Prophylactic granulocyte colony-stimulating factor in patients receiving dose-intensive cancer chemotherapy: a meta-analysis

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Authors' objectives
The authors assessed the extent to which recombinant colony-stimulating factors (CSFs) reduce the severity and duration of neutropenia and the risk of infection associated with dose-intensive cancer chemotherapy. The authors stated that rather than assessing whether recombinant CSFs have a preventive effect, they were interested in the magnitude and generalisability of the effect.

Searching
MEDLINE, EMBASE, the Cochrane Library and the reference lists of published reports were searched; the search terms were reported, but the search dates were not. It was unclear whether unpublished studies, or those in languages other than English, were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Controlled clinical trials were eligible for inclusion in the review. Both randomised placebo-controlled trials and studies with untreated (no placebo) controls were included. The authors did not report the minimum follow-up periods.

Specific interventions included in the review
Studies that assessed the prophylactic efficacy of CSFs on neutropenic complications from chemotherapy were eligible for inclusion in the review. Studies were considered if recombinant CSFs were administered prophylactically before the onset of fever or neutropenia, following systemic chemotherapy for solid tumours or malignant lymphoma.

The CSFs included in the review were filgrastim (recombinant granulocyte CSFs) and lenograstim (glycosylated granulocyte recombinant CSFs). The dose and schedule of the chemotherapy regimens varied widely between the studies. The exact drugs, doses and schedules were tabulated in the review. The control groups received either a placebo or no intervention (untreated, observation only controls). Only trials without dose escalation were considered. Studies of high-dose therapy that required stem cell or bone marrow transplantation support were excluded.

Participants included in the review
Studies of adults undergoing chemotherapy for solid tumours or malignant lymphoma were eligible for inclusion. The authors identified studies of solid tumours and aggressive non-Hodgkin's lymphoma in their search. Studies of people being treated for acute or chronic leukaemia were excluded, as were people receiving high-dose therapy that required stem cell or bone marrow transplantation. The authors did not report disease characteristics, or demographic characteristics such as the average age or gender of the participants included in the review.

Outcomes assessed in the review
Studies with data on any of the primary or secondary outcomes were considered for inclusion. The primary outcomes in the review were risk of febrile neutropenia, documented infection, infection-related mortality and patient reports of bone pain. The secondary outcomes were reduced treatment dose intensity and delay in chemotherapy treatment. The outcomes were measured by collating the proportion of participants with a specific outcome in each study.

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.

Assessment of study quality
Study quality was assessed on the basis of methods of randomisation, double-blinding and description of study withdrawals or drop-outs (see Other Publications of Related Interest no.1). The studies were scored from 0 to 5, with
poor-quality studies represented by a score of less than 3. The authors did not state how the papers were assessed for quality, or how many reviewers performed the quality assessment.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data were extracted on publication details, disease characteristics, chemotherapy schedule and dose, schedule and dose of recombinant CSF, study design, number of enrolled participants, evaluable participants and outcomes.

**Methods of synthesis**
*How were the studies combined?*
Data from the primary studies were combined using a random-effects model. An intention-to-treat analysis was used for each trial, and summary odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to compare the treatment and control groups. The authors presented forest plots and expressed effect measures on a natural logarithm scale for all studies. They also compared subgroups (placebo versus untreated controls; solid tumours versus lymphoma; filgrastim versus lenograstim). Risk in the control group was plotted against risk in the recombinant CSF group using weighted regression.

*How were differences between studies investigated?*
The authors performed formal tests of heterogeneity. They did not report the exact tests used.

**Results of the review**
Eight randomised controlled trials with 1,144 participants (range: 48 to 257 per trial) were included. Five of these trials were double-blind and placebo-controlled. Three included untreated controls.

*Quality assessment.*
On a scale of 0 to 5, the mean quality score of papers included in the review was 3.4 (standard deviation 0.5, range: 3 to 4). There was no significant heterogeneity in the overall effects of treatment on any of the primary outcomes, so the authors included all 8 trials in their meta-analysis (test statistic and P-value not reported). There was some heterogeneity in the summary risk statistics reported, so the authors used ORs to describe the findings.

*Febrile neutropenia.*
The overall mean risk of febrile neutropenia was 32% for people receiving CSFs and 51% for controls (absolute risk difference 19%, 95% CI: 10, 27; 8 trials). There was significant heterogeneity in the risk difference (P=0.002), so the authors focused on the odds of events in the growth factor group versus the controls (OR 0.38, 95% CI: 0.29, 0.49, P<0.001). Recombinant CSFs reduced the risk of febrile neutropenia compared with controls (relative risk 0.63, 95% CI: 0.51, 0.79, P<0.05).

*Other outcomes.*
Recombinant CSFs reduced the risk of documented infection (OR 0.51, 95% CI: 0.36, 0.73, P=0.001; 7 trials). There was a trend towards reduced infection-related mortality, but this was not statistically significant (OR 0.6, 95% CI: 0.3, 1.22, P>0.05; number of trials not reported). Recombinant CSFs increased the risk of bone pain (OR 2.9, 95% CI: 1.6, 4.8, P=0.001; number of trials not reported).

Four trials reported data on dose reduction or treatment delay: 34% of controls and 15% of people receiving CSFs required a chemotherapy dose reduction (risk difference 20%, 95% CI: 12, 27); the summary OR for dose reduction and treatment delay was 0.32 (95% CI: 0.21, 0.47, P=0.001).

*Subgroup analysis.*
Filgrastim tended to have a greater absolute benefit in comparison with lenograstim, but this approached statistical significance only for the outcome of bone pain; the OR was 2.7 (95% CI 1.5, 4.8) for filgrastim and 5.6 (95% CI: 3.2, 9.8, P=0.07) for lenograstim. There was a trend towards greater benefits from CSFs in solid tumours compared with lymphoma, but this did not reach statistical significance (statistics not reported).

**Cost information**
The authors reported that several economic analyses have compared growth factor treatment options (see Other Publications of Related Interest no.2). The authors did not report any specific data on the costs associated with growth CSFs.

**Authors’ conclusions**
Recombinant CSFs reduce the risk of febrile neutropenia and documented infection associated with a number of malignancies and dose-intensive treatment regimens.

**CRD commentary**
The authors clearly specified their research question, although their search strategy may have been a little narrow to address it. The authors did not search databases such as Cancerlit, Current Contents or the Conference Papers Index, or approach experts in the field or industry sources. It appears that only published studies were eligible for inclusion in the review, although this was not clearly specified. It was also unclear whether studies published in languages other than English were eligible. It is possible, therefore, that some studies meeting the inclusion criteria were not identified.

The authors did not provide full details of the methods used to assess the relevance and quality of potential studies, or any inter-rater checks undertaken. The authors also omitted some details about the studies included, such as participant characteristics and the follow-up rate. This is important because one of the stated objectives was to assess the generalisability of any treatment effect. It was difficult to assess whether the results applied to particular subgroups because the authors did not provide details of the participants included in the review.

The data were synthesised using a meta-analysis. The statistical techniques used appear to have been appropriate, although it may have been worthwhile to have provided a fuller narrative description. The authors found no heterogeneity between the studies in the overall treatment effects. This is somewhat surprising given the various disease types and chemotherapy regimens used in the primary studies. The type of heterogeneity tests undertaken and test statistics were not reported. The authors identified some heterogeneity in the summary risk statistics calculated and, appropriately, reported ORs rather than relative risk statistics in these instances.

The authors reported the findings clearly, although they could have addressed their underlying research question in more depth. The stated aim of the review was to assess the magnitude and generalisability of any treatment effect, rather than focus upon whether an effect exists. However, arguably, the conclusions focused on the existence of an effect rather than its size or applicability in different contexts. The authors spent only one paragraph reporting subgroup analyses.

The authors’ conclusions appear to be supported by the data presented in the review. However, the effects of CSFs had already been reported in individual trials.

**Implications of the review for practice and research**
Practice: The authors suggested that recombinant CSFs reduce the risk of febrile neutropenia and documented infections when administered prophylactically to people receiving systemic chemotherapy for solid tumours or lymphoma.

Research: The authors suggested that further research is needed in people receiving less intensive chemotherapy regimens, to confirm the generalisability of the effect of recombinant CSFs.
Bibliographic details

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11904116

Other publications of related interest

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Subject indexing assigned by NLM

MeSH
Antineoplastic Agents /adverse effects; Dose-Response Relationship, Drug; Granulocyte Colony-Stimulating Factor /therapeutic use; Humans; Neoplasms /drug therapy; Neutropenia /drug therapy /etiology /prevention & control; Randomized Controlled Trials as Topic; Recombinant Proteins

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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.