Ten years of docetaxel-based therapies in prostate adenocarcinoma: a systematic review and meta-analysis of 2244 patients in 12 randomized clinical trials
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CRD summary
The review found that men with metastatic prostate cancer and good performance status who received docetaxel combination therapies had a higher prostate specific antigen response rate and longer survival time than those who received docetaxel alone. Limitations in the review, in particular use of inappropriate statistical methods and poor reporting of study quality, mean these conclusions do not appear reliable.

Authors' objectives
To assess the effectiveness of docetaxel-based combination therapies versus docetaxel alone for treatment of metastatic prostate cancer.

Searching
MEDLINE and CancerLit (from 1966), Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE (from 1990) were searched to 2010. Search terms were reported. Proceedings of meetings of the American Society of Clinical Oncology were searched from 1998 to 2010. Reference lists of relevant reviews, guidelines and retrieved articles were checked.

Study selection
Eligible studies were randomised controlled trials (RCTs) that compared docetaxel-based two-drug combination chemotherapy versus docetaxel plus prednisone used as first-line chemotherapy for men with histologically confirmed castration-resistant prostate cancer. Studies were required to report overall survival, disease control or toxicity. The primary review outcome was overall survival. Secondary outcomes were prostate-specific antigen response, time to disease progression, measurable disease response and grade 3 or 4 toxicity. Outcomes were defined in the review. Studies of bisphosphonates, radiopharmaceuticals, immunotherapy and hormone therapy were excluded.

Participants in all but one of the included studies were described as chemotherapy-naive. Performance status (using Eastern Cooperative Ecology Group criteria) varied across study groups from 75% to 100% (where reported). All study arms received docetaxel given intravenously weekly or three weekly (various doses). Cointerventions in the intervention arms included a range of oral or intravenous vitamin-D related agents, cytotoxic agents, anti-angiogenic agents and target agents. Treatment duration was three or four weeks.

The authors did not state how many reviewers performed study selection.

Assessment of study quality
The authors did not state that they assessed validity but they reported in their description of study characteristics which studies were placebo-controlled, double-blinded and/or used intention-to-treat analysis.

Data extraction
Data were extracted from each study on event rates and survival times in each arm. Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for dichotomous data (response rates and adverse event rates) and median survival times for continuous data, with p values for all comparisons. Studies were grouped by the type of combination chemotherapy used in the intervention arm.

Data were extracted independently by three authors. Disagreements were resolved by consensus. Primary study authors were contacted for additional information as required.

Methods of synthesis
Findings were reported both overall (pooling all types of combination therapy versus single agent therapy) and stratified by type of combination therapy. Dichotomous data were combined using a fixed-effect Mantel-Haenszel model to
calculate pooled risk ratios and 95% confidence intervals. Heterogeneity was assessed with the X² test. Continuous data were combined to calculate overall median survival rates (statistical methods not described). P values were reported for all analyses. Pooling of adverse effects data was restricted to neutropenia and thromboembolic events due to variation between studies in the grading of toxicity. A subgroup analysis was conducted, restricted to studies that used three-weekly docetaxel.

Results of the review
Twelve RCTs were included (2,244 participants, range 69 to 350). Five RCTs were placebo-controlled. Four studies were double-blinded. Four studies used intention-to-treat analysis.

There was no statistically significant difference between all the combined therapy groups and the single agent groups in overall survival rate (RR for death 0.93, 95% CI 0.81 to 1.06; eight RCTs; no significant heterogeneity). The median overall survival time was significantly longer in the combined therapy groups (22 months versus 18.4 months, p=0.037, nine RCTs).

There was no statistically significant difference between all the combined therapy groups and the single agent groups in overall response rate (RR 1.15, 95% CI 0.84 to 1.56; 10 RCTs; no significant heterogeneity). There was no significant difference in median progression-free survival (6.7 months versus 6.0 months, p=0.450, 11 RCTs). However, there was a significantly higher prostate specific antigen response rate in the combined therapy groups (RR 1.16, 95% CI 1.04 to 1.30; 10 RCTs; significant heterogeneity, p=0.0006).

There was no significant difference between the combined therapy groups and the single agent groups in the rate of grade 3 or 4 neutropenia (RR 0.87, 95% CI 0.71 to 1.07; 11 RCTs) and thromboembolic events (RR 1.52, 95% CI 0.79 to 2.90; 11 RCTs; no significant heterogeneity).

When analyses were restricted to studies that used three-weekly docetaxel, results were similar to overall findings. When results were stratified by intervention, survival rates were similar to overall findings except for the outcome of prostate specific antigen response. For this outcome docetaxel with cytotoxic agents had a significantly higher prostate specific antigen response rate than controls (RR 1.46, 95% CI 1.22 to 1.76; three RCTs; high heterogeneity, p=0.00007). There was no significant difference between any of the other combined therapies and single agent therapy.

Authors' conclusions
Men with metastatic prostate cancer and good performance status who received docetaxel combination therapies had a higher prostate specific antigen response rate and longer survival time than those who received docetaxel alone.

CRD commentary
The objectives and inclusion criteria of the review were clear. Relevant sources were searched for published and unpublished studies. The risk of publication bias was not formally assessed. It was unclear whether the search was restricted by language: if so, it was possible that studies were missed. Steps were taken to minimise the risk of reviewer error and bias during data extraction; it was not reported whether this also applied to study selection and it was unclear whether study quality was systematically assessed. It was unclear whether the primary review outcome was survival rate or survival duration or both. No details were reported about important characteristics of individual studies such as allocation concealment, rates of loss to follow-up and time-points for outcome reporting.

The statistical methods used to calculate survival rates did not appear appropriate as accurate estimation of survival requires the status of all participants to be known at a fixed time-point or else requires statistical adjustment for differences in follow up times (such as by calculation of a hazard ratio). Similarly, methods used to calculate pooled survival times did not appear valid as pooling of median values is associated with a high risk of bias. There was high heterogeneity in the analysis of prostate specific antigen response and this was not adequately investigated or explained. It appeared that some studies (including the largest) did not contribute to the pooled analyses and it was unclear why this was so. The authors suggested that the review might be limited by publication bias and that there was potential under-reporting of adverse events by the primary studies.

In view of limitations in the review, in particular the use of inappropriate statistical methods and poor reporting of study quality, these conclusions do not appear reliable.
Implications of the review for practice and research

Practice: The authors stated that combination therapy could not be considered as standard or recommended.

Research: The authors stated that the role of performance status as a prognostic factor should be investigated in future prospective trials of treatments for advanced prostate cancer.

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