Role of granulocyte and granulocyte-macrophage colony-stimulating factors in the treatment of small-cell lung cancer: a systematic review of the literature with methodological assessment and meta-analysis


Authors' objectives
To assess the efficacy of granulocyte colony-stimulating factors (G-CSFs) and granulocyte-macrophage colony-stimulating factors (GM-CSFs) in people with small-cell lung cancer (SCLC).

Searching
The authors searched MEDLINE, HealthSTAR, the U.S. National Cancer Institute's electronic databases, reference lists of identified studies, and personal collections for trials published in English or French between 1980 and 2001. They did not report the search terms.

Study selection
Study designs of evaluations included in the review
Published randomised controlled trials (RCTs) were eligible for inclusion. Abstracts were excluded, as were trials published only as abstracts.

Specific interventions included in the review
Studies of the addition of G-CSFs and GM-CSFs to chemotherapy with or without irradiation were eligible for inclusion.

The chemotherapy regimens differed across the studies. Chemotherapy drugs included cisplatin, ifosfamide, adriamycin, vincristin, cyclophosphamide, carboplatin, and VP16. The studies were divided into those assessing maintenance of conventional planned dose-intensity chemotherapy, accelerated chemotherapy, and concentrated chemotherapy (all with CSF support). In studies of conventional dose-intensity chemotherapy, G-CSF doses ranged from 50 to 230 microg/m² every 1 to 3 weeks and GM-CSF doses were between 10 microg/kg and 500 microg/m² every 3 to 4 weeks. In studies of accelerated chemotherapy, the dose of G-CSF in all studies was 5 microg/kg every 2, 3 or 4 weeks, while the dose of GM-CSF was 250 microg/m² every 3 or 4 weeks. In a study of concentrated chemotherapy, the dose of GM-CSF was 5 microg/kg every 4 weeks. Full details of the regimens were provided.

Participants included in the review
Eligible studies included only people with SCLC who were receiving chemotherapy. Most of the studies in the review had participants at all disease stages (limited and extensive disease). The authors did not describe the demographic characteristics of the participants.

Outcomes assessed in the review
The authors did not explicitly state inclusion criteria for the outcomes that studies had to include to be eligible for the review. The authors aimed to assess survival, response rate, toxicity, and the occurrence of infection or febrile neutropenia. Due to inadequate data, the review focused on response rate and survival.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection. Six people helped to assess the studies, but it was unclear if six people also made the selections.

Assessment of study quality
The authors used two published scales to assess quality: the European Lung Cancer Working Party (ELCWP) scale and the Chalmers scale. These scales focus on study protocol and internal and external validity. Five doctors and one
biostatistician performed a qualitative methodological evaluation, using consensus scoring at a meeting.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data on the sample size, participants’ disease stage, treatment (i.e. regimens, doses and intervals), validity assessment and outcomes were extracted. Relative risks (RRs) were calculated for response data and hazard ratios (HRs) for survival data. Trials which, according to the primary objective, achieved a statistically significant effect \((P>0.05)\) were classed as ‘positive’; those that did not were classed as ‘negative’.

**Methods of synthesis**
How were the studies combined?
Response rates and survival data from each study were pooled using fixed-effect and random-effects models. Data for G-CSF and GM-CSF were not analysed separately. Data were pooled separately for three groups: maintenance of conventional planned dose-intensity chemotherapy with CSF support; accelerated chemotherapy with CSF support; and concentrated chemotherapy with CSFs.

How were differences between studies investigated?
The authors used a significance test to assess differences between studies that had statistically significant or non significant findings prior to performing a meta-analysis. They presented a chi-squared test for heterogeneity. When reporting the findings, they divided studies into three groups: maintenance of conventional planned dose-intensity chemotherapy with colony stimulating factor support; accelerated chemotherapy with colony stimulating factor support; and concentrated chemotherapy with CSFs.

**Results of the review**
The review included 12 RCTs with 2,107 participants.

The median quality scores were 59.9% for the ELCWP scale (range: 42.2 to 82) and 55.8% for the Chalmers scale (range: 38 to 76.8). There was no statistical heterogeneity between studies and no statistically significant differences in quality between studies with positive or negative findings.

Maintenance chemotherapy (response rate)(7 trials, \(n=1,420\)).

The pooled analysis found that administering CSFs had a small negative effect on response rate in people receiving maintenance therapy (RR 0.92, 95% confidence interval, CI: 0.87, 0.97).

Survival (6 trials, \(n=1,222\)).

There was no significant effect on survival (HR 1.004, 95% CI: 0.89, 1.13). This result was subject to statistical heterogeneity, but reanalysis with the source of this heterogeneity removed did not alter the result.

Accelerated chemotherapy (5 trials, \(n=707\)).

In people receiving accelerated chemotherapy, CSFs were not associated with any effect on response rate (RR 1.02, 95% CI: 0.94, 1.09) or survival (HR 0.82, 95% CI: 0.67, 1.00; based on 2 studies).

Concentrated chemotherapy (1 trial, \(n=116\)).

In people receiving concentrated chemotherapy, CSFs were associated with reduced survival (8.9 versus 10.8 months, \(P=0.0005\)), although there was no effect on response rate (74.5% standard versus 87.2% concentrated, \(P=0.09\)).

**Authors’ conclusions**
There was no evidence to support the routine use of CSFs in people with SCLC.
CRD commentary

This review focused on a clearly defined research question. The literature search employed several appropriate electronic databases, but was limited to studies published as full papers in English or French. Thus, the review may be subject to some language or publication bias. The authors provided details of how methodological quality was assessed and how it was taken into account when interpreting the findings, although some aspects of the data extraction and relevance assessment were not described in depth. The methods used to analyse the data and the rationale behind this were clearly explained. The methods used appear appropriate.

It appears worthwhile to have divided findings according to the type of chemotherapy regimen the participants were receiving (maintenance, accelerated, or concentrated). However, the drugs, dosages and administration schedules differed between studies within these groups. The authors' conclusions and discussions about why the data do not support routine use of CSFs in SCLC seem appropriate given the data presented.

Implications of the review for practice and research

Practice: The authors stated that the addition of CSFs to chemotherapy to maintain or increase the planned dose intensity does not appear to improve response rate or survival over chemotherapy alone. In fact, CSFs may have negative effects on people with limited disease receiving chemotherapy plus radiotherapy and in people with extensive disease receiving concentrated chemotherapy.

Research: The authors stated that future trials should separate people with limited disease from those with extensive disease because the therapeutic schedules for these groups differ. Future studies should include a sufficiently large number of people to detect differences and focus on survival.

Bibliographic details


PubMedID
12140132

Indexing Status

Subject indexing assigned by NLM

MeSH
Carcinoma, Small Cell /drug therapy; Granulocyte Colony-Stimulating Factor /therapeutic use; Granulocyte-Macrophage Colony-Stimulating Factor /therapeutic use; Humans; Lung Neoplasms /drug therapy; Randomized Controlled Trials as Topic; Treatment Outcome

AccessionNumber
12002002029

Date bibliographic record published
30/06/2006

Date abstract record published
30/06/2006

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.