Impact of intravesical chemotherapy on recurrence rate of recurrent superficial transitional cell carcinoma of the bladder: results of a meta-analysis
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Authors' objectives
To present a meta-analysis of the available clinical trial data in order to quantify the effect of intravesical chemotherapy on tumour recurrence following transurethral resection (TURB), in patients with recurrent superficial bladder cancer.

Searching
MEDLARS was searched from 1966 to 1997. In addition, Cancerlit and Current Contents (CD-ROM) were searched (search dates not provided), and manual searches of the retrieved papers and textbooks were performed. The search terms were not reported. The searches were limited to papers published in the English language; published abstracts were excluded. The authors appear to have employed procedures detailed elsewhere (see Other Publications of Related Interest no.1).

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with at least 1-year of follow-up.

Specific interventions included in the review
Studies of adjuvant intravesical chemotherapy with more than 1-year of follow-up were eligible for inclusion. Chemotherapy was administered intravesically and comprised different dosing schedules of the following drugs: 1-epirubicin (50 mg); 2-epirubicin (80 mg); adriamycin (20 mg); 1-adriamycin (20 to 80 mg); 2-adriamycin (50 mg); 3-adriamycin (50 mg); mitomycin-C (40 mg); 2-mitomycin-C (5 to 40 mg); 2-ethoglucid (1.13 g); thiotepa (30 to 60 mg); 1-thiotepa (30 mg); 2-VM-26 (50 mg). Studies in which only non-intravesical chemotherapy was given, or the treatment arms included immune therapies (e.g. BCG), photodynamic, biologic or other non-cytotoxic therapies, were excluded.

Participants included in the review
Studies of adult patients with superficial transitional cell carcinoma of the bladder were eligible for inclusion. The acceptable tumour stages included Ta, T1 with or without carcinoma in situ, and all tumour grades. Other details of the participants were not provided. Patients with both primary and recurrent tumours, who were not stratified on this characteristic, were included only if the recurrent patients comprised more than 25% of the study group.

Outcomes assessed in the review
Tumour recurrence at 1, 2 and 3 years' post-TURB was assessed.

How were decisions on the relevance of primary studies made?
One reviewer made decisions concerning the eligibility of the papers on the basis of predefined inclusion criteria.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The data were extracted by two reviewers, and any differences in the extraction forms were resolved by consensus. Data were collected on the following: sample size; type of chemotherapy; dosage; treatment schedule; tumour stage and grade; and the proportion of patients with recurrence at 1, 2 or 3 years' post-TURB.
Methods of synthesis

How were the studies combined?
The odds ratios (ORs) for tumour recurrence at specified times following TURB were pooled using the fixed-effect model of Yusuf et al. (see Other Publications of Related Interest no.2). No method of assessing publication bias was reported.

How were differences between studies investigated?
A statistical test (Q) for homogeneity was performed. Sensitivity analyses were performed on statistically heterogeneous sets of data.

Results of the review

Eight RCTs were included in the analysis. These contained 14 treatment arms that fulfilled the inclusion criteria. A total of 1,609 patients were enrolled in these treatment arms.

At the 1-year follow-up, fewer patients who had received intravesical chemotherapy following TURB showed evidence of a recurrence than those who had received TURB alone (OR 0.62, 95% confidence interval, CI: 0.51, 0.76). No significant heterogeneity was found (Q=10.1, d.f.=13). Similarly, at the 2-year follow-up (OR 0.46, 95% CI: 0.33, 0.63) and 3-year follow-up (OR 0.35, 95% CI: 0.23, 0.54), patients receiving intravesical chemotherapy following TURB were less likely to have a recurrence. However, significant heterogeneity was found for these effects (Q=31.7 at 2 years and Q=50.8 at 3 years; d.f.=13). The sensitivity analyses revealed that this heterogeneity at 2- and 3-years’ follow-up was not due to differences in treatment duration (Q=27.8, p=0.006 for recurrence at 2 years; Q=45.3, p=0.001 at 3 years). The authors found evidence to suggest that the type of chemotherapy had contributed towards the heterogeneity. When they analysed data for the 2-year follow-up for Adriamycin alone, heterogeneity was eliminated (Q=5.8, p-value not reported). The results of the heterogeneity test for the remaining trials of alternative forms of chemotherapy and for the 3-year follow-up were not reported. However, recurrence at 2 years was significantly greater following Adriamycin than with the other drugs administered.

Authors’ conclusions

Intravesical chemotherapy appeared to have a major impact on decreasing the chance of recurrence of superficial bladder cancer. Although the analysis demonstrated that all of the drugs included in the meta-analysis had a significant impact on reducing bladder tumour recurrence, Adriamycin appeared less effective than any of the other drugs used.

CRD commentary

The research question was well defined and the inclusion criteria were readily identifiable. The literature search appears to have been adequate, but verification of this is hindered by a lack of detail concerning some dates and search terms. The authors do not appear to have employed a validity assessment, but this may be less of a concern as non-RCT data were excluded. The decision-making was generally adequate, although the validity would have been enhanced if more than one reviewer had made the decisions on relevance. The authors pooled the data statistically and addressed heterogeneity. Publication bias was not addressed. Generally, this was a well-conducted review that sought to answer a much debated question. The conclusions appear to be in line with the data presented, although some caution should be employed in interpreting the results as ORs were presented but were interpreted by the authors as rate ratios. It is unclear from the data whether this is appropriate (i.e. if the event rate is low).

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors state that further clinical trials are needed to clarify whether the biological behaviour of recurrent bladder tumours differs from that of primary disease, with regard to chemotherapeutic sensitivity. Future trials should address whether primary or recurrent tumours respond differently to any given drug or drug type.
Bibliographic details

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Other publications of related interest

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Subject indexing assigned by NLM

MeSH
Administration, Intravesical; Antineoplastic Agents /administration & dosage /therapeutic use; Carcinoma, Transitional Cell /drug therapy /epidemiology /pathology /surgery; Clinical Trials as Topic; Doxorubicin /administration & dosage /therapeutic use; Epirubicin /administration & dosage /therapeutic use; Follow-Up Studies; Humans; Mitomycin /administration & dosage /therapeutic use; Neoplasm Recurrence, Local /epidemiology /prevention & control; Odds Ratio; Prospective Studies; Randomized Controlled Trials as Topic; Teniposide /administration & dosage /therapeutic use; Thiotepa /administration & dosage /therapeutic use; Treatment Outcome; Urinary Bladder Neoplasms /drug therapy /epidemiology /pathology /surgery

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.