Granulocyte colony-stimulating factors for febrile neutropenia prophylaxis following chemotherapy: systematic review and meta-analysis

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Abstract

Background: Febrile neutropenia (FN) occurs following myelosuppressive chemotherapy and is associated with morbidity, mortality, costs, and chemotherapy reductions and delays. Granulocyte colony-stimulating factors (G-CSFs) stimulate neutrophil production and may reduce FN incidence when given prophylactically following chemotherapy.

Methods: A systematic review and meta-analysis assessed the effectiveness of G-CSFs (pegfilgrastim, filgrastim or lenograstim) in reducing FN incidence in adults undergoing chemotherapy for solid tumours or lymphoma. G-CSFs were compared with no primary G-CSF prophylaxis and with one another. Nine databases were searched in December 2009. Meta-analysis used a random effects model due to heterogeneity.

Results: Twenty studies compared primary G-CSF prophylaxis with no primary G-CSF prophylaxis: five studies of pegfilgrastim; ten of filgrastim; and five of lenograstim. All three G-CSFs significantly reduced FN incidence, with relative risks of 0.30 (95% CI: 0.14 to 0.65) for pegfilgrastim, 0.57 (95% CI: 0.48 to 0.69) for filgrastim, and 0.62 (95% CI: 0.44 to 0.88) for lenograstim. Overall, the relative risk of FN for any primary G-CSF prophylaxis versus no primary G-CSF prophylaxis was 0.51 (95% CI: 0.41 to 0.62). In terms of comparisons between different G-CSFs, five studies compared pegfilgrastim with filgrastim. FN incidence was significantly lower for pegfilgrastim than filgrastim, with a relative risk of 0.66 (95% CI: 0.44 to 0.98).

Conclusions: Primary prophylaxis with G-CSFs significantly reduces FN incidence in adults undergoing chemotherapy for solid tumours or lymphoma. Pegfilgrastim reduces FN incidence to a significantly greater extent than filgrastim.

Background

Neutropenia is the major dose-limiting toxicity of many chemotherapy regimens. Grade 3 and grade 4 neutropenia are defined as a neutrophil count < 1.0 × 10⁹/L and < 0.5 × 10⁹/L respectively. Febrile neutropenia (FN) is defined as neutropenia with fever, usually indicating infection, and is associated with substantial morbidity, mortality, and costs [1]. The direct risk of mortality associated with FN has been estimated as 9.5% (95% confidence interval [CI]: 9.2%, 9.8%) in a study of 41,779 cancer patients hospitalised with FN [1]. Management of FN often requires lengthy hospitalisation, [1] with associated costs and detrimental effects on quality of life [2,3]. In addition, an FN episode has been shown to increase the risk of chemotherapy dose reductions and delays [4]. Unplanned reductions in chemotherapy dose may cause further deaths from cancer in the long-term; in a retrospective analysis of breast cancer patients with a 30-year follow-up, the survival rate was 40% (95% CI: 26%, 55%) among patients receiving at least 85% of their planned dose, but only 21% (95% CI: 14%, 26%) among patients who received less than 85% [5].

Recombinant human granulocyte colony-stimulating factors (G-CSFs) stimulate production of mature, functional neutrophils [6]. G-CSFs have been shown to reduce the incidence of FN when used as prophylaxis following chemotherapy. Three G-CSFs are currently in common usage: filgrastim, pegfilgrastim, and
lenograstim. Filgrastim and lenograstim are administered as a series of daily injections; clinical studies suggest an average of 11 injections per chemotherapy cycle are required to achieve recovery of the absolute neutrophil count (ANC) to within the normal range [7-10]. Pegfilgrastim is administered as a single injection per chemotherapy cycle [11,12]. G-CSFs may be administered as primary prophylaxis (in every chemotherapy cycle from cycle 1) or as secondary prophylaxis (in all remaining cycles following a neutropenic event such as FN or prolonged severe neutropenia). The overall FN risk is dependent on chemotherapy regimen as well as individual patient risk factors such as age, performance status and disease stage [13]. Guidelines from the European Organisation for Research and Treatment of Cancer (EORTC), [13] the American Society of Clinical Oncology (ASCO) [14] and the National Comprehensive Cancer Network (NCCN) [15] recommend that prophylactic G-CSFs should be used where the risk of FN associated with the chemotherapy regimen is greater than or equal to 20%, and may be considered where the risk is 10-20%, particularly where additional patient risk factors are present.

This paper reports a systematic review and meta-analysis of the effect of primary G-CSF prophylaxis (with pegfilgrastim, filgrastim or lenograstim) on incidence of FN. The effect of each G-CSF is assessed in comparison with no primary G-CSF prophylaxis and in comparison with other G-CSFs.

Methods
Search strategy
The systematic review followed the recommendations in the PRISMA statement [16,17]. A systematic search was undertaken to identify randomised controlled trials (RCTs) of pegfilgrastim, filgrastim or lenograstim, compared with no primary G-CSF or with one another, for the reduction of FN following chemotherapy. A previous systematic review by Kuderer et al. [18] presented a meta-analysis of FN incidence within RCTs of primary G-CSF prophylaxis versus no primary G-CSF prophylaxis, while a systematic review by Pinto et al. [19] meta-analysed RCTs of primary prophylaxis using pegfilgrastim versus filgrastim. The literature searches within these previous reviews were conducted during 2006. Therefore, databases were searched from 2006 onwards, whereas studies published prior to 2006 were identified from the two existing reviews. Searches were undertaken in December 2009. The following databases were searched: Medline, Medline in Process, EMBASE, Science Citation Index, Cochrane Database of Systematic Reviews, Cochrane CENTRAL Register of Controlled Trials, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database and NHS Economic Evaluation Database (NHS-EED). The Medline search strategy was designed with reference to the previous two reviews, and comprised subject headings and text words for G-CSFs combined with a search filter to identify RCTs (Appendix 1). Searches were not restricted by language. Bibliographies of retrieved papers were searched for any additional relevant studies.

Inclusion and exclusion criteria
Studies were considered suitable for inclusion if they assessed primary G-CSF prophylaxis (pegfilgrastim, filgrastim or lenograstim) administered 1-3 days after the completion of chemotherapy, versus a different G-CSF or versus no primary G-CSF prophylaxis. Studies were only included if they reported incidence of FN. For consistency with the two existing systematic reviews, [18,19] only studies of adult cancer patients with solid tumours or lymphoma were included. Studies allowing concomitant antibiotic prophylaxis were included if identical prophylaxis was administered in both study arms. The following study types were excluded: studies of G-CSFs for treatment of FN; studies in children; studies in patients with leukaemia, myeloid malignancies or myelodysplastic syndromes; studies of G-CSFs for stem cell mobilisation in bone marrow or peripheral blood stem cell transplantation; economic analyses; studies with differing drugs, doses or schedules of chemotherapy in each arm; studies with differing doses of the same G-CSF in each arm; and studies not published in English.

Outcome measures
The outcome measure assessed in this review was the incidence of FN over all cycles of chemotherapy within each study. FN was chosen as a key clinical outcome due to its direct bearing on morbidity, mortality and hospitalisation rates, and also because this review was undertaken alongside the development of an economic model which utilised FN rate as a key parameter.

Data extraction
Data was extracted by two reviewers using a form developed for this review and any discrepancies were resolved through discussion.

Data synthesis
Meta-analyses were undertaken to compare the effectiveness of G-CSFs versus no prophylaxis and versus each other for the reduction of FN. Analyses were undertaken using RevMan software (version 5, Cochrane Collaboration). Results for each comparison were presented as a pooled relative risk and 95% CIs. Although clinical and statistical heterogeneity existed between studies, there was insufficient data on individual populations to facilitate separate analyses. Therefore, for
consistency with existing reviews, all studies were included in the analysis, and a random effects model was used. Heterogeneity was presented using the $I^2$ statistic, which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) [20].

Results

Number and characteristics of included studies

The flow chart for study inclusion is shown in Figure 1 and the included studies are described in Table 1. Studies published from 2006 onwards were identified from the literature search, and studies published prior to 2006 were identified from two previous reviews [18,19]. In total, 23 citations relating to 25 studies satisfied the inclusion criteria: 5 studies of primary pegfilgrastim vs. no primary G-CSF (within 4 citations); [21-24] 10 studies of primary filgrastim vs. no primary G-CSF (within 9 citations); [25-33] 5 studies of primary lenograstim vs. no primary G-CSF; [9,10,34-36] and 5 studies of primary pegfilgrastim vs. primary filgrastim [7,8,37-39]. No studies were identified comparing lenograstim with either pegfilgrastim alone or filgrastim alone.

A previous systematic review of prophylactic G-CSF use [18] included only a single study of pegfilgrastim versus no primary G-CSF [21]. Our literature search identified 4 additional RCTs of pegfilgrastim vs. no primary G-CSF, which were conducted in populations with colorectal cancer, [24] breast cancer, [23] non-Hodgkin’s lymphoma, [22] and various solid tumours; [22] the latter three studies were restricted to elderly patients. Our review also identified an additional large RCT of filgrastim vs. no primary G-CSF in breast cancer [33].

There was heterogeneity among trials of all three G-CSFs in terms of cancer type, patient age, chemotherapy regimen, number of chemotherapy cycles and cycle length (Table 1). Filgrastim and lenograstim were generally given for 10-14 days while the chemotherapy cycle length was 3 weeks (and for fewer days in a small number of trials with shorter cycle lengths). The comparator arm in some of the studies included secondary G-CSFs for those patients having an FN event, and some trials allowed prophylactic antibiotics in both arms. Some studies were open-label rather than double-blind.

Effectiveness of G-CSFs in reducing febrile neutropenia incidence

The relative risks of FN incidence are shown in Figure 2 for trials of G-CSF versus no primary G-CSF, and in Figure 3 for trials of pegfilgrastim versus filgrastim. The pooled relative risks for each G-CSF comparison are summarised in Table 2. Primary prophylaxis with each of the G-CSFs significantly decreased the risk of FN compared with no primary G-CSF, with relative risks of 0.30 (95% CI: 0.14 to 0.65) for pegfilgrastim, 0.57 (95% CI: 0.48 to 0.69) for filgrastim, and 0.62 (95% CI: 0.44 to 0.88) for lenograstim. Overall, the relative risk of FN when using any primary G-CSF prophylaxis versus no primary G-CSF prophylaxis was 0.51 (95% CI: 0.41 to 0.62).

There was a relatively high level of statistical heterogeneity in the analyses as shown by the $I^2$ statistic, which ranged from 50-76%; this is likely to reflect the variations between studies in factors such as cancer type, patient age, chemotherapy regimen, number of chemotherapy cycles and cycle length. Individual studies differed on too many variables for formal sub-analyses to be meaningful. However, Figures 2 and 3 illustrate the cancer type for each study (shown after the author and date) and highlight studies in populations aged ≥ 60 or ≥ 65 years (shown by asterisks). There was no clear difference in G-CSF effectiveness between cancer types, nor in studies restricting to an elderly population. As the majority of studies administered filgrastim and lenograstim for 10-14 days (for 3-week chemotherapy cycles), there was insufficient data to assess the effects of shorter durations of G-CSF treatment.
| Trial | Study design | Cancer type | Cancer stage | Patient age | Chemotherapy regimen | N cycles (max) | Cycle length | Arm 1 G-CSF strategy | Arm 1: N analysed | Arm 2 G-CSF strategy | Arm 2: N analysed | FN definition |
|-------|--------------|-------------|--------------|-------------|----------------------|----------------|-------------|----------------------|-----------------|---------------------|-----------------|---------------|
| Pegfilgrastim vs. no primary G-CSF | RCT, phase II, OL | Breast cancer | Stage II-III, node-positive | Age ≥ 65. Median 68, range 65-77 | FEC-100 | 6 (FN reported cycle 1 only) | 3 weeks | Pegfilgrastim primary: 6 mg day 2 | 30 | No primary G-CSF, pegfilgrastim secondary (following FN or neutropenia) | 29 | Fever + ANC < 1 × 10^9/l |
| | RCT, phase II, DB | Breast cancer | 62% stage IV, 38% other stages | Mean age 52, range 21-88 | Docetaxel 100 mg/m² | 4 | 3 weeks | Pegfilgrastim primary: 6 mg day 2 | 463 | Placebo primary, pegfilgrastim secondary (following FN) | 465 | Fever + ANC < 0.5 × 10^9/l |
| | RCT, phase II | Colorectal cancer | NR | NR | 2 weeks | Pegfilgrastim primary: 6 mg day 4 | 123 | Placebo primary | 118 | Grade 3-4 FN (assumed fever + ANC < 1 × 10^9/l) |
| | RCT, OL | NHL | 38% stage I-II, 62% stage III-IV | Age ≥ 65. Median 72, range 65-88 | CHOP or R-CHOP | 6 | 3 weeks | Pegfilgrastim primary: 6 mg day 2 | 73 | No primary G-CSF, pegfilgrastim secondary (at physician’s discretion) | 73 | Fever + ANC < 1 × 10^9/l |
| | RCT, OL | Solid tumour (lung, ovarian, breast) | 31% stage I-II, 69% stage III-IV | Age ≥ 65. Median 72, range 65-88 | One of 15 regimens with mild-to-moderate risk of neutropenia | 6 | 3 weeks | Pegfilgrastim primary: 6 mg day 2 | 343 | No primary G-CSF, pegfilgrastim secondary (at physician’s discretion) | 343 | Fever + ANC < 1 × 10^9/l |
| Filgrastim vs. no primary G-CSF | RCT, DB | Breast cancer | 21% high-risk stage II, 53% stage III, 25% stage IV | Mean age 51, range 25-75 | Doxorubicin 60 mg/m²/day, docetaxel 75 mg/m² | 4 (FN reported cycle 1 only) | 3 weeks | Filgrastim primary (Neupogen or XM02): 5 µg/kg/d from day 2 up to 14d or to ANC = 10 × 10^9/l | 276 | Placebo in cycle 1; filgrastim (XM02) in subsequent cycles | 72 | Fever + ANC < 0.5 × 10^9/l |
| Reference         | Design | Stage | Age | Chemotherapy | Primary CSF | Secondary CSF | Duration | ANC Criteria | Fever Criteria |
|-------------------|--------|-------|-----|--------------|-------------|---------------|----------|--------------|----------------|
| Timmer-Bonte 2005 | RCT, OL| SCLC  | 69% extensive, 31% limited | CDE | 5 | 3 weeks | Filgrastim primary: 300/450 ug/d from day 4; prophylactic antibiotics | 90 | 10 | No primary G-CSF; prophylactic antibiotics | 85 | 0 | Fever + ANC < 0.5 x 10⁹/l |
| Trillet-Lenoir 1993 | RCT, DB| SCLC  | 64% extensive, 36% limited | CDE | 6 | 3 weeks | Filgrastim primary: 230 ug/m²/d from day 4 up to 14d or until ANC = 10 x 10⁹/l | 65 | 9 to 14 | Placebo primary | 64 | 0 | Fever + ANC < 1 x 10⁹/l |
| Crawford 1991 | RCT, DB| SCLC  | 72% extensive, 28% limited | CDE | 6 | 3 weeks | Filgrastim primary: 230 ug/m²/d from day 4 up to 14d or until ANC = 10 x 10⁹/l | 95 | 9 to 14 | Placebo primary; secondary G-CSF | 104 | 0 | Fever + ANC < 1 x 10⁹/l |
| Doorduijn 2003 | RCT, OL| Aggressive NHL | Stage II-IV | Age ≥ 65. Median 72, range 65-90 | CHOP | 6 to 8 | 3 weeks | Filgrastim primary: 300 ug/d from day 2 for 10d | 197 | 10 | No primary G-CSF | 192 | 0 | Fever + FN not defined in terms of ANC |
| Osby 2003 (CHOP) | RCT, OL| Aggressive NHL | Stage II-IV | Age ≥ 60. Median 71, range 60-86 | CHOP | 4 to 8 | 3 weeks | Filgrastim primary: 5 ug/kg/d from day 2 up to 14d or until ANC = 10 x 10⁹/l | 101 | 10 to 14 | No primary G-CSF | 104 | 0 | Fever + ANC < 0.5 x 10⁹/l |
| Osby 2003 (CNOP) | RCT, OL| Aggressive NHL | Stage II-IV | Age ≥ 60. Median 71, range 60-86 | CNOP | 4 to 8 | 3 weeks | Filgrastim primary: 5 ug/kg/d from day 2 up to 14d or until ANC = 10 x 10⁹/l | 125 | 10 to 14 | No primary G-CSF | 125 | 0 | Fever + ANC < 0.5 x 10⁹/l |
| Zinzani 1997 | RCT, OL| Aggressive NHL | Stage II-IV | Age ≥ 60. Age range 60-82 | VNCOP-B | 8 | 1 week (differs alternate weeks) | Filgrastim primary: 5 ug/kg/d from day 3; prophylactic antibiotics | 77 | 5 | No primary G-CSF; prophylactic antibiotics | 72 | 0 | FN not defined in terms of ANC |
| Pettengell 1992 | RCT, OL| Aggressive NHL | Any stage | Age range 16-71 | VAPEC-B | 11 | 1 week (differs alternate weeks) | Filgrastim primary: 230 ug/m²/d from day 2 up to 14d or until ANC = 10 x 10⁹/l; prophylactic antibiotics | 41 | 12 | No primary G-CSF; prophylactic antibiotics | 39 | 0 | Fever + ANC < 1 x 10⁹/l |
| Fossa 1998 | RCT, phase III, OL| Germ cell cancer | Metastatic, poor-prognosis | Age range 15-65 | BEP/EP or BOP/ VIP-B | 6 | 3 weeks or 10 d | Filgrastim primary: 5 ug/kg/d from day 3 or 6 | 129 | 7 or 14 | No primary G-CSF | 130 | 0 | FN not defined in terms of ANC |
### Table 1 Description of trials of primary G-CSFs (vs. no primary G-CSF, or vs. each other) (Continued)

| Study                          | Design | Primary G-CSF | Non-metastatic | Adjuvant | Dose | Duration | Comparator | Other Details |
|-------------------------------|--------|---------------|----------------|----------|------|----------|------------|---------------|
| Lenograstim                    |        |               |                |          |      |          |             |               |
| **Chevallier 1995**[9]         | RCT, DB| Breast cancer | Non-metastatic | FEC-high-dose | 4   | 3 weeks  | Placebo    | 61 to 10 Placebo primary |
| **Buis 1995**[10]              | RCT, DB| Soft tissues  | Metastatic or locally advanced | MAMD | 6 (FN reported cycle 1 only) | 3 weeks | Pegfilgrastim: primary: 5 ug/kg/d from day 4 up to 14d or until ANC = 10 × 10^9/L |
| **Gisselbrecht 1997**[34]      | RCT, DB| Aggressive NHL | Any stage | LNH-87 (LNH-84 + randomization to anthracyclines) | 4 | 2 weeks | Pegfilgrastim: primary: 5 ug/kg/d from day 4 up to 14d or until ANC = 10 × 10^9/L |
| **Buis 1995**[10]              | RCT, DB| Soft tissue sarcoma | Metastatic or locally advanced | MAMD | 6 (FN reported cycle 1 only) | 3 weeks | Pegfilgrastim: primary: 5 ug/kg/d from day 4 up to 14d or until ANC = 10 × 10^9/L |
| **Gebbia 1993**[36]            | RCT, DB| Various Advanced | Advanced | Various | Various | Various | Pegfilgrastim: primary: 5 ug/kg/d | 23 to ≥ 7d Placebo primary |
| **Gebbia 1994**[35]            | RCT, DB| Various Advanced | Advanced | Various | Various | Various | Pegfilgrastim: primary: 5 ug/kg/d | 43 to 7 to 10 Placebo primary |

| Pegfilgrastim                  |        |               |                |          |      |          |             |               |
| **Green 2003**[7]              | RCT, phase III, DB| Breast cancer | 28% stage II, 27% stage III, 45% stage IV | Mean age 52, range 30-75 | Doxorubicin 60 mg/m^2/docetaxel 75 mg/m^2 | 4 | 3 weeks | Pegfilgrastim: primary: 6 mg day 2, then placebo up to 14d |
| **Holmes 2002**[38]            | RCT, phase III, DB| Breast cancer | High-risk stage II, III or IV | Mean age 51 | Doxorubicin 60 mg/m^2/docetaxel 75 mg/m^2 | 4 | 3 weeks | Pegfilgrastim: primary: 100 ug/kg day 2, then placebo up to 14d |
| **Holmes 2002**[37]            | RCT, phase II, DF| Breast cancer | High-risk stage II, III or IV | Mean age 49 | Doxorubicin 60 mg/m^2/docetaxel 75 mg/m^2 | 4 | 3 weeks | Pegfilgrastim: primary: 100 ug/kg day 2 (other dose groups not included here) |

| **Holmes 2002**[37]            | RCT, phase II, DF| Breast cancer | High-risk stage II, III or IV | Mean age 49 | Doxorubicin 60 mg/m^2/docetaxel 75 mg/m^2 | 4 | 3 weeks | Pegfilgrastim: primary: 100 ug/kg day 2 (other dose groups not included here) |

Fevers +ANC < 1 × 10^9/L
### Table 1 Description of trials of primary G-CSFs (vs. no primary G-CSF, or vs. each other) (Continued)

| Study | Design | Patient Characteristics | Treatment | Duration | Primary G-CSF | Other G-CSF Strategies |
|-------|--------|-------------------------|-----------|----------|---------------|------------------------|
| Grigg 2003[38] | RCT, phase II, OL, DF | NHL | Any stage | CHOP | 6 | Pegfilgrastim primary: 100 ug/kg day 2 (other dose groups not included here) | 14 |
| | | | Age ≥ 60. Mean 68, range 60-82 | | 3 weeks | | 1 |
| | | | | | | Filgrastim primary: 5 ug/kg, from day 2 up to 14d or until ANC = 10 x 10^9/l |
| Vose 2003[39] | RCT, phase II, OL | NHL (n = 56) or HL (n = 4) | Relapsed or refractory | ESHAP | 4 (FN reported cycles 1 & 2 only) | Pegfilgrastim primary: 100 ug/kg day 2 |
| | | | Mean age 49, 85% < 65 | | 3 weeks | | 29 |
| | | | | | | Filgrastim primary: 5 ug/kg, from day 2 up to 12d or until ANC = 10 x 10^9/l |

* Studies added as a result of updated search. ** G-CSF strategy: Primary prophylaxis is in all cycles. Secondary prophylaxis is in all cycles following FN, or following FN or neutropenia, or at physician’s discretion (as noted for individual studies). ANC = absolute neutrophil count; DB = double-blind; DF = dose-finding; HL = Hodgkin’s lymphoma; NHL = non-Hodgkin’s lymphoma; OL = open-label; SCLC = small-cell lung cancer. Chemotherapy regimens used: BEP/EP = etoposide 100 mg/m², cisplatin 20 mg/m², plus or minus bleomycin 30 U. BOP/VIP-B = bleomycin 30 U, vincristine 2 mg, cisplatin 20-50 mg/m²/etoposide 100 mg/m², ifosfamide 1000 mg/m². CDE = cyclophosphamide 1 g/m², doxorubicin 45-50 mg/m², etoposide 100-120 mg/m². CHOP = cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m², prednisolone 100 mg days 1-5. CNOP = cyclophosphamide 750 mg/m², mitoxantrone 10 mg/m², vincristine 1.4 mg/m², prednisolone 50 mg/m² days 1-5. ESHAP = etoposide 40 mg/m², methylprednisolone 500 mg, cisplatin 25 mg/m²/d, cytarabine 2000 mg/m². FEC-100 = 5-fluorouraci1 500 mg/m², epirubicin 100 mg/m², cyclophosphamide 500 mg/m². FEC-high-dose = 5-fluorouracil 750 mg/m², epirubicin 35 mg/m², cyclophosphamide 400 mg/m². FOIL = 5-FU, oxaliplatin, irinotecan, leucovorin. FOLFIRI = 5-FU, irinotecan, leucovorin. FOLFOX = 5-FU, oxaliplatin, leucovorin. LNH-87 = cyclophosphamide 1200 mg/m² days 1, vindesine 2 mg/m² days 1 & 5, bleomycin 10 mg days 1 & 5, prednisolone 60 mg/m² days 1-5, methotrexate 15 mg, with either doxorubicin 75 mg/m² or mitoxantrone 12 mg/m² day 1. MAID = mesna, doxorubicin, ifosfamide, dacarbazine. R-CHOP = CHOP plus rituximab. TAC = doxorubicin 50 mg/m², cyclophosphamide 500 mg/m², docetaxel 75 mg/m². VAPEC-B = vincristine 1.4 mg/m², doxorubicin 35 mg/m², prednisolone 50 mg/d (then tapered), etoposide 100 mg/m², cyclophosphamide 350 mg/m², bleomycin 10 mg/m². VNCOP-B = vincristine 2 mg, mitoxantrone 10 mg/m², cyclophosphamide 300 mg/m², etoposide 150 mg/m², prednisone 40 mg, bleomycin 10 mg/m².
Cooper et al. BMC Cancer 2011, 11:404
http://www.biomedcentral.com/1471-2407/11/404
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Figure 2 Primary G-CSFs versus no primary G-CSF: FN incidence. Cancer types for each study are shown after the author and date. CHOP and CNOP = chemotherapy regimens for NHL (see Table 1 footnote); NHL = non-Hodgkin’s lymphoma; SCLC = small-cell lung cancer; solid = solid tumours. *Indicates studies in patients aged ≥ 60 or ≥ 65 years. In the Holmes 2002 (phase II) study,[37] FN incidence in the filgrastim arm was reported as 2/25, which was incorrectly converted to 12%. The absolute numbers (2/25) have been used in this analysis. Therefore the resulting relative risk differs slightly from that reported in the previous systematic review by Pinto (2007),[19] which used the 12% figure.

| Study or Subgroup | Pegfilgrastim | Filgrastim | Risk Ratio |
|-------------------|--------------|------------|------------|
|                   | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Remieux 2007* (breast) | 34    | 26    | 26    | 12 | 0.63 [0.31, 1.33] |          |
| Vogel 2005 (breast) | 68    | 52    | 28    | 12 | 0.63 [0.31, 1.33] |          |
| Hecht 2006 (colonrectal) | 112   | 54    | 27    | 12 | 0.50 [0.26, 0.95] |          |
| Balslev 2007* (NHL) | 147   | 54    | 43    | 12 | 0.29 [0.13, 0.65] |          |
| Total (95% CI) | 1486   | 708   | 327   | 12 | 0.63 [0.31, 1.33] |          |
| Total events | 327   | 327   | 12 | 12 | 0.63 [0.31, 1.33] |          |

Heterogeneity: Tau² = 0.22; Chi² = 24.50, df = 12 (P = 0.0001); I² = 84%
Test for overall effect: Z = 4.70 (P = 0.0001)

Figure 3 Pegfilgrastim versus filgrastim: FN incidence. Cancer types for each study are shown after the author and date. HL = Hodgkin's lymphoma; NHL = non-Hodgkin’s lymphoma; SCLC = small-cell lung cancer; solid = solid tumours. *Indicates studies in patients aged ≥ 60 or ≥ 65 years.

| Study or Subgroup | Pegfilgrastim | Filgrastim | Risk Ratio |
|-------------------|--------------|------------|------------|
|                   | Events | Total | Events | Total | Weight | M-H, Random, 95% CI | M-H, Random, 95% CI |
| Green 2002 (breast) | 100   | 100   | 50    | 50   | 50.0% | 0.85 [0.31, 1.33] |          |
| Holmes 2002 (breast, ph2) | 14    | 14    | 7    | 7    | 50.0% | 0.85 [0.31, 1.33] |          |
| Holmes 2002 (breast, ph2) | 5    | 5    | 25    | 25    | 50.0% | 0.85 [0.31, 1.33] |          |
| Grigg 2003* (NHL) | 0    | 0    | 13    | 13    | 100.0% | 0.85 [0.31, 1.33] |          |
| Vose 2003 (NHL, HL) | 6    | 6    | 31    | 31    | 100.0% | 0.85 [0.31, 1.33] |          |
| Total (95% CI) | 215    | 215    | 100.0% | 0.85 [0.31, 1.33] |          |
| Total events | 215   | 215   | 100.0% | 0.85 [0.31, 1.33] |          |

Heterogeneity: Tau² = 0.22; Chi² = 24.50, df = 12 (P = 0.0001); I² = 84%
Test for overall effect: Z = 4.70 (P = 0.0001)
In terms of comparisons between different G-CSFs, the relative risk of FN for pegfilgrastim versus filgrastim was 0.66 (95% CI: 0.44 to 0.98). There were no head-to-head trials comparing lenograstim to either of the other two G-CSFs.

**Discussion**

Our systematic review and meta-analyses confirm and strengthen previous evidence that primary prophylaxis with each of the three G-CSFs is effective in reducing the risk of FN following chemotherapy. In particular, our systematic review identified 4 further RCTs of pegfilgrastim vs. no primary G-CSF, [22-24] whereas at the time of a previous systematic review [18] only a single RCT [21] making this comparison was available. Although these 5 RCTs comparing pegfilgrastim with no primary G-CSF were heterogeneous in terms of clinical population and chemotherapy regimen, the pooled relative risk indicated a significant effect of pegfilgrastim in reducing FN incidence. Filgrastim and lenograstim also significantly reduced FN incidence.

This review also strengthens the evidence base regarding the comparative effectiveness of the three G-CSFs; in particular, comparison of the “once-per-cycle” G-CSF pegfilgrastim versus the “once-daily” G-CSF filgrastim. Meta-analysis of five RCTs indicated that FN incidence was significantly lower following primary prophylaxis with pegfilgrastim than with filgrastim. This is consistent with the fact that the reduction in FN risk for pegfilgrastim versus no primary G-CSF was greater than the reduction observed for filgrastim versus no primary G-CSF.

As discussed in previous reviews, [18,19] there was heterogeneity among the studies in terms of the clinical population (age, cancer type), chemotherapy regimen, and cycle length and number. Correspondingly, heterogeneity was observed among the study results. Since individual studies differed on too many variables for formal sub-analyses to be meaningful, all studies were included in the analysis. There was no clear difference in G-CSF effectiveness between cancer types, nor in studies restricting to elderly populations. However, the variation in clinical population, and the corresponding high levels of heterogeneity, indicate that caution should be used when applying the results to individual clinical settings. Conversely, the range of populations and treatment regimens covered by the included studies is likely to reflect the variations which would be observed in clinical practice.

**Conclusions**

This systematic review and meta-analysis demonstrate that primary G-CSF prophylaxis with pegfilgrastim, filgrastim and lenograstim is effective in reducing the risk of FN in adults undergoing chemotherapy for solid tumours or lymphoma. In addition, although heterogeneity existed between studies, a meta-analysis suggests that pegfilgrastim reduces the risk of FN to a greater extent than filgrastim.

**Appendix 1: Search strategy (Medline)**

1 Granulocyte colony-stimulating factor/
2 Granulocyte colony-stimulating factor, recombinant/
3 Colony-stimulating factors, recombinant/
4 Filgrastim/
5 G-CSF$
6 granulocyte colony-stimulating factor$
7 filgrastim
8 Neupogen
9 pegfilgrastim
10 Neulasta
11 lenograstim
12 Granocyte
13 Euprotin
14 r-metHuG-CSF
15 SD-01
16 PEG-rmetHuG-CSF
17 XM02
18 Ratiograstim
19 or/1-18
20 randomized controlled trial.pt.
21 controlled clinical trial.pt.
22 randomized controlled trial/
23 random allocation/
24 double blind method/
25 single blind method/
26 clinical trial.pt.
27 exp clinical trial/
28 (clin$ adj25 trial$).ti,ab.
29 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
30 placebo$.
31 placebo$ti,ab.
32 random$ti,ab.
33 research design/.
34 randomised$ti,ab.
35 randomized$ti,ab.
36 or/20-35
37 19 and 36
("$" indicates truncations; "/" indicates medical subject headings)

List of abbreviations
ANC: Absolute neutrophil count; ASCO: American Society of Clinical Oncology; DARE: Database of Abstracts of Reviews of Effects; EORTC: European Organisation for Research and Treatment of Cancer; FN: Febrile neutropenia; G-CSF: Granulocyte colony-stimulating factor; NCCN: National Comprehensive Cancer Network; NHS-EED: NHS Economic Evaluation Database; RCT: Randomised controlled trial.

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Authors’ contributions
KC undertook the systematic review and drafted the manuscript. JM undertook the statistical analyses. SW contributed to study selection and interpretation. MS contributed to study selection and interpretation and to the statistical analyses. RA participated in the design and coordination of the study and contributed to the statistical analyses. All authors read and approved the final manuscript.

Competing interests
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