Taxanes as first-line therapy for advanced non-small cell lung cancer: a systematic review and practice guideline

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CRD summary
This review assessed the use of taxanes as first-line chemotherapy for patients with advanced non-small-cell lung cancer. The authors concluded that taxane-cisplatin was effective as first-line treatment, whereas taxane-gemcitabine could be considered in the case of contraindication to platinum agents. The review had some methodological weaknesses but the authors’ conclusions appear appropriate and are likely to be reliable.

Authors’ objectives
To evaluate taxanes alone or in combination with other chemotherapy agents as first-line chemotherapy for advanced non-small-cell lung cancer (NSCLC).

Searching
Cancerlit, the Cochrane Library, EMBASE and MEDLINE were searched to April 2005; the search terms were reported. Conference proceedings of the American Society of Clinical Oncology (1996 to 2004), the European Society for Medical Oncology (2002 and 2004), and the European Cancer Conference (2003) were also searched. Only studies published in the English language were considered for inclusion. The reference lists of relevant articles and reviews were checked for additional studies.

Study selection
Study designs of evaluations included in the review
Randomised trials (RCTs) published in full or published in abstract form at a major scientific meeting were eligible. Abstracts of preliminary data were excluded.

Specific interventions included in the review
Studies that compared a taxane-based chemotherapy with best supportive care (BSC) or another chemotherapy regimen as first-line treatment, or compared different doses or treatment schedules, were eligible for inclusion. The included studies evaluated taxanes (paclitaxel and docetaxel) as single agents, as doublets in combination with a platinum or non-platinum agent, or as triplets. Comparator chemotherapies were other platinum-based doublets, single-agent platinum and non-platinum-based doublets. The dosing and schedule of taxanes varied across the studies.

Participants included in the review
Patients with locally advanced or metastatic NSCLC were eligible for inclusion. Studies including patients treated with neoadjuvant chemotherapy at least 1 year prior to the evaluation of taxanes were also included.

Outcomes assessed in the review
The outcomes of interest were survival, tumour response rate, toxicity and quality of life.

How were decisions on the relevance of primary studies made?
Three reviewers selected trials for inclusion according to pre-specified criteria.

Assessment of study quality
The adequacy of allocation concealment, randomisation and blinding were assessed. The authors did not state how many reviewers performed the validity assessment.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Differences in overall survival were reported as hazard ratios (HRs) with the corresponding 95% confidence interval (CI). The response rate and median survival were also extracted.

Methods of synthesis
How were the studies combined?
The studies were combined narratively.

How were differences between studies investigated?
Differences in study design, interventions and outcomes were discussed in the text.

Results of the review
Forty-five RCTs, 29 involving paclitaxel and 18 involving docetaxel, were included.

None of the included trials reported blinding of treatment. Nine RCTs with paclitaxel and 6 with docetaxel used a centralised randomisation process. The number of included patients ranged from 79 to 1,207 in studies with paclitaxel and from 60 to 1,218 in studies with docetaxel.

Taxane as single agent.
Paclitaxel.
One RCT reported a statistically significant overall survival advantage for paclitaxel combined with BSC compared with BSC alone (HR 0.68, 95% CI: 0.49, 1.0, p=0.037), though chemotherapy-related side-effects were more common with paclitaxel. Paclitaxel showed similar survival rates, but lower response rate or median failure-free survival than paclitaxel-carboplatin (1 trial). Grade 3 or 4 toxicity was more common with the combination treatment. Gemcitabine-paclitaxel was associated with a higher overall survival than paclitaxel alone (HR 0.76, 95% CI: 0.59,0.99, p=0.0486; 1 trial).

Docetaxel.
There was no statistically significant difference in median survival between docetaxel with or without cisplatin (1 trial). The objective tumour response was significantly better with the combined treatment (p=0.004), though there was a higher rate of treatment-related deaths and higher rates of grade 3 or 4 toxicity with combined treatment. Overall survival was improved with docetaxel and BSC compared with BSC alone (p=0.026), though adverse effects were generally more frequent with docetaxel (1 trial).

Taxane in combination with other chemotherapy agents.
Paclitaxel.
Paclitaxel in combination with a platinum agent was associated with better response rates and comparable toxicity when compared with the older chemotherapy regimens of teniposide-cisplatin (1 trial), etoposide-cisplatin (1 trial), or cisplatin alone (1 trial). However, there was no statistically significant improvement in overall survival or consistent benefits in quality of life. There was no statistically significant difference in tumour response or overall survival when the paclitaxel-platinum combination was compared with vinorelbine-cisplatin (2 trials), gemcitabine-cisplatin (2 trials), docetaxel-cisplatin (1 trial), gemcitabine-paclitaxel (2 trials), or paclitaxel-vinorelbine (2 trials). Toxicity was generally comparable among these regimens, though there were some differences between the combinations. The addition of paclitaxel to gemcitabine-cisplatin (1 trial) was associated with better overall survival and response rate than gemcitabine-cisplatin alone (HR 0.67, 95% CI: 0.52, 0.91, p<0.01). Response rate and overall survival were not significantly different for high-dose or low-dose paclitaxel (1 trial), or between paclitaxel-carboplatin administered every 3 weeks for 4 cycles compared with administration until disease progression.
Docetaxel.

A statistically significant better response and overall survival were observed for docetaxel-cisplatin compared with vindesine-cisplatin (1 trial); anaemia was less frequent with the docetaxel combination but some non-haematologic toxicities were more common. There was no statistically significant difference in response rate or survival between a platinum-docetaxel combination and paclitaxel-cisplatin (1 trial), docetaxel-gemcitabine (1 trial), or vinorelbine-cisplatin (1 trial). There was no statistically significant difference in survival or quality of life between docetaxel-gemcitabine and vinorelbine-cisplatin (2 trials). Grade 3 or 4 toxicity was more common with vinorelbine-cisplatin, though some toxicities were more common with docetaxel-gemcitabine.

The extended version of this review is available on the Cancer Care Ontario website (accessed 01/06/2007). See Web Address at end of abstract.

**Authors' conclusions**
Taxane (paclitaxel or docetaxel) in combination with cisplatin can be recommended as one of a number of options for first-line chemotherapy for advanced NSCLC, while the combination taxane-gemcitabine can be considered as an alternative for patients with a contraindication to platinum agents. No firm recommendation can be made on the optimal dose and schedule of taxane-based chemotherapy. Where combination therapy is inappropriate, single-agent taxane therapy is acceptable treatment.

**CRD commentary**
This review addressed a well-defined question in terms of the study design, participants, intervention and outcomes. The authors searched several relevant databases and efforts were made to find further published and unpublished studies, thereby reducing the potential for publication bias. Only studies reported in English were included, which might have introduced language bias. Publication bias was not assessed. It was not stated if the data extraction and assessment of study quality were performed in duplicate, therefore reviewer error and bias might have been introduced into the review process. The authors’ decision not to pool the studies in a meta-analysis seems reasonable given the apparent clinical and methodological differences between the studies. The authors’ conclusions appear appropriate, but the lack of reporting of the review process and the potential for language bias must be taken into consideration.

**Implications of the review for practice and research**
Practice: Taxane (paclitaxel or docetaxel) in combination with cisplatin can be recommended as first-line chemotherapy for advanced NSCLC, while taxane-gemcitabine can be considered an alternative for patients with a contraindication to platinum agents. The authors also stated that taxane-based triplet combinations should only be considered in the context of a clinical trial.

Research: Further randomised trials to determine the most effective doses and administration schedules for first-line taxane regimens are warranted.

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