcitabine has a more favourable efficacy and toxicity profile that mitomycin C and may be potentially useful in BCG-refractory patients.

Three randomised trials compared the efficacy and tolerability of intravesical gemcitabine with intravesical BCG (Bendary 2011; Porena 2010; Lorenzo 2010). However, pooling of the data and meta-analysis was considered inappropriate because of considerable clinical heterogeneity

The patients recruited in the Bendary study (Bendary 2011) were of intermediate risk with primary Ta-T1 disease with no concomitant CIS. Forty were randomised to gemcitabine and 40 to BCG, with all patients receiving the allocated treatments and none lost to follow-up. At a follow up of between 3 to 18 months (mean 10.8 $\pm$ 2.7 months), the per cent of patients experiencing 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 experienced a 9.1% progression rate for gemcitabine and 9.5% for BCG (P = 1.0). Dysuria was signif-

icantly more common in patients receiving BCG (12.5% versus 35%, P = 0.05) as was urinary frequency (10% versus 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.

In the Porena 2010 randomised trial (Porena 2010) 32 patients received intravesical BCG and 32 received gemcitabine. At 3 months post 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% versus 53.1%, P = 0.037). The mean recurrence-free interval was also significantly longer with BCG (39.4 months versus 25.6 months, P = 0.042). No patient in either group developed disease progression. There was no significant difference in local toxicity such as cystitis (BCG 12.5%, gemcitabine 9.3%) or systemic toxicity such as 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.

This topic was an area of investigation for a third randomised trial (Lorenzo 2010). BCG-refractory, high-risk patients had a recurrence rate of 52.5% (21/40) following intravesical gemcitabine compared to 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, HR 0.15, 95% CI 0.1 to 0.3, P < 0.008). However, there was no significant difference in the recurrence-free survival (HR 1.1, 95% CI 0.8 to 1.2, P = 0.9). Progression rates were also similar between groups: gemcitabine 33%, 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.

The marker lesion study by Gardmark (Gardmark 2005a) indicated that a single dose of gemcitabine (2 g) induced a complete response in 9%, no response in 36% and progressive tumour development in 45%. When gemcitabine was administered twice weekly for 3 weeks or once per week for 6 weeks, the complete response rate increased to 36% and 40%, respectively. There was no statistical analysis of these data but they suggest that a single dose is sub optimal and multiple doses are more effective. Eight of the 32 patients reported toxicity, mainly in the multiple dose groups. Nausea was seen in 5, anaemia in 1, thrombocytopenia in 1 and fever in 1.

DISCUSSION

This review aimed to determine the role of intravesical gemcitabine in NMIBC using the evidence from published randomised trials. However, an extensive search of the literature resulted in identifying only six relevant studies. The first trial compared a single dose of gemcitabine with a placebo immediately following surgery and found no significant difference in the rate of tumour recurrence or recurrence-free survival (Bohle 2009a). Another study compared gemcitabine with the intravesical mitomycin C and reported that more patients remained recurrence-free with gemcitabine and experienced less chemical cystitis (Addeo 2010). Three trials compared gemcitabine with intravesical BCG (Bendary 2011; Porena 2010; Lorenzo 2010). 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 superior to BCG in reducing the rate of tumour recurrence. These small numbers of trials suggest that intravesical gemcitabine has activity in delaying tumour recurrence. Finally, one study showed that tumour response rates were higher when gemcitabine was given in multiple doses rather than a single dose (Gardmark 2005a).

When a single dose of gemcitabine (2000mg/100mL) was given immediately after surgery no effect on tumour recurrence-free survival was observed compared to a saline placebo (Bohle 2009a). However this study differs from the single dose in the lesion marker study of Gardmark 2005a in a number of 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 following tumour resection (Shelley 2010). Importantly, the Bohle 2010 study (Bohle 2009a) used continuous bladder irrigation post instillation for at least 20 hours and a short dwell time of 30-40 minutes which may have contributed to the lack of effectiveness observed compared to placebo. Possibly gemcitabine may require a longer exposure time for optimum activity since it acts as a phase specific agent. The authors also point out that the recurrence-free survival was exceptionally high in both groups. For example at 12 months the recurrence-free rates were 77.7% for gemcitabine and 75.3% for the placebo group making in difficult to show a difference statistically However, these trial data do not support the use of a single dose intravesical gemcitabine immediately post resection for NMIBC using these drug schedules.

In contrast to the single dose results for gemcitabine, a 6 weekly induction course in patients previously treated with BCG or epirubicin and with recurrent Ta-T1 disease induced encouraging results when compared to intravesical mitomycin C (Addeo 2010). Mitomycin C is an established intravesical agent with proven ac-

tivity in NMIBC (Shelley 2004). At a median follow-up of 36 months 72% of patients randomised to gemcitabine remained recurrence-free compared to 61% for those receiving mitomycin C. In addition, the toxicity associated with gemcitabine, in particular chemical cystitis, was also significantly less compared to mitomycin C. 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.

Intravesical BCG is probably the most commonly used intravesical agent and treatment for NIMIBC and has superior efficacy compared to surgical excision alone (Shelley 2001). It is therefore not surprising that a number of 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 (Bendary 2011; Porena 2010; Lorenzo 2010). They all used gemcitabine at a dose of 2000mg /50mL 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 (Bendary 2011) 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 compared to BCG but with a better safety profile. Intravesical gemcitabine may therefore be a treatment option for low risk patients**.** The Porena 2010 study (Porena 2010) enrolled patients with primary high risk disease according to EAU 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 (Lorenzo 2010) 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.

The dose finding study of Gardmark and colleagues (Gardmark 2005a) 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. However, responses to marker lesions are of greater interest in terms of its biology rather than its clinical importance. Nevertheless, multiple doses of gemcitabine (2 g) given twice per week for 3 week or every week for 6 weeks were active inducing up to 40% responses. However, a single dose was clearly sub optimal, which may reflect the larger instillation volume (100 mL) used and thus the lower concentration of intravesical gemcitabine achieved in this study compared to the standard volume of 50 mL.

Summary of main results

It is not possible to make a generalised statement concerning the role of gemcitabine in NMIBC because all of the reviewed studies were undertaken in different clinical settings with respect to the patients recruited, trial objectives and design. In addition some of the trials recruited very few patients. What is clear is that the evidence base is very limited.

The available evidence suggest that intravesical gemcitabine may have a role in the management of intermediate risk patients, as an alternate choice to mitomycin C 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.

AUTHORS' CONCLUSIONS

Implications for practice

Clinical data on intravesical gemcitabine are limited in quality and consistency and do not typically assess the impact on mortality. However, there is low to moderate evidence to suggest that gemcitabine is an active agent for NMIBC in terms of reducing tumour recurrence rates and has an acceptable safety profile. It should be considered as a treatment option in intermediate risk patients, as an alternate to mitomycin C in high risk patients and as a second-line therapy for BCG-refractory patients.

Implications for research

As previously stated the number of randomised trials evaluating intravesical gemcitabine is limited to six. Further randomised trials are needed to add to the data already published in order 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.

There are other areas that require additional investigation. Randomised trials should aim to determine the optimum dosing schedule for intravesical gemcitabine. Parameters that require addressing include the volume in which gemcitabine is instilled and therefore the urine concentration of gemcitabine achieved, the dwell time, whether post instillation irrigation is beneficial, the frequency of instillations and the role of maintenance therapy with gemcitabine.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Addeo 2010

Methods	A prospective randomised study. No method of randomisation presented. Stratification was by age, stage and tumour grade
Participants	One hundred and twenty patients with recurrent transitional cell carcinoma stages Ta or T1, Grades 1-3 were enrolled from March 2003 to November 2005. Included were those with disease that had progressed or relapsed after intravesical BCG. Mean age of Gemcitabine group 64.9 + 10.7, Mitomycin C group 67.9 + 10.2. Eleven were excluded.
Interventions	Patients randomised to Gemcitabine 2000mg/50ml saline instilled for 1 hour given weekly for 6 weeks (n = 54) or Mitomycin C 40mg/50mL instilled for 1 hour and within 2 days of TUR then weekly for 4 weeks (n = 55). Responders in each group had 10 monthly treatments
Outcomes	Disease-free survival. Recurrence rate. Mean time to recurrence. Relative risk of recurrence. Disease progression. Toxicity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No method of randomisation presented
Allocation concealment (selection bias)	Unclear risk	No allocation procedure reported. Authors describe 'subjects were randomly assigned'
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding of patients or clinicians reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients randomised were assessable.
Selective reporting (reporting bias)	Low risk	All main endpoints reported
Other bias	Unclear risk	No conflict of interest stated by authors.

Bendary 2011

Methods	This study aimed to compare the efficacy and safety of intravesical BCG with gemcitabine. No method of randomisation or blinding procedures were reported. All patients completed the study
Participants	From June 2006 to June 2008, 80 patients with primary Ta-T1 transitional cell cancer were entered into this study. No patient presented with concurrent CIS. The mean age was 56.2 + 11.18 years.
Interventions	All patients underwent complete TUR after which they were randomised to 6 weekly instillations of either BCG 6 x 10^8 CFU in 50 mL saline or 2000 mg gemcitabine in 50 mL saline. The follow-up period ranged from 3-18 months (mean 10.8 + 2.7 months).
Outcomes	Recurrence rate, progression rate, Toxicity.
Notes	This was a short term comparative study. Reported in abstract form only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No method randomisation stated.
Allocation concealment (selection bias)	Unclear risk	No allocation method reported,
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding of patients or clinicians reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients randomised received allocated treatment and none were lost to followup
Selective reporting (reporting bias)	Low risk	Primary outcome reported.
Other bias	Unclear risk	Only presented in abstract form. No full paper identified.

Bohle 2009a

Methods	A multicentre, double-blind, placebo-controlled randomised trial. No randomisation method stated. Stratification by recurrence or primary disease, and centre

Bohle 2009a (*Continued*)

Participants	355 patients with recurrent or primary Ta-T1 G1-3 NMIBC (no CIS) recruited from 24 centres in Germany and Turkey between Jan 2004 - June 2005. Karnofsky performance > 70%.
Interventions	randomised to a single instillation of gemcitabine 2000mg/100ml saline for 30-40 minutes post TUR followed by > 20 hours of continuous saline irrigation (n = 166) or placebo (100ml saline, n = 162). Follow-up cystoscopies were at 3 and 6 months then 6 monthly
Outcomes	Recurrence-free survival (date of randomisation to first positive biopsy (recurrence or progression). Type of recurrence. Disease progression. Adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No randomisation method stated.
Allocation concealment (selection bias)	Unclear risk	No allocation method reported,
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as 'double blind' but no details given.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	92.7% of patients randomised to gemcitabine received it and 92% randomised to placebo received it. All excluded patients were documented
Other bias	Unclear risk	Following an interim analysis, the trial was stopped early. There were fewer events (recurrences and deaths) than expected

Gardmark 2005a

Methods	3 doses of intravesical gemcitabine were compared in randomised marker lesion study. A central randomisation method was used to allocate the doses of gemcitabine. No blinding was reported

Gardmark 2005a (*Continued*)

Participants	Recruitment from Jan 2002 - March 2004 from 5 Swedish centres. 32 patients with recurrent, multiple tumours were recruited (n = 14Ta G1 and 16Ta-G2). Two patients were excluded because of protocol violations. All lesions except one, the marker lesion (0.5-1cm) were resected at TUR. The mean age was 67, with 23 men and 7 women. Cystoscopy was performed at 9 weeks Definition of response: Complete response - complete disappearance of the marker lesion with no new ones No response - unaffected marker lesion but no increase in size Increasing tumour - marker lesion is larger or new lesions developed
Interventions	Gemcitabine 2000mg/100ml saline instilled for 60 minutes either as a single dose (n = 11), twice weekly for 3 weeks (n = 11), or once per week for 6 weeks (n = 10)
Outcomes	Tumour response. Toxicity.
Notes	This was designed as a feasibility study with 20 patients in each arm (planned total 60) but was stopped early

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Centrally randomised.
Allocation concealment (selection bias)	Low risk	Centrally randomised.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No Blinding reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No Blinding reported. Follow-up cystoscopy was performed in the presence of a neutral physician
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 of the 32 patients recruited were excluded. Of the remaining 30 none were lost to follow-up
Selective reporting (reporting bias)	Low risk	All primary outcomes were reported.
Other bias	Unclear risk	Because of recruitment problems the trial was stopped early.

Lorenzo 2010

Methods	A multicentre, prospective randomised open-label phase II study. Randomisation was performed by central computer randomisation. No blinding was observed
Participants	From June 2006 - May 2008, 92 patients with high-risk NMIBC who had failed one cycle of intravesical BCG were recruited. Ta =18, T1 = 62, 49 males/31 females, mean age Gemcitabine group 69, BCG group 71 years
Interventions	Patients randomised to gemcitabine (n = 40), 2000mg/50ml x 6 weeks then weekly x 3 at 3, 6 12 months or BCG (Connaught) 81mg/50ml (same schedule as gemcitabine) n= 40 Both treatments were started 4-6 weeks after the last TUR.
Outcomes	Recurrence rates at 1 year, Time to recurrence, recurrence-free survival, progression and toxicity
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised centrally.
Allocation concealment (selection bias)	Low risk	Randomised centrally.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding - open label study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients received their allocated treatment, none were lost to follow-up and all assessable for outcomes
Selective reporting (reporting bias)	Low risk	All outcomes reported.

Porena 2010

Methods	A single centre, prospective randomised trial. A random number generator was used to develop the randomisation code in conjunction with random permuted blocks. There was no blinding to treatment or outcome assessment
Participants	Between Jan 2004 - Dec 2006 74 patients with high risk NMIBC were recruited. 10 were excluded and 64 randomised. Ta-T1G3 n = 54, T1G3 and/or CIS n = 10

Porena 2010 (*Continued*)

Interventions	All patients underwent TUR, then 4 weeks later a second-look TUR was performed. Patients were randomised to either 6 weekly instillations of BCG 5 x10^8 CFU in 50 mL saline for 2 hours (n = 32) or 6 weekly instillations of gemcitabine 2000 mg/50 mL for 2 hours (n = 32). Maintenance therapy for non-recurring patients in each group was at 3, 6, 12, 18, 24, 30 and 36 months
Outcomes	Tumour recurrence rate, mean recurrence-free interval, progression rate and toxicity
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number generator used.
Allocation concealment (selection bias)	Unclear risk	No allocation method reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding of participants reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No blinding of outcome assessment reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients randomised received their allocated treatment. No patients lost to follow-up
Selective reporting (reporting bias)	Low risk	The primary and secondary outcomes reported in full.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Autorino 2009	A repeat publication of Lorenzo 2010.
Bartoletti 2005a	An observational study.
Bartoletti 2005b	An observational study.
Boehle 2009b	Repeat publication of Boehle 2009a.

(*Continued*)

Boehle 2010	Repeat publication of Boehle 2009a.
Bohle 2009c	Repeat publication of Boehle 2009a.
Cho 2009	Comparative study of gemcitabine plus BCG versus BCG alone - not a randomised study
Faiola 2008	Repeat publication of Addeo 2010.
Gardmark 2003	Early report of Gardmark 2005a.
Gardmark 2005b	Repeat publication of Gardmark 2005a.
Gardmark 2005c	Repeat publication of Gardmark
Gardmark 2005d	Repeat publication of Gardmark
Hadley 2008	A comparative study of gemcitabine in chemotherapy naive patients and failed patients - not a randomised study
Kim 2008	A comparative study of gemcitabine plus BCG versus BCG alone - not a randomised study
Montella 2008	Early report of Addeo 2010.
Morabito 2006	Observational study.
Rampersaud 2011	A commentary on the Addeo 2010 trial.

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Summary of results for randomised trials of intravesical gemcitabine

Study/patients	Interventions	Recurrence Rate	RFS	Progression rate over study duration
Bohle 2009				
	Gemcitabine	38.7%	median 37.2	2.4%
355 primary or recurrent Ta-T1, G1-3	vs			
	Placebo	37.1%	40.2 months	0.8%
Addeo 2010				
	Gemcitabine	28%	Not reached	11%
120 recurrent Ta-T1, G1-3	vs			
	MMC	39%	15.0 months	18%
Bendary 2011				
	Gemcitabine	25%	Not reported	2.5%
80 primary Ta-T1 (no CIS)	vs			
	BCG	30%		2.5%
Porena 2010				
	Gemcitabine	53.1%	Mean 25.6	0%
64 high risk Ta-T1G1-3 and/or CIS	vs			
	BCG	28.1%	39.4 months	0%
Lorenzo 2010				
	Gemcitabine	52.5%	3.9 months	33.0%
80 BCG-refractory high risk Ta-T1	vs			
	BCG	87.5%	3.2	37.5%
Gardmark 2005	Gemcitabine	**Complete response of marker lesion**		
32 recurrent, multiple Ta G1-2	Single dose	1/11 (9%)		
	1 dose/week	4/11 (36%)		
	2 doses/week	4/10 (40%)		

Table 1. Summary of results for randomised trials of intravesical gemcitabine (*Continued*)

RFS = Recurrence-Free Survival, MMC = Mitomycin C, CIS = Carcinoma In Situ, BCG = bacillus Calmette-Guerin.

APPENDICES

Appendix 1. Search strategies and number of identifies studies

CANCER RESEARCH WALES LIBRARY Systematic Review Searching Record				
Database name	**Dates Covered**	**No of references found**	**No of references retrieved**	**Finish date of search**
MEDLINE	1947 - present	89	89	28/04/2011
PREMEDLINE	April 26	4	4	28/04/2011
EMBASE	1980 - present	111	111	28/04/2011
Cochrane Library	Issue 4	38	38	28/04/2011
Web of Science®	1970 - present	165	165	28/04/2011
CINAHL	1981 - present	21	21	28/04/2011
BNI	1985 - present	0	0	28/04/2011
LILACS		0	0	04/05/2011
BIOSIS	1926 - present	141	141	28/04/2011
Biomed Central		0	0	04/05/2011
SCOPUS		225	225	04/05/2011
ASCO	1999 - present	53	53	26/05/2011

(*Continued*)

WHO International Clinical Trials Registry		2	2	04/05/2011

Total References retrieved (after de-duplication): 468 not including ASCO.

MEDLINE search strategy

(This search strategy was adapted to each database.)

1. exp urinary bladder neoplasms/
2. (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3. exp carcinoma, transitional cell/
4. (tcc or transitional cell).mp.
5. exp ureteral neoplasms/
6. bladder neoplasms/
7. urethral neoplasms/
8. ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
9. or/1-8
10. exp deoxycytidine/
11. antimetabolites, antineoplastic/
12. (gemc?tabin$ or Gemzar$).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
13. (gem?cis or gem?cisplat or gem?carbo).mp. [mp=protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier]
14. (gem adj (cis or cisplat or carbo)).mp.
15. or/10-14
16. exp administration, intravesical/
17. (intraves$ or instill$ or region$ or install$).mp.
18. or/16-17
19. 9 and 15 and 18
20. randomized controlled trial.pt.
21. controlled clinical trial.pt.
22. randomized.ab.
23. placebo.ab.
24. drug therapy.fs.
25. randomly.ab.
26. trial.ab.
27. groups.ab.
28. or/20-27
29. humans.sh.
30. 28 and 29
31. 19 and 30

EMBASE search strategy

1. exp bladder tumor/
2. (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
3. exp transitional cell carcinoma/
4. (tcc or transitional cell).mp.

5. exp ureter tumor/
6. exp urethra tumor/
7. ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
8. or/1-7
9. exp deoxycytidine/
10. exp antineoplastic antimetabolite/
11. exp gemcitabine/
12. (gemc?tabin$ or gemzar$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
13. (gem?cis or gem?cisplat or gem?carbo).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
14. (gem adj (cis or cisplat or carbo)).mp.
15. or/9-14
16. exp INTRAVESICAL DRUG ADMINISTRATION/
17. (intraves$ or instill$ or region$ or install$).mp.
18. 16 or 17
19. 8 and 15 and 18
20. crossover procedure/
21. double-blind procedure/
22. randomized controlled trial/
23. single-blind procedure/
24. (random$ or factorial$ or crossover$ or cross over$ or placebo$ or assign$ or allocat$ or volunteer$).mp.
25. ((doubl$ or singl$) adj blind$).mp.
26. or/20-25
27. 19 and 26

BNI

1. exp "urinary system and disorders"/
2. exp Cancer/
3. 1 and 2
4. (bladder$ adj3 (cancer$ or carcinoma$ or neoplas$ or tumo?r$)).mp.
5. (tcc or transitional cell).mp.
6. ((bladder$ or urethra$ or ureter$ or urin$ or urotheli$ or renal pelvis or calice$) adj3 (cancer$ or carcinoma$ or adenoma$ or adenocarcinoma$ or squamous$ or neoplas$ or tum?r$ or malignan$)).tw.
7. or/1-6
8. (gemc?tabin$ or Gemzar$).mp.
9. (gem?cis or gem?cisplat or gem?carbo).mp.
10. (gem adj (cis or cisplat or carbo)).mp.
11. or/8-10
12. (intraves$ or instill$ or region$ or install$).mp.
13. 7 and 11 and 12

CINAHL

S18 S9 and S14 and S17 Search modes - Boolean/Phrase
S17 S15 or S16 Search modes - Boolean/Phrase
S16 TX (intraves* or instill* or region* or install*)
S15 (MH "Administration, Intravesical") Search modes - Boolean/Phrase
S14 S10 or S11 or S12 or S13 Search modes - Boolean/Phrase
S13 gem?cis or gem?cisplat or gem?carbo Search modes - Boolean/Phrase
S12 gemc?tabin* or gemzar Search modes - Boolean/Phrase

S11 (MH “Gemcitabine”) Search modes - Boolean/Phrase
S10 (MH “Deoxycytidine+”) Search modes - Boolean/Phrase
S9 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 Search modes - Boolean/Phrase
S8 tcc or “transitional cell” Search modes - Boolean/Phrase
S7 (MH “Ureteral Neoplasms”) Search modes - Boolean/Phrase
S6 (MH “Urethral Neoplasms”) Search modes - Boolean/Phrase
S5 bladder N3 tumo?r* Search modes - Boolean/Phrase
S4 bladder N3 neoplas* Search modes - Boolean/Phrase
S3 bladder N3 carcinoma* Search modes - Boolean/Phrase
S2 bladder N3 cancer* Search modes - Boolean/Phrase
S1 (MH “Bladder Neoplasms”) Search modes - Boolean/Phrase

Cochrane Library

1. MeSH descriptor Urinary Bladder Neoplasms explode all trees
2. (bladder* NEAR/3 (cancer* or carcinoma* or neoplas* or tumo?r*)):ti,ab,kw
3. MeSH descriptor Carcinoma, Transitional Cell explode all trees
4. (tcc or transitional cell):ti,ab,kw
5. MeSH descriptor Ureteral Neoplasms explode all trees
6. MeSH descriptor Urethral Neoplasms explode all trees
7. ((bladder* or urethra* or ureter* or urin* or urotheli* or renal pelvis or calice*) NEAR/3 (cancer* or carcinoma* or adenoma* or adenocarcinoma* or squamous* or neoplas* or tum?r* or malignan*)):ti,ab,kw
8. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
9. MeSH descriptor Deoxycytidine explode all trees
10. MeSH descriptor Antimetabolites, Antineoplastic explode all trees
11. (gemc?tabin* or Gemzar*):ti,ab,kw
12. (gem?cis or gem?cisplat or gem?carbo):ti,ab,kw
13. (gem NEXT (cis or cisplat or carbo)).:ti,ab,kw
14. (#9 OR #10 OR #11 OR #12 OR #13)
15. MeSH descriptor Administration, Intravesical explode all trees
16. (intraves* or instill* or region* or install*)
17. (#15 OR #16)
18. (#8 AND #14 AND #17)

Scopus

(((TITLE-ABS-KEY(gemc?tabin*) OR TITLE-ABS-KEY(gemzar) OR TITLE-ABS-KEY(gemcis) OR TITLE-ABS-KEY(gemcisplat) OR TITLE-ABS-KEY(gemcarbo))) AND ((TITLE-ABS-KEY(intraves*) OR TITLE-ABS-KEY(instill*) OR TITLE-ABS-KEY(region*) OR TITLE-ABS-KEY(install*))) AND ((((TITLE-ABS-KEY((bladder W/3 tumo?r*)) OR TITLE-ABS-KEY((bladder* W/3 cancer*)) OR TITLE-ABS-KEY((bladder* W/3 carcinoma*)) OR TITLE-ABS-KEY((bladder* W/3 neoplasm*)))) OR ((TITLE-ABS-KEY((ureteral* W/3 tumo?r*)) OR TITLE-ABS-KEY((ureteral* W/3 cancer*)) OR TITLE-ABS-KEY((ureteral* W/3 carcinoma*)) OR TITLE-ABS-KEY((ureteral* W/3 neoplasm*)))) OR ((TITLE-ABS-KEY((urethral* W/3 tumo?r*)) OR TITLE-ABS-KEY((urethral* W/3 cancer*)) OR TITLE-ABS-KEY((urethral* W/3 carcinoma*)) OR TITLE-ABS-KEY((urethral* W/3 neoplasm*)))))))

BIOMED Central

((gemcitabin* OR gemzar* OR gemcis OR gemcisplat OR gemcarbo)[TIAB]) AND ((instill* OR install* OR region* OR intraves*)[TIAB]) AND ((((ureteral* AND (neoplas* OR cancer* OR Tumor* OR tumour* OR carcinoma*))[TIAB]) OR (((urethral* AND (neoplas* OR cancer* OR Tumor* OR tumour* OR carcinoma*))[TIAB]) OR (((bladder* AND (neoplas* OR cancer* OR Tumor* OR tumour* OR carcinoma*))[TIAB]))

LILACS

((bladder$ or bexiga or vejiga or ureter$ or urethr$)) and ((gemcitabin$ or gemzar or gemcis or gemcisplat or gemcarbo)) and ((intraves$ or instill$ or region$ or install$))

Web of Science®

#13 #12 AND #11 AND #6
#12 Topic=(TS=(intraves* or instill* or region* or install*))
#11 #10 OR #9 OR #8 OR #7
#10 Topic=(TS=(gem SAME (cis or cisplat or carbo)))
#9 Topic=(TS=(gem?cis or gem?cisplat or gem?carbo))
#8 Topic=(TS=(gemc?tabin* or gemzar*))
#7 Topic=(TS=deoxycytidine)
#6 #5 OR #4 OR #3 OR #2 OR #1
#5 Topic=(TS=(tcc or transitional cell))
#4 Topic=(TS=((urin* or urotheli* or renal pelvis or calice) SAME (cancer* or carcinoma* or neoplas* or tumo?r*)))
#3 Topic=(TS=(ureteral SAME (cancer* or carcinoma* or neoplas* or tumo?r*)))
#2 Topic=(TS=(urethral SAME (cancer* or carcinoma* or neoplas* or tumo?r*)))
#1 Topic=(TS=(bladder SAME (cancer* or carcinoma* or neoplas* or tumo?r*)))

BIOSIS

#13 #12 AND #11 AND #6
#12 Topic=(TS=(intraves* or instill* or region* or install*))
#11 #10 OR #9 OR #8 OR #7
#10 Topic=(TS=(gem SAME (cis or cisplat or carbo)))
#9 Topic=(TS=(gem?cis or gem?cisplat or gem?carbo))
#8 Topic=(TS=(gemc?tabin* or gemzar*))
#7 Topic=(TS=deoxycytidine)
#6 #5 OR #4 OR #3 OR #2 OR #1
#5 Topic=(TS=(tcc or transitional cell))
#4 Topic=(TS=((urin* or urotheli* or renal pelvis or calice) SAME (cancer* or carcinoma* or neoplas* or tumo?r*)))
#3 Topic=(TS=(ureteral SAME (cancer* or carcinoma* or neoplas* or tumo?r*)))
#2 Topic=(TS=(urethral SAME (cancer* or carcinoma* or neoplas* or tumo?r*)))
#1 Topic=(TS=(bladder SAME (cancer* or carcinoma* or neoplas* or tumo?r*)))

ASCO

Intravesical Gemcitabine Superficial Bladder

WHO International Clinical Trials Registry

Intravesical AND Gemcitabine AND Bladder.

CONTRIBUTIONS OF AUTHORS

Concept: Mike Shelley.

Manuscript preparation: Mike Shelley and Gabriel Jones.

Search Strategy: Anne Cleves.

Screening search lists, trial selection, and data extraction: Mike Shelley, Gabriel Jones, Anne Cleves.

Review methodology: Mike Shelley and Timothy J Wilt.

Review manuscript for clinical content: Howard G Kynaston, Malcolm Mason, Timothy J Wilt, and Mike Shelley.

Critically appraise manuscript: All authors.

DECLARATIONS OF INTEREST

The authors declare no conflict of interest.

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Funded the library facilities

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

As no meta-analysis was performed, the sections in the protocol relating to meta-analysis methodology have been deleted in the full review.

INDEX TERMS

Medical Subject Headings (MeSH)

Adjuvants, Immunologic [administration & dosage]; Administration, Intravesical; Antibiotics, Antineoplastic [administration & dosage; adverse effects]; Antimetabolites, Antineoplastic [*administration & dosage; adverse effects]; BCG Vaccine [administration & dosage]; Deoxycytidine [administration & dosage; adverse effects; *analogs & derivatives]; Disease Progression; Drug Administration Schedule; Mitomycin [administration & dosage; adverse effects]; Neoplasm Recurrence, Local [prevention & control]; Randomized Controlled Trials as Topic; Urinary Bladder Neoplasms [*drug therapy; pathology; prevention & control]

MeSH check words

Humans