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

Cooper KL[1*], Madan J, Whyte S[1], Stevenson MD[1], Akehurst R[1]

1. School of Health and Related Research, University of Sheffield, Sheffield S1 4DA, UK
2. Academic Unit of Primary Health Care, University of Bristol, Bristol, UK

* Correspondence to: Katy Cooper, Health Economics and Decision Science (HEDS), School of Health and Related Research (ScHARR), University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA, UK
Telephone: +44 (0)114 222 0773
Fax: +44 (0)114 272 4095
E-mail: k.l.cooper@sheffield.ac.uk

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 preventing FN 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 – 0.65) for pegfilgrastim, 0.57 (95% CI: 0.48 – 0.69) for filgrastim, and 0.62 (95% CI: 0.44 – 0.88) for lenograstim. Five studies compared pegfilgrastim with filgrastim; FN incidence was significantly lower for pegfilgrastim than filgrastim, with relative risk 0.66 (95% CI: 0.44 – 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.

Keywords: febrile neutropenia, G-CSFs, granulocyte colony-stimulating factors, meta-analysis, prophylaxis, systematic review

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Introduction

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 x 10^9/L and <0.5 x 10^9/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

A systematic search was undertaken to identify RCTs of pegfilgrastim, filgrastim or lenograstim, compared with no primary G-CSF or with one another, for the prevention of FN following chemotherapy. A previous systematic review by Kuderer et al. [16] 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. [17] 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 [16;17], 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 prevention 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) [18].

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 [16;17]. In total, 23 citations relating to 25 studies satisfied the inclusion criteria: 5 studies of pegfilgrastim vs. no primary G-CSF (within 4 citations) [19-22]; 10 studies of filgrastim vs. no primary G-CSF (within 9 citations) [23-31]; 5 studies of primary lenograstim vs. no primary G-CSF [9;10;32-34]; and 5 studies of primary pegfilgrastim vs. primary filgrastim [7;8;35-37.] No studies were identified comparing lenograstim with either pegfilgrastim alone or filgrastim alone.

A previous systematic review of prophylactic G-CSF use [16] included only a single study of pegfilgrastim versus no primary G-CSF [19]. Our literature search identified 4 additional RCTs of pegfilgrastim vs. no primary G-CSF, which were conducted in populations with colorectal cancer [22], breast cancer (elderly patients) [21], non-Hodgkin's lymphoma [20], and various solid tumours [20]. Our review also identified an additional large RCT of filgrastim vs. no primary G-CSF in breast cancer [31].

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 where 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 preventing febrile neutropenia

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 in patient population and chemotherapy regimen described above.

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 [20-22], whereas at the time of a previous systematic review [16] only a single RCT [19] 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 preventing FN. Further analyses demonstrated that both 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 [16;17], 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 there was insufficient data to analyse the various populations separately, all studies were included in the analysis. The included studies covered a range of populations and treatment regimens, as would be observed in clinical practice. This 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.

It may also be relevant to note that the majority of the studies with a 3-week chemotherapy cycle length administered filgrastim and lenograstim until ANC

recovery as recommended in the product labels (generally for 10-11 days per cycle), while in clinical practice these G-CSFs may sometimes be given for a shorter number of days, which may impact on effectiveness [38;39].

Conclusions

This systematic review and meta-analysis demonstrate that primary G-CSF prophylaxis is effective in reducing the risk of FN in adults undergoing chemotherapy for solid tumours or lymphoma. Additionally, direct and indirect evidence suggests that pegfilgrastim reduces the risk of FN to a greater extent than filgrastim.

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Figure 1: Flow chart for identification of relevant studies

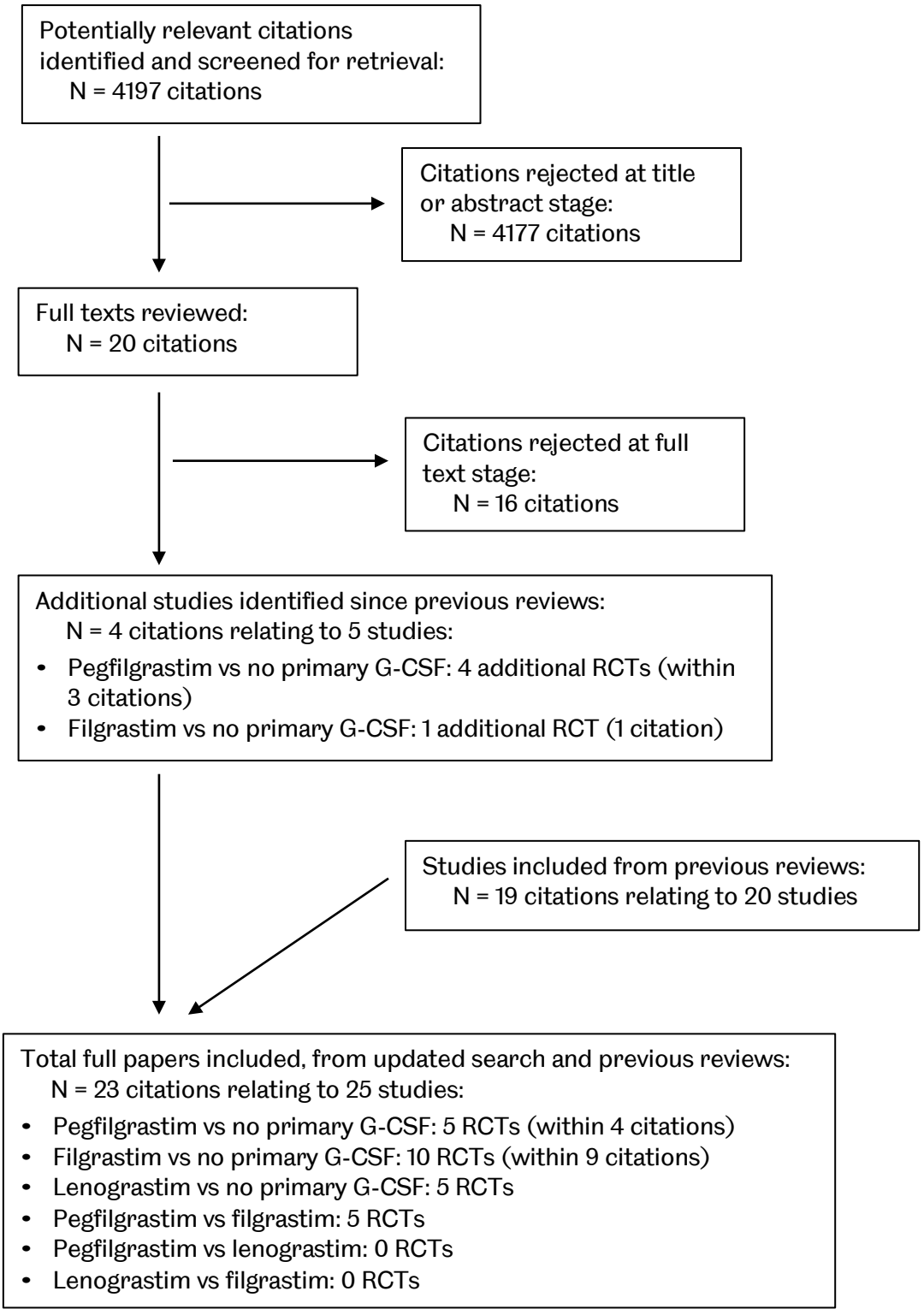


Table 1: Description of trials of primary G-CSFs (vs. no primary G-CSF, or vs. each other)

Trial	Study design	Cancer type	Cancer stage	Patient age	Chemotherapy regimen	N cycles (max)	Cycle length	Arm 1 G-CSF strategy[b]	Arm 1: N analysed	Arm 1: days primary G-CSF	Arm 2 G-CSF strategy[b]	Arm 2: N analysed	Arm 2: days primary G-CSF	FN definition
Pegfilgrastim vs. no primary G-CSF														
Vogel 2005[19]	RCT, phase III, DB	Breast cancer	62% stage IV, 38% other stages	Mean age 52, range 21-88	Docetaxel 100mg/m^2	4	3 weeks	Pegfilgrastim primary: 6mg day 2	463	1	Placebo primary, pegfilgrastim secondary (following FN)	465	0	Fever + ANC <0.5x10^9/l
[a] Romieu 2007[21]	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: 6mg day 2	30	1	No primary G-CSF, pegfilgrastim secondary (following FN or neutropenia)	29	0	Fever + ANC <1x10^9/l
[a] Hecht 2009[22]	RCT, phase II	Colorectal cancer	NR	NR	FOLFOX (49%), FOLFIRI (26%) or FOIL (25%)	4	2 weeks	Pegfilgrastim primary: 6mg day 4	123	1	Placebo primary	118	0	Grade 3-4 FN (assumed fever + ANC <1x10^9/l)
[a] Balducci 2007: solid tumour[20]	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: 6mg day 2	343	1	No primary G-CSF, pegfilgrastim secondary (at physician's discretion)	343	0	Fever + ANC <1x10^9/l
[a] Balducci 2007: NHL[20]	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: 6mg day 2	73	1	No primary G-CSF, pegfilgrastim secondary (at physician's discretion)	73	0	Fever + ANC <1x10^9/l
Filgrastim vs. no primary G-CSF														
Doorduijn 2003[23]	RCT, OL	Aggressive NHL	Stage II-IV	Age ≥65. Median 72, range 65-90	CHOP	6 to 8	3 weeks	Filgrastim primary: 300ug/d from day 2 for 10d	197	10	No primary G-CSF	192	0	FN not defined in terms of ANC
Osby 2003 (C**H**OP)[24]	RCT, OL	Aggressive NHL	Stage II-IV	Age ≥60. Range 60-86	CHOP	4 to 8 (most 8)	3 weeks	Filgrastim primary: 5ug/kg/d from day 2 up to 14d or until ANC=10x10^9/l	101	10 to 14	No primary G-CSF	104	0	Fever + ANC <0.5x10^9/l
Osby 2003 (C**N**OP)[24]	RCT, OL	Aggressive NHL	Stage II-IV	Age ≥60. Range 60-86	CNOP	4 to 8 (most 8)	3 weeks	Filgrastim primary: 5ug/kg/d from day 2 up to 14d or until ANC=10x10^9/l	125	10 to 14	No primary G-CSF	125	0	Fever + ANC <0.5x10^9/l
Zinzani 1997[25]	RCT, OL	Aggressive NHL	Stage II-IV	Age ≥60. Age range 60-82	VNCOP-B	8	1 week (differs alternate weeks)	Filgrastim primary: 5ug/kg/d from day 3; prophylactic antibiotics	77	5	No primary G-CSF; prophylactic antibiotics	72	0	FN not defined in terms of ANC

Trial	Study design	Cancer type	Cancer stage	Patient age	Chemotherapy regimen	N cycles (max)	Cycle length	Arm 1 G-CSF strategy[b]	Arm 1: N analysed	Arm 1: days primary G-CSF	Arm 2 G-CSF strategy[b]	Arm 2: N analysed	Arm 2: days primary G-CSF	FN definition
Pettengell 1992[26]	RCT, OL	Aggressive NHL	Any stage	Age range 16-71	VAPEC-B	11	1 week (differs alternate weeks)	Filgrastim primary: 230ug/m^2/d from day 2 up to 14d or until ANC=10x10^9/l; prophylactic antibiotics	41	12	No primary G-CSF; prophylactic antibiotics	39	0	Fever + ANC <1x10^9/l
Timmer-Bonte 2005[27]	RCT, phase III, OL	SCLC	69% extensive, 31% limited	Age range 36-81	CDE	5	3 weeks	Filgrastim primary: 300/450ug/d from day 4; prophylactic antibiotics	90	10	No primary G-CSF; prophylactic antibiotics	85	0	Fever + ANC <0.5x10^9/l
Trillet-Lenoir 1993[28]	RCT, DB	SCLC	64% extensive, 36% limited	Median 59	CDE	6	3 weeks	Filgrastim primary: 230ug/m^2/d from day 4 up to 14d or until ANC=10x10^9/l	65	9 to 14	Placebo primary	64	0	Fever + ANC <1x10^9/l
Crawford 1991[29]	RCT, DB	SCLC	72% extensive, 28% limited	Age range 31-80	CDE	6	3 weeks	Filgrastim primary: 230ug/m^2/d from day 4 up to 14d or until ANC=10x10^9/l	95	9 to 14	Placebo primary; secondary G-CSF	104	0	Fever + ANC <1x10^9/l
Fossa 1998[30]	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: 5ug/kg/d from day 3 or 6	129	7 or 14	No primary G-CSF	130	0	FN not defined in terms of ANC
[a] del Giglio 2008[31]	RCT, DB	Breast cancer	21% high-risk stage II, 53% stage III, 25% stage IV	Mean age 51, range 25-75	Doxorubicin 60mg/m^2 /docetaxel 75mg/m^2	4 (FN reported cycle 1 only)	3 weeks	Filgrastim primary (Neupogen or XM02): 5ug/kg/d from day 2 up to 14d or to ANC=10x10^9/l	276	5 to 14 (median 9-10)	Placebo in cycle 1; filgrastim (XM02) in subsequent cycles	72	0 (cycle 1)	Fever + ANC <0.5x10^9/l
Lenograstim vs. no primary G-CSF														
Chevallier 1995[9]	RCT, DB	Breast cancer, inflammatory	Non-metastatic	Age range 23-65	FEC-high-dose	4	3 weeks	Lenograstim primary: 5ug/kg/d from day 6	61	10	Placebo primary	59	0	Fever + ANC <1x10^9/l
Gisselbrecht 1997[32]	RCT, DB	Aggressive NHL	Any stage	Age range 15-55	LNH-87 (LNH-84 + randomization to anthracyclines)	4	2 weeks	Lenograstim primary: 5ug/kg/d from day 6	82	8	Placebo primary	80	0	Fever + ANC <1x10^9/l
Bui 1995[10]	RCT, DB	Soft tissue sarcoma	Metastatic or locally advanced	Age range 21-69	MAID	6 (FN reported cycle 1 only)	3 weeks	Lenograstim primary: 5ug/kg/d from day 4 up to 14d or until ANC=30x10^9/l	22	10 to 14	Placebo primary; secondary G-CSF	26	0	Fever + ANC <1x10^9/l
Gebbia 1994[33]	RCT, DB	Various	Advanced	Age range 40-75	Various	Various	Various	Lenograstim primary: 5ug/kg/d	23	≥7d	Placebo primary	28	0	Fever + ANC <1x10^9/l
Gebbia 1993[34]	RCT, DB	Various	Advanced	Age range 38-66	Various	Various	Various	Lenograstim primary: 5ug/kg/d	43	7 to 10	Placebo primary	43	0	Fever + ANC <1x10^9/l

Trial	Study design	Cancer type	Cancer stage	Patient age	Chemotherapy regimen	N cycles (max)	Cycle length	Arm 1 G-CSF strategy[b]	Arm 1: N analysed	Arm 1: days primary G-CSF	Arm 2 G-CSF strategy[b]	Arm 2: N analysed	Arm 2: days primary G-CSF	FN definition
Pegfilgrastim vs. 10- or 11-day filgrastim														
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 60mg/m^2 /docetaxel 75mg/m^2	4	3 weeks	Pegfilgrastim primary: 6mg day 2; then placebo up to 14d	77	1	Filgrastim primary: 5ug/kg, from day 2 up to 14d or until ANC=10x10^9/l	75	11 (median)	Fever + ANC <0.5x10^9/l
Holmes 2002: phase III[8]	RCT, phase III, DB	Breast cancer	High-risk stage II, III or IV. 37% stage IV	Mean age 51	Doxorubicin 60mg/m^2 /docetaxel 75mg/m^2	4	3 weeks	Pegfilgrastim primary: 100ug/kg day 2; then placebo up to 14d	149	1	Filgrastim primary: 5ug/kg, from day 2 up to 14d or until ANC=10x10^9/l	147	11 (mean)	Fever + ANC <0.5x10^9/l
Holmes 2002: phase II[35]	RCT, phase II, DF	Breast cancer	High-risk stage II, III or IV. 30% stage IV	Mean age 49	Doxorubicin 60mg/m^2 /docetaxel 75mg/m^2	4	3 weeks	Pegfilgrastim primary: 100ug/kg day 2 (other dose groups not included here)	46	1	Filgrastim primary: 5ug/kg, from day 2 up to 14d or until ANC=10x10^9/l	25	10.6; 10.2; 10.4; 11.0 (mean in cycles 1-4)	Fever + ANC <0.5x10^9/l
Grigg 2003[36]	RCT, phase II, OL, DF	NHL	Any stage	Age ≥60. Mean 68, range 60-82	CHOP	6	3 weeks	Pegfilgrastim primary: 100ug/kg day 2 (other dose groups not included here)	14	1	Filgrastim primary: 5ug/kg, from day 2 up to 14d or until ANC=10x10^9/l	13	10 (mean)	Fever + ANC <0.5x10^9/l
Vose 2003[37]	RCT, phase II, OL	NHL (n=56) or HL (n=4)	Relapsed or refractory	Mean age 49. 85% <65	ESHAP	4 (FN reported cycles 1 & 2 only)	3 weeks	Pegfilgrastim primary: 100ug/kg day 2	29	1	Filgrastim primary: 5ug/kg, from day 2 up to 12d or until ANC=10x10^9/l	31	11 (median)	Fever + ANC <0.5x10^9/l

[a] Studies added as a result of updated search. [b] 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: FEC-100=5-fluorouracil 500mg/m^2, epirubicin 100mg/m^2, cyclophosphamide 500mg/m^2. FEC-high-dose=5-fluorouracil 750mg/m^2, epirubicin 35mg/m^2, cyclophosphamide 400mg/m^2. TAC= doxorubicin 50mg/m^2, cyclophosphamide 500mg/m^2, docetaxel 75mg/m^2 CHOP=cyclophosphamide 750mg/m^2, doxorubicin 50mg/m^2, vincristine 1.4mg/m^2, prednisolone 100mg days 1-5. R-CHOP=CHOP plus rituximab. ESHAP= etoposide 40mg/m^2, methylprednisolone 500mg, cisplatin 25mg/m^2/d, cytarabine 2000mg/m^2. LNH-87=cyclophosphamide 1200mg/m^2 day 1, vindesine 2mg/m^2 days 1 & 5, bleomycin 10mg days 1 & 5, prednisolone 60mg/m^2 days 1-5, methotrexate 15mg, with either doxorubicin 75mg/m^2 or mitoxantrone 12mg/m^2 day 1. MAID=mesna, doxorubicin, ifosfamide, dacarbazine. CNOP=cyclophosphamide 750mg/m^2, mitoxantrone 10mg/m^2, vincristine 1.4mg/m^2, prednisolone 50mg/m^2 days 1-5. VNCOP-B=vincristine 2mg, mitoxantrone 10mg/m^2, cyclophosphamide 300mg/m^2, etoposide 150mg/m^2, prednisone 40mg, bleomycin 10mg/m^2. VAPEC-B=vincristine 1.4mg/m^2, doxorubicin 35mg/m^2 prednisolone 50mg/d (then tapered), etoposide 100mg/m^2, cyclophosphamide 350mg/m^2, bleomycin 10mg/m^2. CDE=cyclophosphamide 1g/m^2, doxorubicin 45-50mg/m^2, etoposide 100-120mg/m^2. BEP/EP=etoposide 100mg/m^2, cisplatin 20mg/m^2, plus or minus bleomycin 30 U. BOP/VIP-B=bleomycin 30 U, vincristine 2mg, cisplatin 20-50mg/m^2/etoposide 100mg/m^2, ifosfamide 1000mg/m^2. FOIL=5-FU, oxaliplatin, irinotecan, leucovorin. FOLFOX=5-FU, oxaliplatin, leucovorin. FOLFIRI=5-FU, irinotecan, leucovorin.

Table 2: Summary of febrile neutropenia incidence based on meta-analyses of trials of G-CSFs

Treatment 1	Treatment 2	No of studies	No of patients	Relative risk of FN (95% CI), p-value	I^2 (heterogeneity)
Pegfilgrastim	No primary G-CSF	5	2060	0.30 (0.14 to 0.65), p = 0.002	76%
Filgrastim	No primary G-CSF	10	2183	0.57 (0.48 to 0.69), p < 0.00001	50%
Lenograstim	No primary G-CSF	5	467	0.62 (0.44 to 0.88), p = 0.007	64%
Any G-CSF	No primary G-CSF	20	4710	0.51 (0.41 to 0.62), p < 0.00001	74%
Pegfilgrastim	Filgrastim	5	606	0.66 (0.44 to 0.98), p = 0.04	0%

Figure 2: Primary G-CSFs versus no primary G-CSF: FN incidence

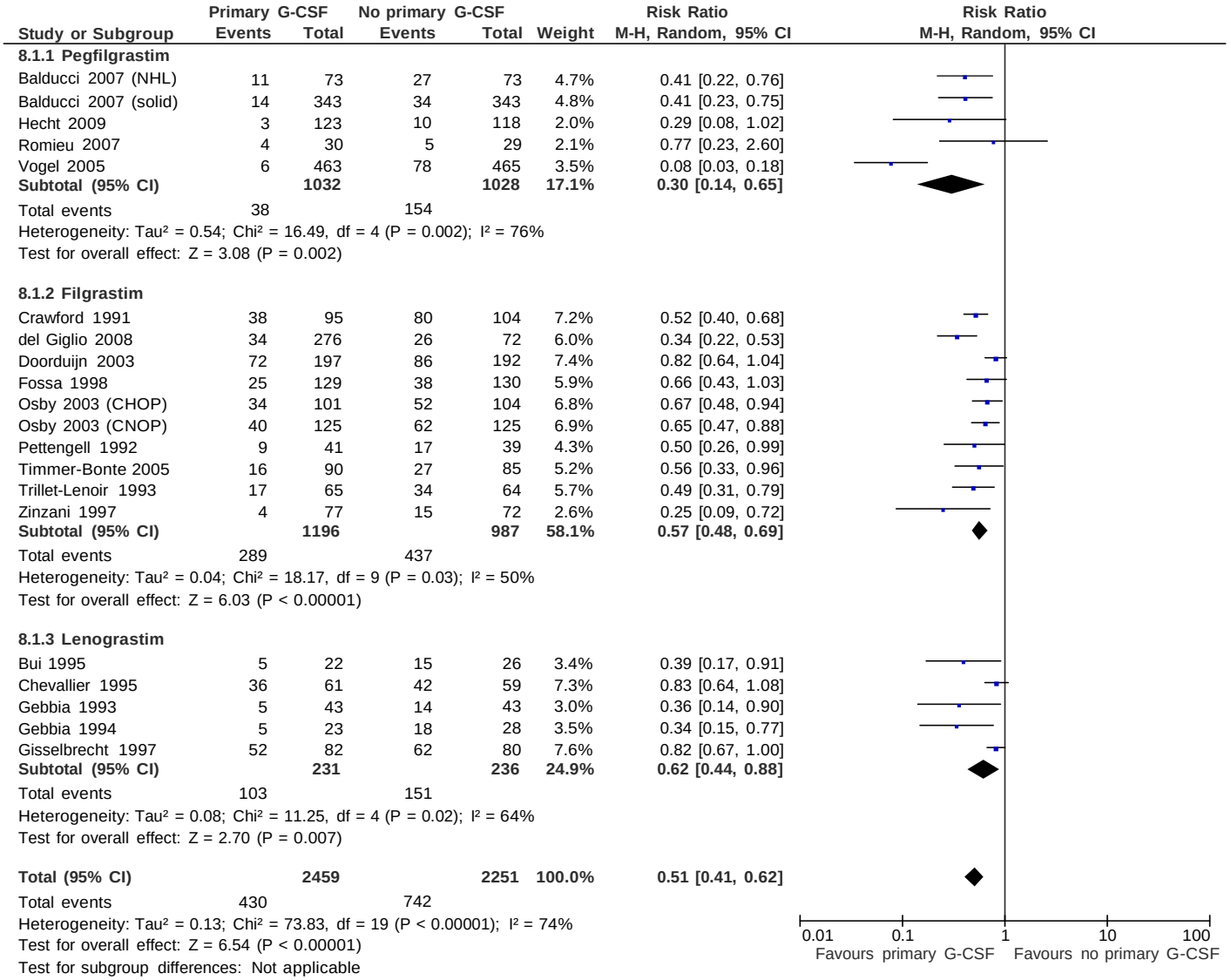
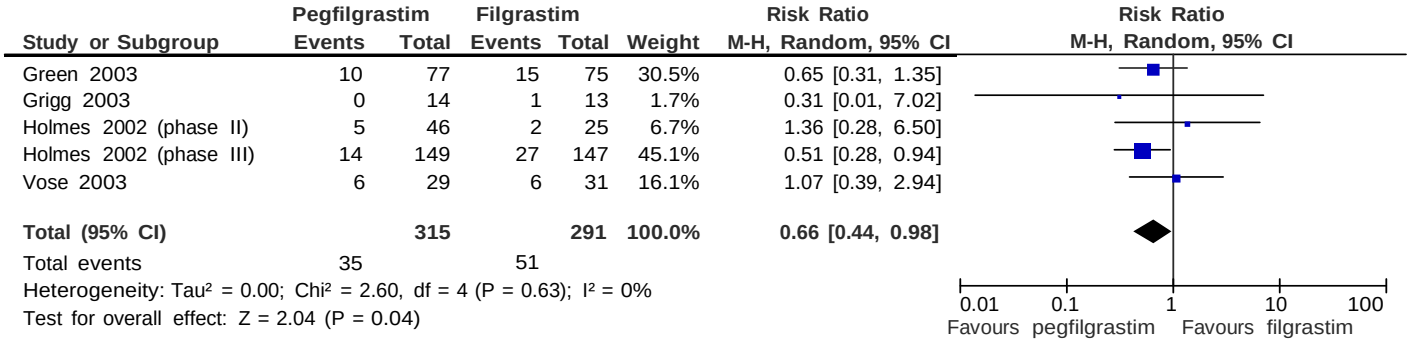


Figure 3: Pegfilgrastim versus filgrastim: FN incidence*



* In the Holmes 2002 (phase II) study,[35] 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),[17] which used the 12% figure.

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 placebos/
31 placebos.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 subject headings)