The safety and efficacy of EGFR TKIs monotherapy versus single-agent chemotherapy using third-generation cytotoxics as the first-line treatment for patients with advanced non-small cell lung cancer and poor performance status


CRD summary
This review concluded that EGFR (epidermal growth factor receptor) TKIs (tyrosine kinase inhibitors) and single-agent chemotherapy had low response rates in treatment of advanced non-small cell lung cancer for patients with poor performance status. EGFR TKIs tended to more effective disease control and had lower toxicity. Quality and process limitations make the reliability of the conclusions unclear.

Authors' objectives
To evaluate the safety and efficacy of EGFR (epidermal growth factor receptor) TKIs (tyrosine kinase inhibitors) monotherapy and single-agent chemotherapy using third-generation cytotoxics as first line treatment for patients with advanced non-small cell lung cancer and poor performance status.

Searching
MEDLINE, EMBASE, The Cochrane Library and ClinicalTrials.gov were searched from January 1980 to March 2010; search terms were reported. Abstracts from recent major oncology meetings were searched. Bibliographies of key studies and reviews were handsearched. Only publications in peer-reviewed journals were included.

Study selection
Randomised and non-randomised prospective phase II or III trials of EGFR TKIs (gefitinib and erlotinib) monotherapy and single-agent chemotherapy using third-generation cytotoxics (gemcitabine, vinorelbine and taxanes) as first line treatment for chemo-naive patients with advanced non-small cell lung cancer and poor performance status (defined in the review) were eligible for inclusion. Studies of irinotecan, sequential chemotherapy, platinum-based doublets and concurrent chemo-radiotherapy were excluded. Preliminary reports of larger trials were excluded. Relevant efficacy outcomes included response rate, disease control rate (overall response and stable disease), one-year survival, median survival, progression-free survival/time to progression and improvement in symptoms or quality of life. Relevant adverse event outcomes for non-haematological toxicity included elevated serum transaminase, interstitial lung disease or pulmonary fibrosis, skin damage, fatigue, diarrhoea and nausea/vomiting and for haematological toxicity included anaemia, neutropenia and thrombocytopenia.

Most trials had only one treatment arm. None of the studies directly compared EGFR TKIs with third-generation cytotoxics. One third of the studies were of EGFR TKIs (250mg/day gefitinib or 150mg/day erlotinib). Most of the third-generation cytotoxic studies were of gemcitabine; two studies compared different cytotoxics and two studies compared different cytotoxic concentrations. Median age of patients ranged from 62.8 to 76.6 years and 10% to 79% were female. Zero to 100% of participants had an ECOG (Eastern Cooperative Oncology Group) performance status score of 3 or more. From 60% to 93% of participants were stage IV patients. The proportion of patients with adenocarcinoma or bronchioalveolar carcinoma ranged from 29% to 93%. One study of gefitinib selectively enrolled patients with EGFR gene exon 18-21 mutations. Most studies enrolled only poor performance status patients; half of the third-generation cytotoxic studies enrolled poor performance status patients plus elderly patients not selected according to performance status.

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

Assessment of study quality
Methodological quality was assessed by two reviewers independently. Disagreements were resolved by a third independent reviewer.

Data extraction
Numbers of events for each outcome were extracted and percentages for each group were calculated.
Two independent reviewers performed data extraction. Disagreements were resolved by a third independent reviewer.

**Methods of synthesis**
The maximum likelihood method was used to pool results. Summary estimates with 95% confidence intervals (CI) were determined for efficacy outcomes and cumulative incidences with 95% CIs were determined for safety indices. When there were few adverse events or few relevant studies, the beta-binomial distribution was collapsed to a simple binomial distribution and Wald CIs were calculated. For risk estimates corresponding to no events, the adjusted Wald method was used to calculate point estimates with 95% CIs. Subgroup analyses were performed for performance status and EGFR mutation.

**Results of the review**
Fifteen studies were identified (1,425 participants, range 30 to 190). Median follow-up was reported in seven studies and ranged from 12 to 34 months.

Studies that excluded patients with EGFR gene exon 18-21 mutations found no significant difference in the pooled response rate (RR) for EGFR TKIs (RR 6%, 95% CI 3% to 8%; four studies) in unselected populations than for single agent chemotherapy using third-generation cytotoxics (RR 9%, 95% CI 6% to 13%; five studies) in studies that targeted poor performance status. In the same studies EGFR TKIs (RR 40%, 95% CI 33% to 47%; four studies) had significantly higher disease control rates than cytotoxics (RR 30%, 95% CI 20% to 41%; five studies).

The response rate for the study of EGFR TKIs that targeted patients with EGFR mutations was significantly higher (RR 66%, 95% CI 46 to 81%; one study) than that for EGFR TKIs and unselected patients (four studies).

Trials of single agent chemotherapy that targeted patients with poor performance status (five studies) had a non-significantly lower response rate than those that enrolled both elderly and low performance status patients (RR 13%, 95% CI 11% to 16%; five studies). The disease control rate for EGFR TKIs was significantly lower for unselected patients (four studies) than for patients with EGFR mutations (RR 90%, 95% CI 75% to 99%). Trials of single agent chemotherapy that targeted patients with poor performance status (five studies) had a significantly lower disease control rate than those that enrolled both elderly and low performance status patients (RR 41%, 95% CI 36% to 46%; five studies).

There was no significant difference in one-year survival rates for EGFR TKIs and single agent chemotherapy. Median survival time was similar. Data was reported for subgroups with performance status 2 and performance status 3 to 4.

Haematological toxicity was generally lower for EGFR TKIs than single agent chemotherapy; with pooled data for anaemia (2.4%, 95% CI 0.8 to 4.1% and RR 7.7%, 95% CI 3.4% to 12.0%), neutropenia (0.3%, 95% CI 0 to 1.0% and 9.3%, 95% CI 7.6% to 11.2%) and thrombocytopenia (0.3%, 95% CI 0 to 1.0% and 3.0%, 95% CI 2.1% to 4.2%).

For non-haematological toxicity, EGFR TKIs had higher incidences than single agent chemotherapy for skin damage (4.0%, 95% CI 0.3% to 8.3% and 0.4%, 95% CI 0.1% to 0.8%) and diarrhoea (3.9%, 95% CI 1.8% to 6.0% and 1.2%, 95% CI 0.6% to 1.9%), possibly higher levels for elevated serum transaminase (1.2%, 95% CI 0 to 2.4% and 0.1%, 95% CI 0 to 0.3%) and interstitial lung disease and pulmonary fibrosis (0.6%, 95% CI 0.2% to 1.4% and 0.2%, 95% CI 0 to 0.6%), but similar levels for fatigue and nausea/vomiting.

**Authors' conclusions**
Both treatments had low response rates. EGFR TKIs tended to be more effective than single agent chemotherapy in control of tumour progression, reduction of therapy-related toxicities and improvement of symptoms or quality of life in first-line treatment of advanced non-small cell lung cancer patients with poor performance status. Elderly patients not selected according to their performance status should be separated from this population.

**CRD commentary**
The review addressed a well-defined question in terms of participants, interventions and outcomes. Study designs were not described clearly. Relevant databases were searched and efforts were made to identify unpublished studies. It was not clear whether language restrictions were applied and only studies published in peer-reviewed journals were included, so some studies may have been missed. Study quality was assessed but the criteria used were not described clearly and few details were reported. Data extraction and validity assessment were carried out with efforts to reduce...
error and bias; it was unclear whether this was also the case for study selection.

Some relevant study details were reported but there were relatively few details of study design and the significance of individual results. The statistical method used for the meta-analysis may not have been appropriate as indirect comparisons were used not head-to-head comparisons. According to the authors, comparisons could also be impaired due to different dosages, therapy schedules, study populations and enrolment of elderly patients. Statistical heterogeneity was not assessed. Some relevant subgroup analyses were performed.

Potential limitations in the review process, uncertainties about the quality of the included studies and the authors' own suggestion that the results were inconclusive mean that the authors’ conclusions should be treated with caution.

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

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

**Research:** The authors suggested that randomised controlled trials directly comparing the two treatments were required in order to better define the optimum treatment, formally confirm that treatment with EDFR TKIs was suitable for performance status 3 to 4 patients and compare one-year survival rates and median survival times. They suggested that disease control rate might be a more suitable main efficacy outcome than response rate.

**Funding**

Not stated.

**Bibliographic details**


**PubMedID**

21211862

**DOI**

10.1016/j.lungcan.2010.12.006

**Original Paper URL**


**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Antineoplastic Agents /adverse effects /therapeutic use; Carcinoma, Non-Small-Cell Lung /drug therapy; Clinical Trials as Topic; Deoxycytidine /adverse effects /analogos & derivatives /therapeutic use; Erlotinib Hydrochloride; Humans; Lung Neoplasms /drug therapy; Quinazolines /adverse effects /therapeutic use; Receptor, Epidermal Growth Factor /antagonists & inhibitors; Taxoids /adverse effects /therapeutic use; Vinblastine /adverse effects /analogos & derivatives /therapeutic use

**AccessionNumber**

12011004507

**Date bibliographic record published**

26/10/2011

**Date abstract record published**

16/05/2012
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.