Special report: maintenance therapy in advanced non-small-cell lung cancer

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CRD summary
The authors concluded that well-powered studies suggested maintenance therapy may improve outcomes in non-small cell lung cancer, at least for pemetrexed and erlotinib. Ongoing studies may clarify optimal treatment choices. Given the small evidence base and potential bias in the review, the authors’ conclusions should be interpreted with caution and results from ongoing studies should be awaited.

Authors’ objectives
To assess the effects of maintenance therapy on outcomes in patients treated with first-line platinum doublet therapy for advanced non-small cell lung cancer.

Searching
PubMed was searched up to February 2011. Search terms were reported. Reference lists of identified articles were manually searched and abstracts from recent meetings were screened for unpublished data. In addition, review articles and the 2009 USA Food and Drug Administration database were searched for additional studies.

Study selection
Eligible for inclusion were randomised controlled trials (RCTs) in patients with advanced non-small cell lung cancer (stage IIIB or IV disease). Eligible trials assessed patients who had responded to first-line standard chemotherapy and were followed up with maintenance treatment using either standard chemotherapy or molecularly targeted therapy. The primary outcomes of interest were progression-free survival, time to progression and/or overall survival. Other outcomes included toxicity and quality of life.

Included trials were conducted between 1989 and 2010. All trials included patients who had responded to initial first-line chemotherapy with either complete or partial remission or stable disease. Definitions of maintenance therapy (treatment given continuously until there was evidence of disease progression or drug toxicity) included use of continuous and switch therapies with chemotherapeutic agents and a molecularly targeted agent (erlotinib). Included trials used methotrexate, doxorubicin, cyclophosphamide or lomustine (two to three cycles), carboplatin plus paclitaxel (two to four cycles) or gemcitabine plus cisplatin (four cycles) as continuous maintenance treatment. Switch maintenance chemotherapy involved various platinum doublets (four cycles). Controls received best supportive care, placebo or observation only until disease progression.

The authors did not state how many reviewers screened studies for inclusion.

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

Data extraction
The authors did not state how data were extracted or how many reviewers performed the data extraction.

Methods of synthesis
Data were presented as a narrative synthesis and in tables.

Results of the review
Five studies (3,293 patients) were included in the review.

Continuous chemotherapy as maintenance therapy compared to control did not show a statistically significant difference in median overall survival, but did increase toxicity, such as nausea and vomiting, neuropathy, asthenia and neutropenia (three RCTs). Only one of the three RCTs reported a statistically significant improvement in progression-free survival (1.6 months, p<0.001, reported as 1.1 months in the text). One RCT reported no statistically significant differences in quality of life.
Switch chemotherapy as maintenance therapy (pemetrexed) compared to placebo showed a statistically significant increase in overall survival (2.8 months, reported as 4.9 months in the text) and in progression-free survival (1.7 months) in patients with non-squamous non-small cell lung cancer (one RCT). Patients who received maintenance treatment reported statistically significant improvements in quality of life in terms of pain only.

No studies that compared continuous molecularly targeted maintenance therapy to observation alone were identified.

One study using erlotinib as switch molecularly targeted therapy as maintenance therapy showed a statistically significant increase in overall survival (one month) and progression-free survival (1.2 weeks) compared to observation alone. There were no statistically significant differences in quality of life, and toxicities were mild to moderate and typical for erlotinib (including diarrhoea and skin rash).

No studies directly compared maintenance therapy after an initial response to first-line therapy versus second-line therapy.

**Authors’ conclusions**
Well-powered studies suggested maintenance therapy may be used to improve outcomes in non-small cell lung cancer, at least for pemetrexed and erlotinib. Numerous studies were in progress that promised to clarify optimal treatment choices and improve outcomes in this difficult and fatal disease.

**CRD commentary**
The review question and inclusion criteria were clearly stated. The literature search included only one database and did not name sources of unpublished data, which made it difficult to judge the adequacy of the search. The quality of the included trials did not appear to have been assessed. The authors concluded that the studies were well-powered, but they did not appear to have assessed whether studies had adequate sample size calculations so it was not possible to judge the reliability of this conclusion. There was no mention of duplication of effort for study screening and data extraction, which meant that reviewer error and bias could not be ruled out. Only a small number of trials were included in the review, few patient details were reported, and quality of life data were very limited.

Given the small evidence base and potential issues with the methodological reporting in the review, the authors’ conclusions should be interpreted with caution and results from ongoing studies should be awaited.

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

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

**Research:** The authors mentioned ongoing research that was being undertaken to compare maintenance therapy to second-line therapy and suggested that approaches to research may benefit from use of more vigilant disease patient follow-up to ensure timely initiation of second-line therapy before disease progression. Determination of a pre-selected time following first-line therapy for second-line therapy may also be useful to minimise risk or recurrence, but should allow for a period of time during which the patients was drug free. The authors mentioned other ongoing research, and the need for studies using multi-arm approaches.

**Funding**
The review was associated with the Blue Cross Blue Shield Association, Kaiser Permanente Medical Care Programme and a Technology Evaluation Centre Programme, but it was unclear whether any funding was received.

**Bibliographic details**
Gutman SI. Special report: maintenance therapy in advanced non-small-cell lung cancer. Chicago, IL, USA: Blue Cross and Blue Shield Association, Technology Evaluation Center. Assessment Program; 26,4. 2011

**PubMedID**
22022747

**Original Paper URL**
Indexing Status
Subject indexing assigned by NLM

MeSH
Antibodies, Monoclonal /administration & dosage /therapeutic use; Antineoplastic Combined Chemotherapy Protocols /administration & dosage /therapeutic use; Blue Cross Blue Shield Insurance Plans; Carcinoma, Non-Small-Cell Lung /therapy; Clinical Trials as Topic; Disease Progression; Drug Approval; Humans; Lung Neoplasms /therapy; Outcome and Process Assessment (Health Care); Platinum Compounds /administration & dosage; Practice Guidelines as Topic; Randomized Controlled Trials as Topic; Technology Assessment, Biomedical; Treatment Outcome; United States; United States Food and Drug Administration

Accession Number
12012007136

Date bibliographic record published
27/03/2012

Date abstract record published
07/08/2012

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.