G-CSF for the prophylaxis of neutropenic fever in patients with small cell lung cancer receiving myelosuppressive antineoplastic chemotherapy: meta-analysis and pharmacoeconomic evaluation
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Authors' objectives
To determine the clinical effectiveness and the cost-effectiveness ratio of the prophylactic administration of granulocyte-colony stimulating factor (G-CSF) to patients with small cell lung cancer (SCLC) treated with conventional myelosuppressive cytotoxic chemotherapy.

Searching
MEDLINE (via CD-ROM) was searched from January 1990 to July 1995 using the index terms 'G-CSF' and 'lung cancer', and 'filgrastim' and 'lenograstim'. The same search was carried out on IOWA-IDIS (Iowa Drug Information System) from January 1985 to September 1995, and Cancerlit from October 1993 to February 1995. Additional studies were located by examining reviews, textbooks and other material at the authors' Drug Information Centre, by consulting experts in the field, and by reviewing all cited references.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) evaluating the effectiveness of G-CSF for the prophylaxis of infections in patients with SCLC who were being treated with a myelosuppressive antinucleoplastic chemotherapy regime. Studies were included if they fulfilled the following criteria: the trial was published in English in the form of a full-length article, all patients were afebrile and without neutropenia at the start of the study, the projected duration of the study corresponded to the administration of 6 cycles of chemotherapy, and the end points were the specified outcomes.

Specific interventions included in the review
Interventions studied include the administration of the following types of G-CSF: filgrastim or lenograstim in daily doses of 230 microg/m2 for 9 or 14 days, and lenograstim in a daily dose of 5 microg/kg for between 8 and 22 days.

Participants included in the review
Participants were patients with SCLC who were receiving a myelosuppressive antinucleoplastic chemotherapy regime based on the conventional 3-week or 4-week cycle. The median age of patients in treatment groups ranged from 58 to 63 years.

Outcomes assessed in the review
The outcomes assessed were: the number of patients who developed an episode of fever, the number of patients in whom infection was documented microbiologically, and the number of deaths from infection.

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
The authors do not report the criteria used to assess validity, or how the validity assessment was performed.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. The end points were evaluated as cumulative rates over 6 cycles and recorded separately for the treatment
and control groups.

**Methods of synthesis**

**How were the studies combined?**

The pooled odds ratios (ORs) were calculated using the Mantel-Haenszel method with the 95% confidence intervals (CIs) being calculated according to Breslow and Day (see Other Publications of Related Interest no.1), or by the grand-total method when the analysis included at least one study that found no events in the control group. The percentage reduction of risk and the number-needed-to-treat were estimated using the method of Laupacis (see Other Publications of Related Interest no.2).

**How were differences between studies investigated?**

Inter-trial heterogeneity was assessed using the procedure described by Collins (see Other Publications of Related Interest no.3).

**Results of the review**

Three RCTs (N=393) were used to assess the cost-effectiveness of prophylactic G-CSF.

A meta-analysis was not carried out on the number of patients in whom infection was documented microbiologically, because it was thought that the 2 studies reporting information for this outcome provided insufficient data.

An assessment of publication bias, based on an estimate of the minimum number of negative (or null) studies required to lead a significant meta-analysis to non significance, found the minimum number of studies required to lead to non significant results for neutropenic fever to be 21.

For those given G-CSF, the cumulative incidence of neutropenic fever over 6 cycles of chemotherapy was 38.7% (95% CI: 31.5, 46.5) and the OR was 0.29 (95% CI: 0.21, 0.40, P<0.001); heterogeneity (chi-squared) was 4.3 (P>0.10). For controls, the cumulative incidence of neutropenic fever over 6 cycles of chemotherapy was 68.3%. Mortality rate for infection: OR 1.13 (95% CI: 0.41, 3.1, P=0.82). Heterogeneity (chi-squared) was 2.6 (P>0.20).

The number-needed-to-treat to prevent at least one episode of neutropenic fever was 3.4 (95% CI: 2.7, 4.6).

**Cost information**

Using price data for Italian hospitals, the cost-effectiveness ratio is US$14,372 (95% CI: 11,560, 19,514). American hospital costs, which include a considerably higher drug price, give a cost-effectiveness ratio of US$41,088 (95% CI: 33,049, 55,789).

For a full discussion of the economic aspects of this study see NHS EED record 21996000732.

**Authors' conclusions**

Prophylactic G-CSF does not affect mortality but does significantly reduce the incidence of neutropenic fever from 68.3 to 38.7%. The cost-effectiveness ratios were US$14,372 and 41,088 when using the Italian and US prices of the drug, respectively.

**CRD commentary**

This was a clearly written and presented review, which included an assessment of the heterogeneity among trials and publication bias. The authors acknowledged that the meta-analysis was limited by including only three studies, and that further clinical trials may have been identified by a more extensive search. There was some discussion of the possible reasons for the differences found between this economic assessment and other economic studies investigating the prophylactic use of G-CSF.

The inclusion criteria for the primary studies were clearly stated, although there were no details of the methods used to
select the primary studies, assess validity or to extract the data. The criteria used to assess the validity of the primary studies were not mentioned. Some of the baseline characteristics of the participants, such as age and stage of disease, were compared between treatment groups. However, further details of the included studies such as the method of randomisation, criteria used for diagnosis and outcome measures, adverse reactions and withdrawals (with reasons) by treatment group would have been welcome, in addition to a validity assessment.

The authors reported a lack of clarity in the categorisation of some patients in the primary studies, but it is not stated whether any attempt was made to contact the original authors for clarification. At least two of the primary studies were not analysed by intention to treat though the effect on the pooled OR appears minimal. The effectiveness of G-CSF on mortality was based on a small number of events in the primary studies. An assessment of the validity of the primary studies, with details of the method of randomisation and consideration of the representativeness of the studied patients to the general population of patients with SCLC, are required before the authors' conclusions can be considered as supported and generally applicable.

**Implications of the review for practice and research**
The results of cost-effectiveness analysis of the use of G-CSF appears to be sensitive to the incidence of neutropenic fever in the populations studied. Further investigation of the reasons for the variability of the incidence of neutropenic fever among studies mentioned in this review is required. In addition, further adequately-powered studies are required to assess the effect of G-CSF on mortality and other outcomes considered relevant to patients with SCLC.

**Bibliographic details**

**PubMedID**
8809640

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

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**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.