Second-line treatment for advanced non-small cell lung cancer: a systematic review  
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CRD summary
This review assessed the effects of second-line treatments for advanced non-small-cell lung cancer. The authors concluded that second-line chemotherapy can produce a small but significant survival advantage, but further research is required. The lack of a quality assessment and the lack of supporting data for some outcomes mean that the reliability of the authors’ conclusions about efficacy is unclear.

Authors’ objectives
To assess the effects of second-line treatments in patients with advanced non-small-cell lung cancer (NSCLC).

Searching
PubMed was searched from 1996 to February 2005 for publications in the English language; the search terms were reported. The reference lists of selected full papers were screened and manual and electronic searches of the abstracts of meetings of the American Society of Clinical Oncology, the International Association for the Study of Lung Cancer and the European Society of Medical Oncology were conducted.

Study selection
Study designs of evaluations included in the review
Studies with a minimum median duration of follow-up of 1 year were eligible for inclusion. The search terms included the word ‘randomised’, suggesting that randomised controlled trials (RCTs) were eligible for inclusion, though specific inclusion criteria relating to study design were not reported.

Specific interventions included in the review
Inclusion criteria for the interventions were not explicitly reported, but it was clear that studies of second-line treatments were eligible for inclusion. The included studies evaluated single-agent drugs (e.g. docetaxel, paclitaxel, gemcitabine and pemetrexed), platinum- and non-platinum-based two-drug combinations (e.g. docetaxel plus vinorelbine, ifosfamide, paclitaxel and pemetrexed), and weekly and 3- to 4-weekly regimens containing docetaxel or paclitaxel either alone or in combination with gemcitabine, vinorelbine or irinotecan. Comparator treatments were best supportive care (BSC) and other chemotherapy regimens. The review also included studies of novel agents of chemotherapy. Full details of the drugs and doses were reported.

Participants included in the review
Studies in patients with histological or cytologically proven advanced NSCLC were included if the patients had previously received first-line treatment with chemotherapy. The characteristics of the patients included in the selected studies were not reported.

Outcomes assessed in the review
Inclusion criteria for the outcomes were not explicitly reported. The review assessed the percentage of patients achieving a partial or complete response, median survival, overall survival at 1 year, toxic deaths, grade 3 to 4 haematological and non-haematological toxicities, time to progression, quality of life (QoL) and symptom control.

How were decisions on the relevance of primary studies made?
The authors did not state how the studies were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Studies were assessed for: method of randomisation (where appropriate); defined hypothesis underlying statistical analysis; description of the participants' prognostic factors; definition of treatment protocol and definition of survival;
reporting of evaluable patients; methods used to evaluate response and toxicity (particularly toxic deaths); verification of the number of patients lost to follow-up; and methods of analysis (intention-to-treat basis or fully eligible patients only).

Two reviewers independently assessed some aspects of validity but it was unclear whether both performed the entire validity assessment.

Data extraction
Two reviewers independently extracted the number of accrual patients, the number of eligible patients, the number lost to follow-up, performance status, the proportion of patients with stage IIIB, the number of patients with each event of interest and the overall response rate.

Methods of synthesis
How were the studies combined?
The studies were grouped according to their relevance to the following questions and combined in a narrative: Does chemotherapy improve survival?; Is one single-agent chemotherapy superior to another?; Is a combination of two or more drugs superior to single-agent chemotherapy?; Is a weekly chemotherapy schedule better than a 3- or 4-weekly schedule?; How many cycles of second-line chemotherapy should NSCLC patients receive?; and Were any new second-line treatments identified?

How were differences between studies investigated?
Differences between the treatment regimens were described in the text.

Results of the review
Eleven phase II studies (n=712) evaluated single-agent chemotherapy regimens.

One RCT (n=204) compared second-line chemotherapy with BSC.

Three RCTs (n=821) compared single-agent chemotherapy regimens with other single-agent regimens.

Twelve phase II studies (n=359) evaluated two-drug platinum-based regimens.

Twenty phase II (n=733) studies evaluated two-drug non-platinum-containing regimens.

Five RCTs (n=585) evaluated combinations of two drugs.

Ten phase II studies (n=387) evaluated weekly schedules of single agents, 3 phase II and phase III RCTs (n=561) evaluated weekly schedules of single agents, and 3 phase II studies (n=109) evaluated weekly schedules of combinations of two agents.

Eight phase II studies (n=328) evaluated novel chemotherapy agents.

Does chemotherapy improve survival?
The only RCT (204 patients who had previously received platinum-based chemotherapy) that compared chemotherapy plus BSC with BSC alone reported that docetaxel every 3 weeks significantly improved median time to progression (10.6 weeks versus 6.7 weeks, p=0.001), median survival (7.0 months versus 4.6 months, p=0.04) and 1-year survival (37% versus 12%, p=0.03) compared with BSC alone. With 75 mg/m2 docetaxel, there were no toxic deaths and there was a low rate of febrile neutropenia (1.8%), but grade 3 to 4 neutropenia was common (67.3%). Patient-rated pain was lower with docetaxel on the Lung Cancer Symptom scale but there were no significant differences in various QoL domains assessed using the EORT QLQ-C30 (no supporting data were presented).

Is one single-agent chemotherapy superior to another?
Three RCTs compared docetaxel with vinorelbine or ifosfamide, paclitaxel and pemetrexed. One RCT reported significantly improved 1-year survival with docetaxel compared with vinorelbine or ifosfamide (32% versus 19%, p=0.02). One RCT reported similar 1-year survival for docetaxel and pemetrexed (29.7% for both), but reported increased grade 3 and 4 neutropenia (40.2% versus 5.3%, p<0.001) and febrile neutropenia (12.7% versus 1.9%, p<0.001), leading to increased hospital admissions (13.4% versus 1.5%, p<0.001). The third RCT was underpowered and reported poor 1-year survival rates for both docetaxel and paclitaxel (6% for both).

Is a combination of two or more drugs superior to single-agent chemotherapy?

Five RCTs compared docetaxel with combination chemotherapy regimens containing docetaxel plus gemcitabine or irinotecan or vinorelbine. Studies reported no convincing improvement in survival with combination regimens: median survival was 6.5 versus 6.4 months for docetaxel plus irinotecan (p=0.4); 6.2 versus 7.3 months for docetaxel plus irinotecan (p=0.6); 9.0 versus 7.0 months for docetaxel plus gemcitabine (p=0.5); and 6 versus 6 months for docetaxel plus either gemcitabine or vinorelbine. Two RCTs were halted prematurely due to increased toxicity in the combination drug treatment group: one of the RCTs reported significantly higher interstitial lung toxicity with the combination treatment (21% versus 2%) and a 5% rate of toxic deaths; the second RCT reported that 70% of patients receiving docetaxel plus vinorelbine developed neutropenic fever. Another study reported significantly higher rates of grade 3 to 4 thrombocytopenia (17% versus 6%, p=0.04) and increased grade 3 to 4 diarrhoea (12% versus 3%, p=0.05) with docetaxel plus irinotecan compared with docetaxel alone.

Is a weekly chemotherapy schedule better than a 3- to 4-weekly schedule?

Relevant studies compared weekly and 3- to 4-weekly regimens containing docetaxel or paclitaxel either alone or in combination with gemcitabine, vinorelbine, or irinotecan. The overall response rate varied widely for single-agent regimens (0% to 37.5%) and two-drug combination regimens (9.5% to 53%). The differences between studies made it impossible to draw firm conclusions.

Three RCTs compared weekly docetaxel with 3-weekly docetaxel. The studies reported median survival times of 5.5 versus 5.8 months, 6.7 versus 5.8 months, and more than 8 months versus 5.8 months (p=0.08 for the latter). One study reported improved safety and improved QoL for the weekly schedule (no supporting data were presented), while another reported fewer grade 3 to 4 haematological toxicities with the weekly schedule.

How many cycles of second-line chemotherapy should NSCLC patients receive?

The mean number of cycles reported in studies ranged from two to four. Reasons for discontinuation of treatment were not consistently reported.

Were any new second-line treatments identified?

The results reported in studies of an alkylating agent (1 study), platinum compound (1 study), taxanes (1 study) and/or II topo-isomerase inhibitors (1 study), ifosfamide derivatives (2 studies), vinca-alkaloid derivative (1 study) and capcitabine plus irinotecan (1 study) were similar or worse than results reported for studies of standard single-agent regimens. The results for studies of cyclooxygenase-2-enzyme inhibitors and epidermal growth factor receptor tyrosine kinase inhibitors were also discussed.

Cost information

One RCT compared docetaxel every 3 weeks with BSC and reported that docetaxel was cost-effective (the costs were approximately $30,000 per year of life gained), but the study reported no cost-savings with chemotherapy compared with BSC.

Authors' conclusions

Second-line chemotherapy can produce a small but significant survival advantage in patients with NSCLC, but further research is required.
CRD commentary
The review addressed a clear question, but inclusion criteria were only explicitly defined for the participants and those for study design were only defined in terms of the minimum duration of follow-up. Although only one database was searched, the search was supplemented by screening abstracts of relevant scientific meetings; this attempt to locate unpublished studies limits the possibility of publication bias. By restricting the included studies to those in English, the authors might have missed some relevant studies. Methods were used to minimise reviewer errors and bias in the extraction of data, including some aspects of validity, but it was unclear whether similar steps were taken in the study selection process. Validity was assessed but the results of this assessment were not reported, thus the results from these studies and any synthesis may not be reliable.

The studies were appropriately grouped under the review questions and combined in a narrative. However, data supporting results quoted in the text were not consistently reported, particularly for QoL and symptoms control measures; this means it is not possible to verify some of the conclusions. A considerable number of studies were included in the tables, but data from these studies were not mentioned in the text and reasons for focusing on particular studies were not always clear. The lack of reporting of the quality assessment and lack of supporting data for some outcomes mean that the reliability of the authors’ conclusions regarding efficacy are unclear. The authors’ conclusions about the need for further research seem reasonable.

Implications of the review for practice and research
Practice: The authors made the following recommendations. Docetaxel is recommended as second-line therapy for patients with locally advanced or metastatic NSCLC, but with adequate performance status, whose condition has progressed after first-line platinum-based chemotherapy. Single-agent chemotherapy regimens are preferable to combinations of two drugs. Weekly second-line chemotherapy schedules cannot currently be recommended.

Research: The authors stated that further research linked to quality-adjusted life-years and cost-effectiveness analysis is required. They also stated the need for research into new agents and schedules with improved safety and different health care systems, as less than 50% of NSCLC patients currently receive second-line treatment. They further stated that there is a need to further assess the safety of combinations of gemcitabine plus docetaxel, particularly with respect to severe pulmonary events.

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