Febrile neutropenia and related complications in breast cancer patients receiving pegfilgrastim primary prophylaxis versus current practice neutropaenia management: results from an integrated analysis

CRD summary
This review concluded that use of pegfilgrastim primary prophylaxis for preventing febrile neutropenia and enabling delivery of planned treatment in breast cancer patients with high or moderately high risk was supported. These conclusions reflected the results of the review, but serious concerns about the quantity of excluded data and nature of the review process mean that their reliability is unclear.

Authors' objectives
To compare pegfilgrastim primary prophylaxis with current practice management for prevention of febrile neutropenia and related events in breast cancer patients.

Searching
MEDLINE was searched up to August 2005. Search terms were reported. A review of data from a study of cancer care in Europe was also carried out. The clinical trials database of Amgen and abstracts from the American Society of Clinical Oncology (between 2000 and 2005) were also searched. Only studies reported in English were eligible for inclusion.

Study selection
Studies that were phase II to IV clinical trials performed in accordance with good clinical practice or well-designed observational studies (either prospective or retrospective) were eligible for inclusion. Studies were required to assess protocol-stipulated supportive care using pegfilgrastim as primary prophylaxis from the first cycle of chemotherapy, or current practice for the management of neutropenia. Current practice was defined as any currently used approach including no granulocyte colony-stimulating factor (G-CSF) use, daily G-CSF use in any cycle, or pegfilgrastim in any cycle. Eligible studies examined patients with breast cancer undergoing chemotherapy with a regimen which conferred at least a 15% risk of febrile neutropenia. Details of such regimens were specified in the paper; they included therapies using carboplatin, docetaxel, doxorubicin, epirubicin, gemcitabine, paclitaxel and vinorelbine.

The primary outcome was incidence of febrile neutropenia. Other outcomes assessed were incidence of febrile neutropenia in the first cycle of chemotherapy, hospitalisation due to febrile neutropenia, incidence of grade 3 or 4 febrile neutropenia, incidence of grade 3 or 4 leukopenia, chemotherapy dose reduction of 15% or more, and delay in chemotherapy of three days or longer.

In included studies, patients treated with pegfilgrastim primary prophylaxis received a dose of 6mg. Most patients were scheduled to receive four or six cycles of chemotherapy; 79% received all planned cycles. Included patients had a mean age of 51.4 (intervention group) or 52.0 (control group) years; over half (55% intervention and 58% control group) were aged over 50 years and considered menopausal. The great majority of patients had an Eastern Cooperative Oncology Group status of 0 to 1; all four stages of cancer were represented; oestrogen receptor status varied. Most patients had undergone prior treatment and were treated with combination chemotherapy which included docetaxel; other agents were carboplatin, cyclophosphamide, doxorubicin, epirubicin and paclitaxel.

The authors did not state how the papers were selected for the review.

Assessment of study quality
The authors did not report checking or verifying data with trial investigators.

Data extraction
Individual patient data (IPD) were obtained where possible. Studies where data could not be obtained by the cut-off date were not included in the review. Summaries of patient characteristics were prepared for each study and for each
treatment population. Granulocyte colony-stimulating factor (G-CSF) use for each cycle was coded by type of G-CSF administered and number of daily doses given.

Methods of synthesis
An IPD analysis was conducted using a mixed-effect model to calculate odds ratios (OR) with 95% confidence intervals, with the type of neutropenia prophylaxis included as a fixed-effect and individual study as a random-effect. Covariates assessed for inclusion in the model were age, disease stage (I to III versus IV) and receipt of prior chemotherapy or radiotherapy. A 25% significance level was applied as an inclusion criterion for these variables. A similar development process was used to construct the model for the analysis of secondary outcomes.

A sensitivity analysis which removed patients in the control group who received any granulocyte colony-stimulating factor within the last seven days of chemotherapy in cycle one was also carried out. Subgroup analyses based on study size were planned, but only that of the two largest studies was implemented.

Results of the review
Data were available on 1,569 patients treated with pegfilgrastim primary prophylaxis and 979 patients treated with current practice. Two hundred and sixty-six patients in the pegfilgrastim primary prophylaxis treatment groups were excluded from the analysis, as they did not receive pegfilgrastim from cycle one of chemotherapy treatment. The analysis included 2,282 patients, of which 1,303 received pegfilgrastim primary prophylaxis and 979 current practice. These data were drawn from eight randomised controlled trials (RCTs), two prospective observational studies and one retrospective observational study, a total of 11 of the 19 identified studies that met inclusion criteria.

There was a lower incidence of febrile neutropenia in patients treated with pegfilgrastim primary prophylaxis (OR 0.124, 95% CI 0.08 to 0.194; n=2,210 patients). Analysis of patients from the two largest studies only (n=1,507 patients) produced similar results to the main analysis. There were also lower incidences of febrile neutropenia in the first cycle of chemotherapy (OR 0.108, 95% CI 0.057 to 0.203; n=2,210 patients), hospitalisation due to febrile neutropenia (OR 0.205, 95% CI 0.124 to 0.338; n=2,210 patients), dose reduction of 15% or greater (OR 0.578, 95% CI 0.405 to 0.827; n=2,210 patients), grade 3 or 4 neutropenia (OR 0.042, 95% CI 0.031 to 0.056; n=1,983 patients) and grade 3 or 4 leukopenia (OR 0.059, 95% CI 0.044 to 0.079; n=2,132 patients). There was no statistically significant difference for the outcome of dose delay of at least three days.

The analysis also showed an increased risk of febrile neutropenia for older patients and those with stage IV disease.

Authors' conclusions
The use of pegfilgrastim primary prophylaxis to prevent febrile neutropenia and to enable delivery of planned treatment, in breast cancer patients with a high or moderately high risk of febrile neutropenia, was supported by this analysis.

CRD commentary
The review question and the inclusion criteria were clear. The authors searched one major database as well as some relevant conference abstracts and the manufacturer's own database. While the search for unpublished studies was likely to have reduced publication bias, the restriction to studies published in English may have increased the chances of language bias, as well as the probability of some relevant studies. The fact that nineteen studies were identified but that IPD were available for only 11 is a potentially serious concern, since no analysis of summary data was employed to take account of the patients in almost half the extant studies. The authors also did not report using methods designed to reduce reviewer bias and error in the selection of studies for the review, neither did they report checking the IPD with the study investigators or double-checking the summaries of patient characteristics. The use of a mixed-effect analysis was reasonable and attempts were made to control for variables other than the intervention.

The authors' conclusions accurately reflected the results of the review, but serious concerns about the quantity of excluded data and the nature of the review process mean that their reliability is unclear.

Several authors disclosed financial relationships with or were employed by various pharmaceutical manufacturers including Amgen (the manufacturers of pegfilgrastim).
Implications of the review for practice and research

**Practice:** The authors stated that the use of pegfilgrastim primary prophylaxis to prevent febrile neutropenia and to enable delivery of planned treatment, for breast cancer patients undergoing chemotherapy with a high or moderately high risk of febrile neutropenia, was supported.

**Research:** The authors did not state any implications for further research.

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