Use of granulocyte colony-stimulating factor (G-CSF) in patients receiving myelosuppressive chemotherapy for the treatment of cancer

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Authors' objectives
To evaluate the evidence for the role of granulocyte colony-stimulating factor (G-CSF) in patients receiving myelosuppressive chemotherapy for the treatment of cancer.

Searching
MEDLINE and Cancerlit were searched from 1996 to May 1997 using the terms 'granulocyte colony-stimulating factor' (textword or MeSH), 'clinical trial' (publication or MeSH), 'review' (publication type or MeSH term) and 'meta-analysis' (publication type or MeSH). Publications in any language were considered. In addition, recommendations on the use of G-CSF from the American Society of Clinical Oncology and the Ontario Drug Benefit Plan were reviewed.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs). One Japanese trial was excluded due to translation difficulties, while another trial was excluded because the comparison was between G-CSF and G-CSF plus thymostimulin, with no control group.

Specific interventions included in the review
Myelosuppressive chemotherapy with or without G-CSF for prophylactic or therapeutic indication. The dosages of G-CSF tested by the included studies were 2, 5, 6 (230 microg/m2) and 50 microg/kg. The chemotherapy regimens used included: cyclophosphamide plus doxorubicin; adriamycin, cyclophosphamide, vincristine, bleomycin, etoposide, prednisolone, cotrimaxazole and ketoconazole; cyclophosphamide, doxorubicin and etoposide; carboplatin, ifosfamide (with mesna), etoposide, and vincristine (plus radiotherapy during first cycle); doxorubicin, ifosfamide and dacarbazine; any chemotherapy agent with the antibiotic agents ceftaxidime and amikacin (for the treatment of neutropenia); fluorouracil, epirubicin and cyclophosphamide, with or without radiotherapy; mitomycin, mitoxantrone and methotrexate; mitomycin, vindesine and cisplatin; cisplatin, vincristine, doxorubicin and etoposide. Some studies also included placebo therapy.

Participants included in the review
Patients receiving myelosuppressive chemotherapy for cancer. Studies that included children were excluded. The included studies examined the following types of cancer: small-cell lung cancer (SCLC), non-Hodgkin's lymphoma, sarcoma, inflammatory and advanced breast cancer, non-SCLC, and various other.

Outcomes assessed in the review
Important adverse clinical outcomes due to infection and the maintenance of chemotherapy were assessed. The outcome measures reported for the included studies were: the mean or median number of hospital days; the mean or median days on intravenous antibiotics; percentage with febrile neutropenia (FN) or incidence of infection; the mean or median number of days with FN; tumour response rate; percentage alive or median value for disease-free survival or progression-free survival; percentage alive or median value for overall survival; the median number of days to recovery to an absolute neutrophil count (ANC) greater than or equal to 0.5, or greater than or equal to 1.0; median days with an ANC of less than 0.5; and median dose intensity of chemotherapy.

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 reviewers performed the selection.

Assessment of study quality
The authors do not state that quality was assessed, although they note how many studies used blinding and were placebo-
controlled.

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 extracted data included: study details; the number of participants randomised; disease site; whether the study was blinded or not; whether the study was placebo-controlled; daily G-CSF dose; chemotherapy or radiotherapy regimen; and outcome measures. The outcomes measures were divided into four categories: clinical outcomes related to quality of life; other clinical outcomes; biological outcomes; and chemotherapy dose intensity.

Methods of synthesis

How were the studies combined?
The studies were combined in a narrative summary. For the outcome measure relating to the number of events of FN, the studies were combined using a random-effects model. The results were expressed as both the odds ratio with a 95% confidence interval (CI) and the relative risk.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated. However, forest plots were presented.

Results of the review

Ten RCTs with 770 participants were included. Four studies were placebo-controlled and double-blind, 2 were said to be placebo-controlled but there was no clear statement that they were blinded, and the remaining 4 studies were neither blinded nor placebo- controlled. G-CSF was used as a prophylactic in 9 studies (prophylactic to moderate neutropenia in 8 studies), and as a therapeutic agent in the remaining study of patients with FN who received antibiotics.

There was heterogeneity between the included studies.

Data from 8 studies showed that the odds of experiencing FN with G-CSF were statistically significantly reduced (odds ratio 0.38, 95% CI: 0.27, 0.52, P<0.00001). G-CSF reduced the risk of FN by 34% (risk ratio 0.66, 95% CI: 0.51, 0.86, p=0.0015). The use of G-CSF was associated with a statistically-significant reduction in antibiotic usage and days spent in hospital in 2 studies, but had no effect in the other 4 studies in which it was measured. Five studies reported no difference in overall median survival, with 2 small studies detecting a statistically-significant increase related to G-CSF.

G-CSF was associated with a relatively high incidence of bone pain in 3 studies (20, 22 and 50% of the patients), but this was not consistent across all studies. Mild bone pain was reported in all but one case.

Authors' conclusions

When the two different clinical settings were considered separately, there were no compelling differences in important outcomes except for the reduction in days spent in hospital for patients treated with G- CSF for established FN. G-CSF produces the predicted biological effects on neutrophils in cancer patients treated with mylosuppressive agents. There was no evidence that the use of G-CSF is associated with either improved tumour-related outcomes or cost- savings. There has also been no formal assessment of the effect of G-CSF on quality of life. There is currently insufficient evidence to indicate that the inclusion of G-CSF into standard chemotherapy regimens will result in increased patient survival.

CRD commentary

Overall, this does not appear to be a well-conducted systematic review. The inclusion and exclusion criteria were clearly defined. However, the literature search was not extensive and only included two electronic databases. No attempt was made to search for unpublished data, which means that publication bias cannot be ruled out. Information about the
review process was poorly reported, with no indication of how decisions were made about the relevance of the included studies or how many reviewers were involved in either this process or the data extraction.

The quality of the included studies was not assessed, although only RCTs were included in the review and the authors noted how many studies used blinding and were placebo-controlled. Relevant details of the primary studies were presented in tabular format and as a narrative summary. The authors note that there was heterogeneity between the studies but they did not report how this was assessed statistically, although forest plots were presented. The authors also did not discuss any of the differences found between the included studies. In view of these differences, and the fact that the authors did not explore them, it may have been inappropriate to pool the data.

The authors' conclusions follow from the results.

**Implications of the review for practice and research**
Practice: The authors state that this systematic review was undertaken to inform the development of a clinical practice guideline for the Ontario Cancer Treatment and Research Foundation. The clinical practice guideline reports that G-CSF may be beneficial for some patients.

Research: The authors state that further research is needed to confirm the results of the review.

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**Other publications of related interest**
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Subject indexing assigned by NLM

**MeSH**
Adult; Antineoplastic Agents /pharmacology /therapeutic use; Antineoplastic Combined Chemotherapy Protocols /therapeutic use; Bone Marrow /drug effects; Canada; Cisplatin /therapeutic use; Confidence Intervals; Disease-Free Survival; Doxorubicin /therapeutic use; Etoposide /therapeutic use; Female; Granulocyte Colony-Stimulating Factor /adverse effects /therapeutic use; Humans; Male; Meta-Analysis as Topic; Neoplasms /drug therapy; Neutropenia
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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.