Meta-analysis: effects of prophylactic hematopoietic colony-stimulating factors on mortality and outcomes of infection

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CRD summary
This review evaluated the efficacy of colony-stimulating factors (CSFs) in patients with cancer and in those undergoing stem-cell transplantation. The authors concluded that CSFs have no significant effects on short-term all-cause mortality or infection-related mortality, but that CSF prophylaxis reduces the duration of febrile neutropenia, hospitalisation and documented infections. These conclusions appear appropriate and are likely to be reliable.

Authors’ objectives
To compare the efficacy of prophylactic colony-stimulating factors (CSFs) with placebo or no therapy, in patients with cancer and in patients undergoing stem-cell transplantation (SCT).

Searching
MEDLINE and EMBASE were searched from inception to April 2007, and the Cochrane CENTRAL Register until the second quarter of 2006; the search terms were reported. No restrictions on language or publication status were applied. Pharmaceutical manufacturers of G-CSFs and GM-CSFs were contacted for additional studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies comparing CSFs with placebo or no therapy were eligible for inclusion if prophylactic CSFs were given concurrently with or after initiation of chemotherapy or conditioning for SCT, before the occurrence of neutropenia. Studies were excluded if there were differences in chemotherapy, conditioning regimens, or other supportive care was provided to the study groups. The CSFs evaluated included granulocyte CSF (G-CSF) and granulocyte-macrophage CSF (GM-CSF). Antibiotic prophylaxis was not given in the majority of the included studies.

Participants included in the review
Studies of patients with cancer or patients undergoing SCT were eligible for inclusion. The type of cancers included leukaemia, solid tumours or lymphoma. The included studies were of paediatric, adult and older populations.

Outcomes assessed in the review
The primary outcome measure was short-term all-cause mortality. Where possible this was assessed 1 month after the start of study treatment; failing this, the time closest to 3 to 6 weeks was used for studies in patients undergoing chemotherapy, and the time closest to 100 days (or survival to discharge) was used for patients undergoing SCT. The secondary outcomes were infection-related mortality, documented infections, microbiologically documented infections, febrile neutropenia, sterile-site bacterial infections, documented fungal infections, clinically documented infections, duration of febrile neutropenia, fever, neutropenia, antibacterial and antifungal administration, and hospitalisation.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies, with any disagreements resolved through discussion.

Assessment of study quality
Study quality was assessed for adequacy of randomisation, double-blinding, and the description of withdrawals and drop-outs, using the Jadad scale. A score from 0 (lowest) to 5 (highest) was assigned to each included study. Two
reviewers assessed study quality, with inter-reviewer agreement estimated by the kappa statistic.

Data extraction
Two reviewers independently extracted the data onto standardised forms. When necessary, trialists were contacted for additional information.

Methods of synthesis
How were the studies combined?
For all-cause and infection-related mortality, the pooled relative risk and absolute risk reduction were calculated. For categorical data, the natural logarithm of the rate ratio was determined by the delta method and for continuous outcome variables the mean difference (MD) was calculated. A random-effects model was used for all analyses. Ninety-five per cent confidence intervals (CIs) were calculated when necessary. Publication bias was evaluated by funnel plots.

How were differences between studies investigated?
Sources of heterogeneity were explored by random-effects meta-regression. Analyses were stratified by age group (paediatric, adult, or older patients), diagnosis (leukaemia, solid tumour/lymphoma, or SCT), mandated use of antibacterial prophylaxis (yes or no), CSF type (G-CSF or GM-CSF), timing of CSF administration relative to chemotherapy start, concealed allocation (yes or no) and double-blinded design (yes or no).

Results of the review
One hundred and forty-eight RCTs (16,839 participants or cycles) were included in the review.

The median Jadad score for study quality was 2 (range: 0 to 5). Short-term all-cause mortality (rate ratio 0.95, 95% CI: 0.84, 1.08) and infection-related mortality (rate ratio 0.82, 95% CI: 0.66, 1.02) appeared to be similar between CSF and control groups. Compared with placebo or no therapy, prophylactic CSFs were associated with a lower incidence of documented infections, (rate ratio 0.85, 95% CI: 0.79, 0.92), microbiologically documented infections (rate ratio 0.86, 95% CI: 0.77, 0.96), clinically documented infections (rate ratio 0.75, 95% CI: 0.62, 0.92), and episodes of febrile neutropenia (rate ratio 0.71, 95% CI: 0.63, 0.80).

Prophylactic CSFs reduced the duration of febrile neutropenia (MD -1.38 days, 95% CI: -2.21, -0.56, p=0.001) and fever (MD -0.45 days, 95% CI: -0.87, -0.04, p=0.030), while the incidence of sterile-site bacterial infections and fungal infections were comparable to controls. Prophylactic CSF was associated with a shorter duration of parenteral antibiotic therapy (MD -1.81 days, 95% CI: -2.52, -1.11, p=0.001) and hospitalisation (MD -2.41 days, 95% CI: -3.13, -1.70, p=0.001). There was no interaction between age or population diagnosis group and CSF effect.

In studies that mandated antibiotic prophylaxis, CSFs were associated with a significant reduction in infection-related mortality compared with control (rate ratio 0.47, 95% CI: 0.28, 0.80, p=0.010).

The reduction in documented infections (p=0.034) and febrile neutropenia (p=0.001) was larger with G-CSFs than with GM-CSFs, while all-cause mortality and infection-related mortality did not differ. Concurrent administration of CSF and chemotherapy reduced infection-related mortality compared with CSF use after chemotherapy (p=0.031). Aspects of study quality had no effect on the final results. Meta-regression showed no interaction between the rate of febrile neutropenia and the effect of CSFs on infection-related mortality (p>0.2).

The reviewers stated that funnel plots showed no evidence of publication bias for either primary or secondary outcomes.

Authors’ conclusions
In cancer patients receiving chemotherapy and in patients undergoing SCT, CSFs have no significant effects on short-term all-cause mortality or infection-related mortality. CSF prophylaxis shortens the duration of febrile neutropenia, parenteral antibiotic therapy and hospitalisation, and reduces the rates of documented infections and microbiologically documented infections.
CRD commentary
This review addressed a well-defined question in terms of the study design, participants, intervention and outcomes. The authors searched several relevant database and efforts were made to identify unpublished studies, thus limiting the risk of publication bias. No language restrictions were applied, thus reducing the potential for language bias. The authors stated that there was no evidence of publication bias, although funnel plots were not shown. The authors attempted to minimise bias and error during the review process by carrying out critical review steps in duplicate. Sources of variation were explored and the authors stated that there was no heterogeneity for the primary outcome (and most secondary outcomes), which supports their decision to pool the data in a meta-analysis. Sensitivity analysis was conducted to investigate interaction between treatment assignment and a priori-specified subgroups. The authors’ cautious conclusions appear appropriate and are likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that future studies should focus on quality of life associated with CSF administration; preferences of health care professionals, patients and family; and more precise estimation of costs in different clinical scenarios.

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