Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review

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CRD summary
The authors concluded that prophylactic granulocyte colony-stimulating factors reduce the risk of febrile neutropenia and early death in adults with solid tumours and malignant lymphoma, but increase relative dose intensity and musculoskeletal pain. Overall, this was a well-conducted review and the authors' conclusions are likely to be reliable.

Authors' objectives
To evaluate the efficacy and toxicity of prophylactic granulocyte colony-stimulating factor (G-CSF) in adults with solid tumours or malignant lymphoma.

Searching
MEDLINE, EMBASE, Cancerlit, the Cochrane Library (including the Cochrane CENTRAL Register), DARE and conference proceedings from two specified societies were searched to December 2006; the search terms were reported. No language restrictions were applied. In addition, references from included studies and relevant published reports were screened and experts contacted for additional studies.

Study selection
Randomised controlled trials (RCTs) that compared primary G-CSF prophylaxis (G-CSF given 1 to 3 days after the completion of the first and every subsequent cycle before the onset of neutropenia) with placebo or untreated control treatment in adults who were receiving conventional-dose chemotherapy for solid tumours or malignant lymphoma were eligible for inclusion. G-CSF had to be given continuously until neutrophil recovery. The patients in control groups could receive secondary G-CSF prophylaxis after the first chemotherapy cycle. Studies in which prophylactic antibiotics were given to both treatment groups were eligible. Studies of patients with multiple myeloma, granulocyte-macrophage colony stimulating factor, dose-dense/dose-escalating chemotherapy, G-CSF for established neutropenia or febrile neutropenia (FN), and studies that used different chemotherapy regimens in each treatment arm were excluded. The primary review outcome was the proportion of patients with FN. The secondary outcomes included infection-related mortality, all-cause early mortality (during chemotherapy), relative dose intensity (RDI), and bone or musculoskeletal pain.

Most of the included studies evaluated filgrastim or lenograstim; one study evaluated pegfilgrastim. The majority of studies were in patients with solid tumours; other studies were in patients with aggressive non-Hodgkin’s lymphoma. The participants were aged from 15 to 90 years; some studies only included elderly patients with lymphoma. Treatment duration appeared to range from 5 to 14 days.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The validity of the studies was assessed using the Jadad scale (reporting and method of randomisation, blinding and withdrawals). Studies scoring 2 or less out of the maximum 5 points were considered to be low quality.

Two reviewers independently assessed validity and resolved any discrepancies by consensus.

Data extraction
For each study, relative risks (RRs) of outcomes of interest were calculated with 95% confidence intervals (CIs). A value of 0.5 was added to all cells in studies with zero events in one treatment group. The standardised mean difference was calculated for RDI.
Two reviewers independently extracted the data and resolved any discrepancies by consensus.

**Methods of synthesis**

Pooled RRs and 95% CIs were calculated using the fixed-effect Mantel-Haenszel method in the absence of significant heterogeneity and the DerSimonian and Laird random-effects model in its presence. Statistical heterogeneity was assessed using the Cochran Q statistic and the $I^2$ statistic. Pre-specified subgroup analyses were used to examine the influence of type of G-CSF, type of tumour (solid tumours versus malignant lymphoma), patient age (age >60 years versus all adults or excluding elderly patients), use of concurrent prophylactic antibiotics, use of secondary G-CSF prophylaxis in the control group, type of control and number of centres (multiple or single). Publication bias was assessed using funnel plots.

**Results of the review**

Seventeen RCTs (n=3,493) were included.

Nine studies scored 2 or less on the Jadad scale and were considered low-quality studies. Five studies described blinding, four described the method of randomisation and seven described withdrawals.

G-CSF was associated with a statistically significant reduction in the number of patients with one or more episodes of FN compared with control (15 studies, n=3,182): 22.4% versus 39.5% (random-effects RR 0.54, 95% CI: 0.43, 0.67, p<0.0001). There was a significant reduction with G-CSF in FN for all age groups, blinded and unblinded studies, and for studies permitting secondary prophylaxis with G-CSF in control groups.

G-CSF was associated with a statistically significant increase in bone and musculoskeletal pain compared with control (14 studies, n=3,029): 19.6% versus 10.4% (random-effects RR 4.023, 95% CI: 2.16, 7.52, p<0.0001).

G-CSF was associated with a statistically significant reduction in infection-related mortality (12 studies, n=2,917): 1.5% versus 2.8% (RR 0.55, 95% CI: 0.34, 0.90, p=0.018). It was also associated with a statistically significant reduction in early mortality (13 studies, n=3,122): 3.4% versus 5.7% (RR 0.60, 95% CI: 0.43, 0.83, p=0.002). Fixed-effect models were used for both of these analyses ($I^2$=0%).

Average RDI (10 studies) ranged from 91.0 to 99.0% (mean 95.1, median 95.5) in patients receiving G-CSF and from 71.0 to 95.0% (mean 86.7, median 88.5) in control patients. The average difference between treatment groups was 8.4% (range: 2.8 to 20.0).

**Authors' conclusions**

Prophylactic G-CSF reduced the risk of FN and early death, but increased RDI and musculoskeletal pain, in adults with solid tumours and malignant lymphoma.

**CRD commentary**

The review question was stated clearly. Several relevant sources were searched and attempts were made to minimise language and publication bias. Appropriate methods were used to minimise reviewer error and bias during the validity assessment and data extraction processes, but it was unclear whether similar methods were employed at the study selection stage. Only RCTs were included and validity was assessed and reported. Appropriate methods were used for the meta-analyses, heterogeneity was assessed, and various predefined subgroup analyses conducted. Significant heterogeneity was found for some analyses but studies showed a similar direction of treatment effect. Overall, this was a well-conducted review and the authors' conclusions are likely to be reliable.

All of the review authors hold stock in Amgen Inc. and some have received honoraria or research funds from this company.

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

Practice: The authors did not state any implications for practice.
Research: The authors stated that factors that predict FN need to be identified. They also highlighted the need for an updated cost analysis, and for further studies to determine the most effective and cost-effective use of G-CSF prophylaxis in patients at low risk of FN.

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Other publications of related interest

This additional published commentary may also be of interest.


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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.