Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis

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CRD summary
This was a well-conducted meta-analysis of patient level data on the effect of neoadjuvant chemotherapy on survival in invasive bladder cancer. The findings showed that neoadjuvant platinum combination chemotherapy confers a clear survival benefit in patients with invasive bladder cancer. There is no evidence to support the use of single-agent platinum neoadjuvant chemotherapy.

Authors' objectives
To assess the effect of neoadjuvant chemotherapy on survival in invasive bladder cancer.

Searching
MEDLINE and Cancerlit were searched using a version of the Cochrane Collaboration optimal search strategy. The reference lists of retrieved articles, reviews and relevant books were checked. The National Cancer Institute PDQ Clinical Protocols, the UK Coordinating Committee for Cancer Research trials register and the Current Controlled Trials metaRegister were also searched for unpublished studies. Searches were updated throughout the review, up to September 2002.

Study selection

Specific interventions included in the review
Studies that compared neoadjuvant chemotherapy plus standard local treatment with standard treatment alone were eligible for inclusion. The same standard local treatment had to be used in the active and control arm, and the comparison had to be unconfounded by additional agents or interventions. The neoadjuvant chemotherapy in the included studies was: cisplatin alone; cisplatin in combination with doxorubicin; cisplatin in combination with methotrexate; cisplatin in combination with methotrexate, vinblastine and epirubicin or doxorubicin; and carboplatin in combination with methotrexate and vinblastine. Treatment was administered as 2 or 3 cycles every 2, 3 or 4 weeks. The standard local therapy was surgery (usually radical) and/or radiotherapy. Neoadjuvant therapy was defined as that given before the standard local treatment.

Participants included in the review
Studies of patients with biopsy proven invasive (defined as stage T2-T4a) transitional cell carcinoma of the bladder were eligible for the review. Around 85% of the participants in the included studies were male and 80% were aged 55 years or older. Details of T category, N category and grade of disease were given in the review together with details of performance status, tumour diameter and renal function.

Outcomes assessed in the review
The primary outcome was overall survival, defined as time from randomisation to death. Death was all-cause. Living patients were censored on date of last follow-up. The secondary outcomes were disease-free survival, loco-regional disease-free survival and metastases-free survival. Not all of the included studies provided data for all outcomes. The median length of follow-up in the included studies was 6.2 years.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed all articles for relevance. Any disagreements were resolved within the project secretariat and the international advisory group.
Assessment of study quality
Information for all patients, including those who had been excluded from the investigators' original analyses, was checked. All data were thoroughly checked for consistency, plausibility, and integrity of randomisation and follow-up. The authors did not state how many reviewers performed the validity assessment.

Data extraction
Individual patient data were sought: data of randomisation, survival status, local recurrence status, status of metastases, date of last follow-up and other patient details. Any queries were resolved and the final database entries verified by the trial investigator or statistician. The log rank expected number of deaths and variance were used to calculate individual trial hazard ratios (HRs) for recurrence, progression or death.

Methods of synthesis
How were the studies combined?
The overall pooled HRs were calculated using a fixed-effect model.

How were differences between studies investigated?
A chi-squared test for heterogeneity was conducted across all trials. In addition, prospectively planned analyses investigated important features of the trials that might influence the effect of chemotherapy. The trials were grouped by characteristic and a chi-squared test for quantitative interaction was used to test whether the effect of neoadjuvant chemotherapy differed significantly between these groups. These analyses focused on overall survival.

Results of the review
Eleven trials were eligible, but the patient data could not be obtained for one. Therefore, 10 trials (n=2,492) were included in the meta-analysis.

Overall survival (all 10 trials, n=2,492): the confidence intervals (CI) of the effect sizes for the individual studies were wide and the results of individual trials were inconclusive. There was no statistical heterogeneity and the pooled HR was 0.91 (95% CI: 0.83, 1.01) (i.e. no statistically significant benefit).

Overall survival with single-agent chemotherapy (i.e. cisplatin) (3 trials, n=376): the HR was 1.15 (95% CI: 0.90, 1.47), indicating no benefit of neoadjuvant chemotherapy.

Overall survival with combination neoadjuvant chemotherapy (6 trials, n=2,116): the HR was 0.87 (95% CI: 0.78, 0.97), indicating a statistically significant reduction in risk of death. A sensitivity analysis that excluded the largest trial found this result to be robust and not driven by that one trial. The difference between the results for combination chemotherapy and single-agent chemotherapy was statistically significant.

A further analysis, which included the summary data of the one extra trial for which individual patient data could not be obtained, did not alter the findings of the main meta-analysis but did narrow the overall CI.

Findings for the secondary outcomes closely reflected those for overall survival.

Authors' conclusions
The findings showed that neoadjuvant platinum combination chemotherapy confers a survival benefit in patients with invasive bladder cancer. There was no evidence to support the use of single-agent platinum neoadjuvant chemotherapy.

CRD commentary
This was a well-conducted meta-analysis of patient level data. The review question and the inclusion criteria were clearly defined. The literature searches appeared thorough and it is likely that all relevant studies were included in the review. The review methodology appears to have been careful and correct, with efforts made to check the integrity of
the source of the data.

A good level of detail on the primary studies was provided in the review, thus enabling the reader to interpret the findings. The statistical methods employed were appropriate and the review's findings appear reliable. Although the review did not limit itself to platinum-based therapies, only platinum-based therapies were included. Therefore, the findings may not be generalisable to other different combination regimens.

**Implications of the review for practice and research**

**Practice:** The authors suggested that the improvement in survival with platinum-based combination neoadjuvant chemotherapy encourages the use of these regimens for patients with invasive bladder cancer.

**Research:** The authors suggested that promising new drug regimens should be compared with platinum-based combination neoadjuvant chemotherapy in RCTs.

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