Prophylactic colony-stimulating factors in children receiving myelosuppressive chemotherapy: a meta-analysis of randomized controlled trials

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CRD summary
This review evaluated the efficacy of prophylaxis with colony-stimulating factors (CSF) in children with cancer receiving myelosuppressive chemotherapy. CSF significantly reduced the incidence of febrile neutropenia, the duration of hospitalisation, and the use of antibiotics. Prophylaxis did not decrease the incidence of documented infections. These conclusions appear to be supported by the evidence presented and are likely to be reliable.

Authors’ objectives
To evaluate the impact of prophylactic colony-stimulating factors (CSFs) on the risk of febrile neutropenia (FN) in children receiving myelosuppressive chemotherapy

Searching
The Cochrane Library, MEDLINE, ACP Journal Club and Evidence-Based Medicine were searched to July 2004; the search terms were reported. Retrieved articles and major paediatric oncology textbooks were cross-checked for additional published studies.

Study selection
Study designs of evaluations included in the review
Parallel and crossover randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Inclusion criteria for the intervention were not explicitly stated, but by implication prophylactic CSFs were the interventions of interest. Three of the included studies used granulocyte-macrophage CSF and 13 used granulocyte CSF. The doses and schedules of CSF prophylaxis varied (details were provided in the paper). The authors stated that the dose and schedules were reasonable and unlikely to affect the outcomes of interest. Two studies used placebo as the comparator whereas all the other studies had no treatment as the control. The chemotherapy regimen varied between the studies.

Participants included in the review
Studies of children with cancer aged 18 years or younger or those aged 25 years or younger and being treated on paediatric oncology cooperative group protocols were eligible. Studies of patients receiving CSFs after established FN or who were treated with high-dose chemotherapy followed by bone marrow or stem cell transplantsations were excluded. Ten of the included studies were of patients with acute lymphoblastic leukaemia and non-Hodgkin lymphoma, 4 studies included solid tumours, and 2 studies included both solid and haematological cancer patients.

Outcomes assessed in the review
Inclusion criteria for the outcomes were not explicitly stated. The primary outcomes were the incidence of FN, documented infection (DI), duration of neutropenia, length of hospitalisation and length of antibiotic therapy.

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
Two independent reviewers extracted the data on study quality. All studies were evaluated according to the guidelines provided by the Consolidated Standards of Reporting Trials (CONSORT) statement.
Data extraction
Two independent reviewers extracted data on basic study design, patient characteristics, study outcomes and measures of study quality. Where more than one chemotherapy cycle was reported the first cycle only was used, therefore only the first sequence of crossover trials was extracted. The odds ratio (OR) and associated 95% confidence interval (CI) were calculated for dichotomous data and the mean difference and 95% CI for continuous data.

Methods of synthesis

How were the studies combined?
For FN and DI, the studies were pooled using a fixed-effect model (Peto) since no significant heterogeneity was detected for these outcomes across the studies. Mean differences in durations were estimated using a random-effects model (Cohen) because of significant heterogeneity. The z-statistic was used to test summary measures of effect. There was no adjustment for multiple testing. Publication bias was visually assessed using a funnel plot.

How were differences between studies investigated?
Statistical heterogeneity was evaluated using the chi-squared test and the I-squared statistic. Interactions between treatment and a priori-specified subgroups (study design, cancer type and type of CSF) were evaluated.

Results of the review
Sixteen RCTs (934 patients), 6 with a crossover design and 10 with parallel design, were included. The study size ranged from 12 to 287 patients.

The randomisation process was described in detail in 2 studies. Two RCTs were double blinded. All studies clearly stated inclusion and exclusion criteria, accounted for withdrawals and missing data, and used an intention-to-treat analysis.

There was a statistically significant lower incidence of FN with CSF prophylaxis compared with control (12 trials; OR 0.59, 95% CI: 0.43, 0.81, p=0.001). There was no heterogeneity (I-squared 0%). This benefit was evident both for leukaemia and high-grade lymphoma (OR 0.62, 95% CI: 0.43, 0.90, p=0.012) and for solid tumours (OR 0.51, 95% CI: 0.28, 0.94, p=0.029). There was no statistically significant difference in effect estimates between cancer types, study design, or type of CSF. CSF prophylaxis did not reduce the incidence of DI compared with the control (9 trials; OR 0.75, 95% CI: 0.52, 1.08, p=0.12). There was moderate statistical heterogeneity (I-squared 41%). The duration of neutropenia was decreased by prophylactic CSF (13 trials) by a mean of 3.40 days (95% CI: 1.85, 4.96, p<0.0001). Compared with controls, there was a decrease with CSF of 1.7 days (95% CI: 0.9, 2.5, p<0.001) in the mean length of hospitalisation and as well as a decrease of 2.0 days (95% CI: 0.35, 3.6, p=0.017) of antibiotic use (10 trials). Eight studies did not report on side-effects. Four studies reported no side-effects. Visual examination of the funnel plot suggested no publication bias.

Authors' conclusions
The prophylactic use of CSFs in paediatric cancer patients receiving systemic chemotherapy for leukaemia, lymphoma or solid tumours significantly reduces the risk of FN, but not DI, and shortens the length of severe neutropenia, antibiotic use and the duration of hospitalisation.

CRD commentary
This review had clearly stated inclusion criteria with respect to the study design, participants, treatments and outcomes. The authors searched four relevant databases and efforts were made to find further information by reviewing reference lists. It was not stated whether any language restrictions were applied, therefore language bias cannot be ruled out. Publication bias was assessed and there was no evidence of it for the outcomes evaluated. Two reviewers independently assessed study quality according to the guidelines provided by the CONSORT statement. It was not stated if the study selection procedure was also performed in duplicate, therefore reviewer error and bias might have been introduced into the review process.
Statistical heterogeneity was assessed and the authors stated that there was no significant heterogeneity for the main outcomes. The statistical analysis methods used in the meta-analysis were appropriate. A subgroup analysis was conducted to investigate interaction between treatment assignment and a priori-specified subgroups. The poor reporting of some aspects of the review process makes it difficult to judge if studies might have been missed, or errors made in the study selection. The review was generally well conducted and the authors’ conclusions seem reliable.

**Implications of the review for practice and research**
The authors did not state any implication for practice or further research.

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