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Keywords: granulocyte colony-stimulating factors, G-CSFs, febrile neutropenia, prophylaxis, systematic review, mixed treatment comparison

Running title: G-CSFs for FN prophylaxis: review and MTC

Abstract

Background
This study assesses the efficacy of three granulocyte colony-stimulating factors (G-CSFs; pegfilgrastim, filgrastim and lenograstim) in preventing febrile neutropenia (FN).

Methods
A systematic review was undertaken. Head-to-head studies were combined using direct meta-analyses. In addition, an indirect Bayesian mixed treatment comparison (MTC) was undertaken to facilitate comparison between G-CSFs where there were no direct trials, and to allow data from all trials to be synthesised into a coherent set of results.

Results
The review identified the following studies comparing G-CSF prophylaxis to no primary G-CSF prophylaxis: 5 studies of pegfilgrastim, 9 studies of filgrastim and 5 studies of lenograstim. In addition, 5 studies were identified comparing pegfilgrastim to filgrastim. The two synthesis methods (meta-analysis and MTC) demonstrated that all three G-CSFs significantly reduced FN rate. Pegfilgrastim reduced FN rate to a greater extent than filgrastim (significantly in the head-to-head meta-analysis and in the MTC of all studies, and not quite significantly when the MTC was restricted to RCTs only). In the absence of direct trials, the MTC gave an 80-86% probability that pegfilgrastim is superior to lenograstim in preventing FN, and a 71-72% probability that lenograstim is superior to filgrastim.

Conclusions
Prophylaxis with G-CSFs significantly reduces FN rate. A head-to-head meta-analysis shows pegfilgrastim to be significantly superior to filgrastim in preventing FN events, while an MTC demonstrates that pegfilgrastim is likely to be superior to lenograstim.

Introduction

Neutropenia is the major dose-limiting toxicity of many chemotherapy regimens. Febrile neutropenia (FN) is defined as neutropenia with fever, usually indicating infection, and is associated with substantial morbidity, mortality, and costs.[1] Grade 3-4 neutropenia is defined as a neutrophil count either $<1.0 \times 10^9$/L or $<0.5 \times 10^9$/L. The direct risk of mortality associated with FN has been estimated as 9.5% (95% 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 intensity, 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.[7-28] Three G-CSFs are currently in use: 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.[11;12;24;25] Pegfilgrastim is given as a single injection per chemotherapy cycle.[29;30] G-CSFs may be administered as primary prophylaxis (in every chemotherapy cycle from cycle 1) or as secondary prophylaxis (in all remaining cycles following an FN event 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.[31] Guidelines from the European Organisation for Research and Treatment of Cancer (EORTC),[31] the American Society of Clinical Oncology (ASCO)[32] and the National Comprehensive Cancer Network (NCCN)[33] 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.

The aim of this study is to assess the relative efficacy of the three G-CSFs (pegfilgrastim, filgrastim and lenograstim) in preventing FN, using both direct head-to-head meta-analyses and a Bayesian mixed treatment comparison.

Methods

Obtaining data on the efficacy of each intervention

Two systematic reviews and meta-analyses of G-CSFs in relation to reducing FN events have been published.[34;35] Kuderer et al.[34] analysed studies of primary G-CSF prophylaxis (pegfilgrastim, filgrastim or lenograstim) versus no primary G-CSF prophylaxis, whilst Pinto et al.[35] analysed studies of primary prophylaxis with pegfilgrastim versus filgrastim. The literature searches within these existing reviews were conducted during 2006.

A systematic search was undertaken to identify further studies of pegfilgrastim, filgrastim or lenograstim for FN prophylaxis during chemotherapy, compared to each other or to no primary prophylaxis, published between January 2006 and June 2009. The following databases were searched: Medline, EMBASE, the Cochrane Database of Systematic Reviews, the Cochrane CENTRAL Register of Controlled Trials, the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment Database and the NHS

Economic Evaluation Database (NHS-EED). The Medline search strategy was designed with reference to the previous two reviews, and comprised subject headings (granulocyte colony-stimulating factor; granulocyte colony-stimulating factor recombinant; colony-stimulating factors recombinant; filgrastim) as well as text words (G-CSF; granulocyte colony-stimulating factor; filgrastim; Neupogen; pegfilgrastim; Neulasta; lenograstim; Granocyte; Euprotin; r-metHuG-CSF; SD-01; PEG-rmetHuG-CSF). Searches were not restricted by language. Bibliographies of retrieved papers were hand-searched and experts in the field were consulted, according to the QUOROM statement for reporting of systematic reviews.[36]

Studies were considered suitable for inclusion if they compared the prophylactic efficacy of a G-CSF (pegfilgrastim, filgrastim or lenograstim) at any dose to another G-CSF or to no primary G-CSF prophylaxis, for the prevention of FN. For consistency with the two existing systematic reviews,[34;35] only studies of adult cancer patients with solid tumours or lymphoma were included. Studies allowing concomitant antibiotic prophylaxis were included if this 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 (due to limited safety and efficacy data in these conditions); 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; and studies with differing doses of the same G-CSF in each arm.

This study was undertaken alongside the development of an economic model, and FN was chosen as the key clinical outcome both in the economic model and in this review, due to its direct bearing on morbidity, mortality and hospitalisation rates. Therefore the outcome measure assessed in this analysis was the incidence of FN over all cycles of chemotherapy within each clinical study. Data was extracted by two reviewers using a form developed for this review and any discrepancies resolved through discussion.

Meta-analysis of head-to-head studies

Meta-analyses were undertaken to compare the effectiveness of G-CSFs versus no prophylaxis and versus each other in prevention of FN, where comparative studies were available. This was undertaken using RevMan software (version 4.2.10, Cochrane Collaboration). Due to heterogeneity between studies, random effects models were used.

Bayesian mixed treatment comparison (MTC)

To strengthen the validity of the results, and also to provide an indirect comparison where head-to-head trials were not available (i.e. to compare lenograstim to the other G-CSFs), a mixed treatment comparison (MTC)[37] of the entire dataset was carried out using the Bayesian modelling software WinBugs.[38] Where there are trials comparing interventions both to no treatment and to other interventions, an MTC synthesises all the trials into a single network and uses the evidence from all the trials to estimate a relative risk for each comparison. This allows for estimates of treatment effect to 'borrow strength' from all studies in the network.[39] The Bayesian approach allows analysis which differs from testing for statistical significance at conventional levels (such as 95%), and enables estimation of a percentage likelihood that one treatment is more efficacious than another. A random-effects model was again used, due to heterogeneity between studies. Median values are given for the point estimates of the relative risks, for consistency with standard meta-analysis.

Results

Number and characteristics of included studies

The QUOROM flow chart for study inclusion is shown in Figure 1. The included studies are described in Table 1. In total, 22 citations relating to 24 studies satisfied the inclusion criteria: 5 studies of pegfilgrastim vs. no primary G-CSF[7-10]; 9 studies of filgrastim vs. no primary G-CSF;[16-23] 5 studies of primary lenograstim vs. no primary G-CSF;[24-28] and 5 studies of primary pegfilgrastim vs. primary filgrastim.[11-15] No studies were identified comparing lenograstim to either pegfilgrastim alone or filgrastim alone. The network of trials for the mixed treatment comparison is shown in Figure 2.

Our literature search identified 4 additional studies of pegfilgrastim vs. no primary G-CSF, in addition to the single RCT in breast cancer patients[7] reported in an existing systematic review.[34] These additional studies included an RCT in elderly breast cancer patients,[9] RCTs in lymphoma patients and solid tumour patients (reported as a single citation),[8] and a large non-randomised study in which the study arms were generated by successive protocol amendments allowing greater levels of prophylaxis as the toxicity of TAC chemotherapy became apparent.[10] 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.

There was heterogeneity among trials of all three G-CSFs in terms of their clinical population (age, cancer type, chemotherapy regimen, number of chemotherapy cycles; see Table 1) and in terms of their efficacy results (Tables 2 and 3). As already reported in previous reviews, study quality was mixed,[34;35] with some studies being open-label rather than double-blind (Table 1). However, there was insufficient data to analyse the populations separately. Therefore, for consistency with existing reviews and to provide a clinical overview and avoid risk of bias, all RCTs were included in the main analysis. An additional analysis was also undertaken including a non-randomised study which was considered potentially relevant for inclusion. The recruitment of participants to each arm appeared to be unbiased (the different study arms were generated following protocol amendments requiring additional FN prophylaxis due to the toxicity of the chemotherapy regimen), and patient characteristics appeared similar between arms.[10]

Efficacy of G-CSFs in preventing febrile neutropenia

The incidence of FN across all chemotherapy cycles for all included studies is shown in Table 2. The pooled results for each comparison are summarised in Table 3, firstly using a meta-analysis of head-to-head trial data, and secondly using a Bayesian MTC.

Both the meta-analyses and the MTC indicated that each of the G-CSFs significantly decreases the risk of FN compared to no primary G-CSF (Table 3). At the time of the previously-reported meta-analysis,[34] only a single trial of pegfilgrastim vs. no primary G-CSF had been published.[7] This review strengthens the evidence base by including further trials of pegfilgrastim vs. no primary G-CSF.[8-10] Following the addition of these studies, pegfilgrastim remained significantly more efficacious than no primary G-CSF in preventing FN, with the meta-analysis of RCTs giving a relative risk for FN of 0.31 (95% CI: 0.12, 0.76). If including the non-randomised study,[10] this became 0.29 (95% CI: 0.15, 0.55). The MTC based on analysis of RCTs gave a relative risk of 0.36 (95% credible interval 0.22, 0.61); this became 0.34 (95% credible interval: 0.23, 0.54) if the non-randomised study[10] was included.

Filgrastim and lenograstim also decreased the risk of FN compared to no primary G-CSF, with the head-to head meta-analyses giving relative risks for FN of 0.61 (95% CI: 0.53, 0.72)

for filgrastim and 0.62 (95% CI: 0.44, 0.88) for lenograstim, as described in a previous review.[34] The relative risks generated by the MTC are shown in Table 3.

The head-to-head meta-analysis showed primary pegfilgrastim to be significantly more efficacious than primary filgrastim in preventing FN. This was also demonstrated in the MTC of all studies, but was not quite significant when the MTC was restricted to RCTs only (Table 3).

There were no head-to-head trials of lenograstim vs. the other G-CSFs; however, the MTC allows us to make an estimation of comparative efficacy. The relative risk of FN for pegfilgrastim vs. lenograstim based on analysis of RCTs was estimated as 0.75 (95% credible interval: 0.38, 1.60), equating to an 80% probability that pegfilgrastim is superior to lenograstim in preventing FN. Based on analysis of all studies including the non-randomised study, the relative risk was 0.71 (95% credible interval: 0.39, 1.42), with an 86% probability that pegfilgrastim is superior to lenograstim. The relative risk of FN for lenograstim vs. filgrastim based on analysis of RCTs was estimated as 0.88 (95% credible interval: 0.49, 1.40), equating to a 72% probability that lenograstim is superior to filgrastim in preventing FN. Based on analysis of all studies including the non-randomised study, the relative risk was 0.88 (95% credible interval: 0.49, 1.41), with an 71% probability that lenograstim is superior to filgrastim.

Discussion

Our analysis updates the findings of previous reviews by incorporating further trials of pegfilgrastim vs. no primary G-CSF (only a single trial made this comparison at the time of the existing review).[7;34] In addition, the MTC allowed comparison of lenograstim to the other G-CSFs in the absence of head-to-head trials.

Our results confirm that primary prophylaxis with G-CSFs is effective in reducing the risk of FN; this was the conclusion reached by Kuderer et al.,[34] and we show that this holds following the inclusion of the additional studies of pegfilgrastim vs. no primary G-CSF. Our results also allow comparison of the relative FN risk reduction between the “once-per-cycle” G-CSF pegfilgrastim and the “once-daily” G-CSFs filgrastim and lenograstim. As described by Pinto et al.,[35] pegfilgrastim reduced FN to a greater extent than filgrastim (this was significant in the head-to-head meta-analysis and in the MTC of all studies, though not quite significant in the MTC of RCTs only). Our MTC analysis demonstrates that, in the absence of direct trials, there is an 80-86% probability that pegfilgrastim is superior to lenograstim in preventing FN.

As discussed in previous reviews,[34;35] there was heterogeneity among the studies in terms of the clinical population studied, which varied in terms of cancer type, chemotherapy regimen and patient age. Correspondingly, heterogeneity was observed among the study results. Since there was insufficient data to analyse the various populations separately, it was felt to be most clinically useful to include all studies 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.

One aspect of heterogeneity is the fact that different chemotherapy regimens are associated with differing “baseline” FN risks in the absence of G-CSF prophylaxis. As described by Kuderer et al.,[34] there is a suggestion that studies with a lower baseline FN risk may

demonstrate a greater reduction in the relative risk of FN when G-CSF prophylaxis is administered. For example, the Vogel et al. study[7] of docetaxel (100mg/m^2) demonstrated a relatively low baseline FN risk of 17% in the control arm and a corresponding large reduction in FN risk in the pegfilgrastim arm (relative risk of 0.08). However, Kuderer et al. demonstrated that if the one or two studies with the lowest baseline FN risk were excluded from the analysis, no significant relationship between relative risk and baseline FN risk was observed.[34] Our analysis produced similar results (data not reported). Future studies in populations with differing baseline FN risks may shed further light on this issue.

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 efficacy.[40;41]

Our findings are also relevant in terms of methodologies for evidence synthesis. MTC methods enable comparison of efficacy using a single consistent dataset incorporating data from all trials. In this review, the MTC allowed assessment of the consistency of the direct and indirect evidence for the efficacy of the three G-CSFs in preventing FN. The fact that both methods gave similar results adds weight to the findings. Also, as there are no direct trials of lenograstim against other G-CSFs, the MTC allowed estimation of the relative effectiveness of lenograstim using the indirect evidence.

Conclusions

This analysis incorporates recent trials of pegfilgrastim vs. no primary G-CSF and confirms that primary prophylaxis with G-CSFs is effective in reducing the risk of FN. A head-to-head meta-analysis shows pegfilgrastim to be significantly superior to filgrastim in preventing FN events, while a Bayesian MTC demonstrates that pegfilgrastim is likely to be superior to lenograstim in reducing FN events.

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Figure 1: QUOROM flow chart for identification of relevant studies

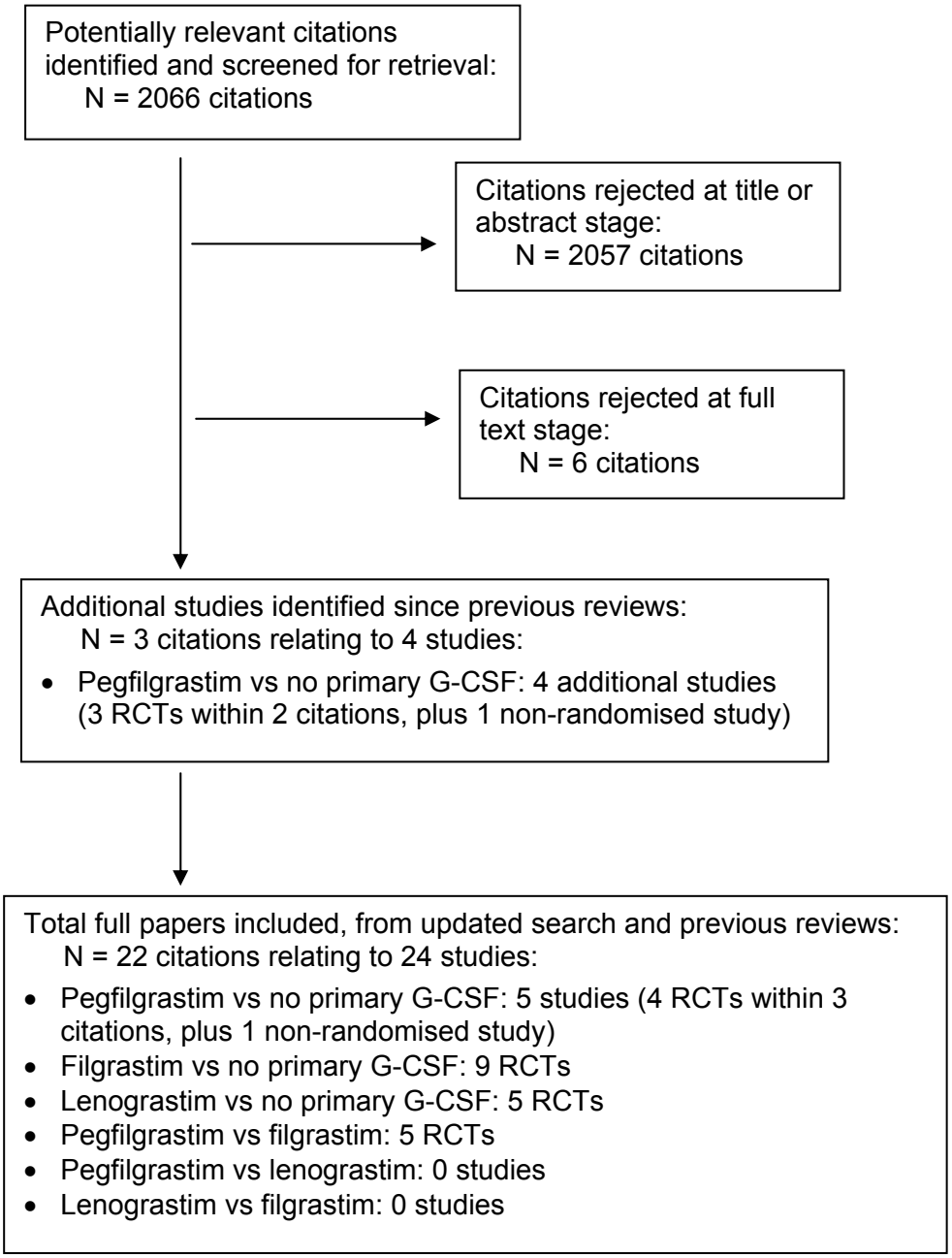

Figure 2: Network of trials for mixed treatment comparison

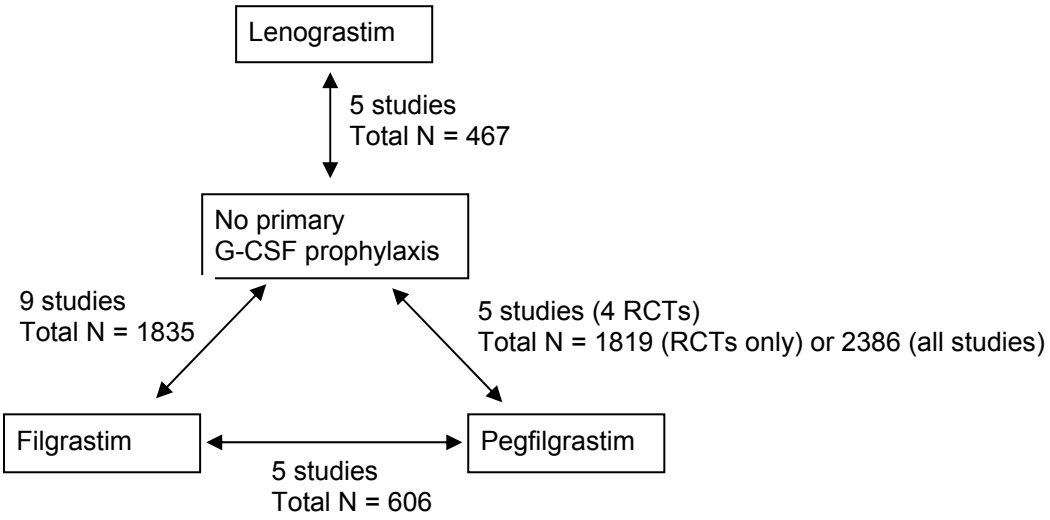

Table 1: Description of trials of primary G-CSFs (vs. no primary G-CSF, or vs. each other)

Trial	Study design	Cancer type	Cancer stage	Patient age	Chemotherapy regimen	No of cycles (max)	Cycle length	Arm 1 G-CSF strategy*	Arm 1: N analysed	Arm 1: days primary G-CSF	Arm 2 G-CSF strategy*	Arm 2: N analysed	Arm 2: days primary G-CSF
Pegfilgrastim vs. no primary G-CSF													
Vogel 2005[7]	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†	465	0
Balducci 2007: solid tumour#[8]	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†††	343	0
Balducci 2007: NHL#[8]	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†††	73	0
Romieu 2007#[9]	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††	29	0
von Minckwitz 2008#[10]	Not RCT; study arms from successive protocol amendments	Breast cancer	74% stage I-II, 26% stage III-IV	Age ≥18	TAC	8	3 weeks	Pegfilgrastim primary: 6mg day 2 + primary antibiotic prophylaxis	314	1	No primary G-CSF; primary antibiotic prophylaxis; filgrastim / lenograstim secondary††	253	0
Filgrastim vs. no primary G-CSF													
Doorduijn 2003[16]	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
Osby 2003 (C**H**OP)[17]	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
Osby 2003 (C**N**OP)[17]	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

Trial	Study design	Cancer type	Cancer stage	Patient age	Chemotherapy regimen	No of cycles (max)	Cycle length	Arm 1 G-CSF strategy*	Arm 1: N analysed	Arm 1: days primary G-CSF	Arm 2 G-CSF strategy*	Arm 2: N analysed	Arm 2: days primary G-CSF
Zinzani 1997[18]	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
Pettengell 1992[19]	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
Timmer-Bonte 2005[20]	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
Trillet-Lenoir 1993[21]	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
Crawford 1991[22]	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
Fossa 1998[23]	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
Lenograstim vs. no primary G-CSF													
Chevallier 1995[24]	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
Gisselbrecht 1997[26]	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
Bui 1995[25]	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

Trial	Study design	Cancer type	Cancer stage	Patient age	Chemotherapy regimen	No of cycles (max)	Cycle length	Arm 1 G-CSF strategy*	Arm 1: N analysed	Arm 1: days primary G-CSF	Arm 2 G-CSF strategy*	Arm 2: N analysed	Arm 2: days primary G-CSF
Gebbia 1994[27]	RCT, DB	Various	Advanced	Age range 40-75	Various	Various	Various	Lenograstim primary: 5ug/kg/d	23	≥7d	Placebo primary	28	0
Gebbia 1993[28]	RCT, DB	Various	Advanced	Age range 38-66	Various	Various	Various	Lenograstim primary: 5ug/kg/d	43	7 to 10	Placebo primary	43	0
Pegfilgrastim vs. 10- or 11-day filgrastim													
Green 2003[11]	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)
Holmes 2002: phase III[12]	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)
Holmes 2002: phase II[13]	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)
Grigg 2003[14]	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)
Vose 2003[15]	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)

[#]Studies added as a result of updated search. *Prophylaxis 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[†††]. DB=double-blind; OL=open-label, DF=dose-finding. NHL=non-Hodgkin's lymphoma, HL= Hodgkin's lymphoma, SCLC=small-cell lung cancer. 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.

Table 2: Incidence of febrile neutropenia (FN) across all chemotherapy cycles in each study

Study	Total N (arm 1)	FN rate (%)		Total N (arm 2)	FN rate (%)		p-value	Relative risk of FN (95% confidence interval)
	Primary pegfilgrastim			**No primary G-CSF**				
Vogel 2005‡‡	463	6/463	(1.3%)	465	78/465	(17%)	<0.001	0.08 (0.04-0.18)
*Balducci 2007: solid tumour‡	343		(4%)	343		(10%)	0.001	0.40 (0.22-0.73)
*Balducci 2007: NHL‡	73		(15%)	73		(37%)	0.004	0.41 (0.22-0.76)
*Romieu 2007 (cycle 1 only)‡	30	4/30	(13%)	29	5/29	(17%)		0.77 (0.23-2.62)
*von Minckwitz 2008‡	314	17/314	(5%)	253	55/253	(22%)	<0.001	0.25 (0.15-0.43)
	Primary filgrastim			**No primary G-CSF**				
Doorduijn 2003‡‡‡	197	72/197	(37%)	192	86/192	(45%)	NR	0.82 (0.64-1.04)
Osby 2003 (C**H**OP)‡‡	101		(34%)	104		(50%)	<0.001	0.68 (0.49-0.95)
Osby 2003 (C**N**OP)‡‡	125		(32%)	125		(50%)	<0.001	0.64 (0.47-0.87)
Zinzani 1997‡‡‡	77	4/77	(5%)	72	15/72	(21%)	0.004	0.25 (0.09-0.73)
Pettengell 1992‡	41	9/41	(22%)	39	17/39	(44%)	0.04	0.50 (0.25-0.98)
Timmer-Bonte 2005‡‡	90	16/90	(18%)	85	27/85	(32%)	0.01	0.56 (0.33-0.96)
Trillet-Lenoir 1993‡	65	17/65	(26%)	64	34/64	(53%)	0.002	0.49 (0.31-0.78)
Crawford 1991‡	95		(40%)	104		(77%)	<0.001	0.52 (0.4-0.68)
Fossa 1998‡‡‡	129	25/129	(19%)	130	38/130	(29%)	NR	0.66 (0.42-1.03)
	Primary lenograstim			**No primary G-CSF**				
Chevallier 1995‡	61	36/61	(59%)	59	42/59	(71%)	NS	0.83 (0.64-1.08)
Gisselbrecht 1997‡	82	52/82	(63%)	80	62/80	(78%)	NS	0.82 (0.67-1.0)
Bui 1995 (cycle 1)‡	22	5/22	(23%)	26	15/26	(58%)	0.02	0.39 (0.17-0.90)
Gebbia 1994‡	23	5/23	(22%)	28	18/28	(64%)	<0.001	0.34 (0.15-0.77)
Gebbia 1993‡	43		(12%)	43		(33%)	<0.05	0.36 (0.14-0.90)
	Primary pegfilgrastim			**Primary filgrastim**				
Green 2003‡‡	77	10/77	(13%)	75	15/75	(20%)	NS	0.65 (0.31-1.35)
Holmes 2002: phase III‡‡	149	14/149	(9%)	147	27/147	(18%)	0.029	0.51 (0.28-0.94)
Holmes 2002: phase II‡‡	46	5/46	(11%)	25	2/25	(8%)†	NS	1.36 (0.28-6.49)
Grigg 2003‡‡	14	0/14	(0%)	13	1/13	(8%)	NR	N/A
Vose 2003 (cycles 1 & 2)‡‡	29	6/29	(21%)	31	6/31	(19%)	NS	1.07 (0.39-2.95)

FN=febrile neutropenia. ANC=absolute neutrophil count. *Studies added as a result of updated search. Febrile neutropenia definition: ‡fever and ANC <1x10^9/l; ‡‡fever and ANC <0.5x10^9/l; ‡‡‡FN not defined in terms of ANC. †Reported by Holmes et al. as 2/25=12%, which is incorrect; therefore the absolute numbers have been reported here (2/25), with the associated percentage (8%).

Table 3: Febrile neutropenia incidence: a) head-to-head meta-analysis; b) Bayesian mixed treatment comparison

Treatment 1 (T1)	Treatment 2 (T2)	No of studies	No of patients	a) Head-to-head meta-analysis: Relative risk of FN (95% confidence interval); I^2 statistic for heterogeneity (%)	b) Bayesian mixed treatment comparison: Relative risk of FN (95% credible interval); probability T1 more effective than T2 in preventing FN (%)	
					RCTs only:	All studies:
Pegfilgrastim	No primary G-CSF	RCTs: 4* All studies: 5*	RCTs: 1819 All studies: 2386	RCTs only: 0.31 (0.12 – 0.76); I^2=82.1% All studies: 0.29 (0.15 – 0.55); I^2=75.7%	0.36 (0.22 – 0.61); >99%	0.34 (0.23 – 0.54); >99%
Filgrastim	No primary G-CSF	9 †	1835	0.61 (0.53 – 0.72); I^2=28.7%	0.56 (0.44 – 0.68); >99%	0.55 (0.43 – 0.67); >99%
Lenograstim	No primary G-CSF	5 †	467	0.62 (0.44 – 0.88); I^2=64.4%	0.49 (0.28 – 0.72); >99%	0.49 (0.28 – 0.71); >99%
Pegfilgrastim	Filgrastim	5 ‡	606	0.64 (0.43 – 0.97); I^2=0%	0.65 (0.39 – 1.11); 95%	0.62 (0.41 – 0.99); 98%
Pegfilgrastim	Lenograstim	0	0	No direct trials	0.75 (0.38 – 1.60); 80%	0.71 (0.39 – 1.42); 86%
Lenograstim	Filgrastim	0	0	No direct trials	0.88 (0.49 – 1.40); 72%	0.88 (0.49 – 1.41); 71%

*Pegfilgrastim vs no primary G-CSF: 5 studies in total; 4 RCTs (reported in 3 citations) and 1 non-randomised study. †As reported by Kuderer et al.[34] ‡As reported by Pinto et al.[35]