Single agent versus combination chemotherapy in patients with advanced nonsmall cell lung carcinoma: a meta-analysis of response, toxicity, and survival

Lilenbaum R C, Langenberg P, Dickersin K

Authors' objectives
To compare the effects of single-agent versus combination chemotherapy in patients with advanced non-small-cell lung carcinoma (NSCLC).

Searching
The authors searched the MEDLINE database (1976 to 1995) using MeSH terms and strategies to identify articles on NSCLC (carcinoma, non-small-cell lung) as well as RCTs of combination drug therapies (drug therapy combination, drug combinations, randomized controlled trials), comparative studies (comparative study), and meta-analyses (meta-analysis). The authors also searched the EMBASE database (1974 to 1996) using terms that combined the following concepts: 'nonsmall cell lung cancer' or 'neoplasm' or 'carcinoma', 'advanced or Stage III or IV', 'single agent' or 'combination chemotherapy', and 'controlled study', or 'clinical trial'. This was supplemented by a manual search of meetings abstracts as well as the reference lists of books and original and review articles. The Physician Data Query (PDQ), lung carcinoma experts, and pharmaceutical companies were also consulted. There were no language restrictions.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) which randomised participants between at least one single agent treatment arm and at least one combination chemotherapy treatment arm. Trials including sequential single agents or cross-over to a combination regimen after relapse were also eligible. Trials where patients received chemotherapy before randomisation were excluded.

Specific interventions included in the review
Single-agent or combination chemotherapy treatment regimens using: procarbazine (PCZ), nitrogen mustard (N), vinblastine (VBL), prednisone (PRED), cyclophosphamide (CTX), methotrexate (MTX), 5-flourouracil (F), hydroxyurea (H), lomustine (CCNU), doxorubicin (DOX), cyclophosphamide + adriamycin + methotrexate + procarbazine (CAMP), L-asparaginase (L-ASP), leucovorin (LV), vindesine (VDS), cisplatin (CDDP), mitomycin-C (MMC), carboplatin (CBDCA), mitomycin + vinblastine + cisplatin (MVP), etoposide (VP-16), 6-thioguanine (6-TG), cisplatin + 5-flourouracil + leucovorin (PFL), and vinorelbine (NVB).

Participants included in the review
Patients undergoing treatment for advanced non-small-cell lung cancer (NSCLC).

Outcomes assessed in the review
Response rate, survival rate (at 6 and 12 months) and toxicity (adverse effects) or treatment-related death.

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

Assessment of study quality
No formal assessment of quality was undertaken.

Data extraction
The authors do not state who, or how many of the reviewers, performed the data extraction. Data were extracted for the categories of: year of publication, number of patients (randomised and eligible), gender, disease stage and performance status of patients randomised, objective response rate, median survival time, survival at 6 months and 12 months, and specific toxicity data including hematologic, gastrointestinal, renal, and neurologic toxicity. The number of treatment-related deaths was also recorded.

The relative risk (RR) and 95% confidence intervals (CIs) for objective response rate and for survival at 6 and 12 months were calculated for each trial. Some studies had more than one single-agent treatment arm and/or more than one combination chemotherapy arm. In these cases, a combined response rate (weighted average) was calculated for all single-agent arms and for all combination arms, assigning each arm a weight equal to its sample size. For the survival analysis, the combined number of patients alive at 6 and 12 months in all single-agent arms divided by their combined denominators were compared with the equivalent summed numerators and denominators in all combination arms.

Methods of synthesis

How were the studies combined?
Pooled relative risk (RR) with 95% confidence intervals (CIs) were calculated using the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest).

For the toxicity analysis, a summary RR comparing combination chemotherapy to single-agent chemotherapy was estimated using the Mantel-Haenszel method, stratifying on trial.

A subgroup analysis was performed on a group of 10 trials published between 1989 and 1996 to assess response, toxicity and survival for comparisons of platinum analogue or vinorelbine with platinum- or vinorelbine-based combinations.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review

Twenty-five RCTs were included in the review with 5,156 participants.

Combination chemotherapy produced a 2-fold increase in response rate (24 trials, n = 4,642) compared with single-agent chemotherapy (RR 1.93, 95% CI: 1.54, 2.42) which was statistically significant. In the subgroup analysis of platinum analogue or vinorelbine compared with platinum analogue or vinorelbine-based combination chemotherapy, response showed results favouring combination chemotherapy (RR 1.79, 95% CI: 1.37, 2.33) which was statistically significant.

Combination chemotherapy increased the risk of dying (toxicity) (22 trials, n = 4,845), (RR 3.7, 95% CI: 2.2, 6.4) which was statistically significant. The subgroup analysis of platinum analogue or vinorelbine compared with platinum analogue or vinorelbine-based combination chemotherapy, showed a nearly 3-fold increase in toxicity with combination chemotherapy (RR 2.9, 95% CI: 1.4, 6.1) which was statistically significant. Adverse events in trials comparing a platinum analogue or vinorelbine with combination chemotherapy were 16.5% versus 39.7% for leukopenia, 3% versus 9.5% for febrile neutropenia, 19.9% versus 37.8% for nausea/emesis, 1.8% versus 7.2% for nephrotoxicity, 4.1% versus 8.6% for peripheral neuropathy, and 5.7% versus 4.4% for ototoxicity.

Survival at 6 months (RR 1.10, 95% CI: 1.02, 1.19) and 12 months (RR 1.22, 95% CI: 1.03, 1.45) (combining 25 trials) was greater with combination chemotherapy. In the subgroup analysis of platinum analogue or vinorelbine compared with platinum analogue or vinorelbine-based combination chemotherapy, survival at 6 months showed no statistically significant difference between the two treatment strategies (RR 1.03, 95% CI: 0.92, 1.15). Survival at 12 months also showed no statistically significant difference between the two treatment strategies (RR 1.10, 95% CI: 0.94, 1.43).

Cost information

The authors state that there is a lack of cost-effectiveness information on lung carcinoma. One trial showed that the
modest improvement in median survival observed with the combination of cisplatin and vinorelbine resulted in additional costs that are within the benchmark for medical interventions ($17,700 per year of life gained). (see Smith, in Other Publications of Related Interest).

Authors' conclusions
The authors state that their results confirm that combination chemotherapy increases the response rate compared with single-agent treatment. The results also show that toxicity is more severe in patients receiving combination chemotherapy. In particular, the risk of dying from the treatment is increased more than three-fold with combination chemotherapy compared with single-agent therapy. Survival was prolonged only modestly with combination chemotherapy but not significantly so when more active single agents were used. Further, it appears that when a more active single agent is used, toxicity is less compared with combination regimens.

CRD commentary
The authors have clearly stated their research question and some inclusion and exclusion criteria. The literature search appears thorough. The quality of the included studies was not formally assessed and the authors have not reported on how the articles were selected, or how many of the reviewers were involved in the data selection and extraction.

The data extraction is reported in tables and text and the statistical pooling was appropriate. There were no formal tests for heterogeneity. The authors have discussed several data limitations in the review including the need to exclude eight eligible trials for which complete survival data was unavailable. There are small differences between the results reported in the abstract and those reported in the text of the review. The authors conclusions appear to follow from the results but these should be viewed with caution because of the methodological limitations of the review.

Implications of the review for practice and research
The authors state that the interpretation and application of these data to clinical practice is complicated by the scarcity of prospective and validated quality of life data and that RCTs are needed which address these outcomes and the issues of cost- effectiveness. The authors also state that the controversy between single-agent chemotherapy and combination chemotherapy in advanced NSCLC needs to be addressed in a RCT (which is currently underway) that prospectively integrates efficacy data with quality of life and cost effectiveness data.

Bibliographic details

PubMedID
9428487

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Antineoplastic Agents /adverse effects /therapeutic use; Antineoplastic Agents, Phytogenic /therapeutic use; Antineoplastic Combined Chemotherapy Protocols /adverse effects /therapeutic use; Carcinoma, Non-Small-Cell Lung /drug therapy; Cause of Death; Cisplatin /analogs & derivatives /therapeutic use; Confidence Intervals; Follow-Up
AccessionNumber
11998000209

Date bibliographic record published
31/07/2000

Date abstract record published
31/07/2000

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.