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REVIEW ARTICLE

Efficacy, effectiveness and safety of long-acting granulocyte colony-stimulating factors for prophylaxis of chemotherapy-induced neutropenia in patients with cancer: a systematic review

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Abstract
Purpose Pegfilgrastim was introduced over a decade ago. Other long-acting granulocyte colony-stimulating factors (G-CSFs) have recently been developed. We systematically reviewed the efficacy, effectiveness and safety of neutropenia prophylaxis with long-acting G-CSFs in cancer patients receiving chemotherapy.
Methods We performed a systematic literature search of the MEDLINE, EMBASE and Cochrane Library databases, and abstracts from key congresses. Studies of long-acting G-CSFs for prophylaxis of chemotherapy-induced neutropenia (CIN) and febrile neutropenia (FN) were identified by two independent reviewers. Abstracts and full texts were assessed for final inclusion; risk of bias was evaluated using the Cochrane's tool. Effectiveness and safety results were extracted according to study type and G-CSF used.
Results Of the 839 articles identified, 41 articles representing different studies met the eligibility criteria. In five randomised controlled trials, 11 clinical trials and 17 observational studies across several tumour types and chemotherapy regimens, pegfilgrastim was used alone or compared with daily G-CSF, no G-CSF, no upfront pegfilgrastim or placebo. Studies generally reported lower incidence of CIN (4/7 studies), FN (11/14 studies), hospitalisations (9/13 studies), antibiotic use (6/7 studies) and adverse events (2/5 studies) with pegfilgrastim than filgrastim, no upfront pegfilgrastim or no G-CSF. Eight studies evaluated other long-acting G-CSFs; most (5/8) were compared to pegfilgrastim and involved patients with breast cancer receiving docetaxel-based therapy. Efficacy and safety profiles of balugrastim and lipegfilgrastim were comparable to pegfilgrastim in phase 3 studies. Efficacy and safety of other long-acting G-CSFs were mixed.
Conclusions Pegfilgrastim reduced the incidence of FN and CIN compared with no prophylaxis. Most studies showed better efficacy and effectiveness for pegfilgrastim than filgrastim. Efficacy and safety profiles of lipegfilgrastim and balugrastim were similar to pegfilgrastim.

Keywords Balugrastim · Granulocyte colony-stimulating factor · Lipegfilgrastim · Neutropenia · Pegfilgrastim · Systematic review

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Introduction

In patients with cancer receiving cytotoxic chemotherapy, chemotherapy-induced neutropenia (CIN) and febrile neutropenia (FN) are frequent complications. CIN is graded according

to severity of the reduction of the absolute neutrophil count (ANC) and FN is commonly defined as ANC $<0.5\times10^9$/L with an oral temperature ≥38 °C for more than 1 h [1]. Patients experiencing neutropenic events are more susceptible to subsequent infections [2]. As a consequence of FN, patients often require hospitalisation and antibiotic treatment and frequently have their chemotherapy dose reduced or delayed [3, 4]. Modifications to chemotherapy may decrease its effectiveness, thereby potentially compromising treatment outcomes [4].

Granulocyte colony-stimulating factors (G-CSFs) stimulate the production and maturation of neutrophils during chemotherapy and reduce the incidence and duration of CIN and incidence of FN [5, 6]. Prophylactic G-CSF use from the first cycle of chemotherapy is recommended by the European Organisation for Research and Treatment of Cancer [7] and other international guidelines [1, 8, 9] if the planned chemotherapy regimen is associated with an FN risk of 20 % or more. For chemotherapy regimens with an intermediate FN risk of 10–20 %, guidelines recommend that patient-related and disease-related factors should also be considered when deciding whether or not to give G-CSF support.

Daily G-CSFs are primarily cleared through the kidneys and require dosing until recovery of the neutrophil count. Long-acting G-CSFs are primarily cleared by neutrophils and have significantly reduced renal clearance compared with daily G-CSFs. They therefore require only a single dose per chemotherapy cycle. Pegfilgrastim (Neulasta®; Amgen Inc., CA, USA), consisting of the human recombinant G-CSF filgrastim pegylated at the N terminus with a 20-kDa polyethylene glycol molecule, is administered subcutaneously as a single 6 mg dose [10]. It was approved in both the USA and Europe in 2002. Lipegfilgrastim (Lonquex®; Teva Pharma B. V.), a long-acting filgrastim molecule that is pegylated at a different site from pegfilgrastim, was approved in Europe in 2013 [11]. Other long-acting G-CSFs, such as balugrastim, are in clinical development [12].

The emergence of these recently developed long-acting G-CSFs necessitates a re-evaluation of the evidence. Direct comparative data are limited, and there are no systematic reviews of long-acting G-CSFs that include data from both observational studies and randomised controlled trials (RCTs). Therefore, we conducted a systematic review to capture the available data on the efficacy, safety and effectiveness of long-acting G-CSFs for prophylaxis of CIN and FN in adult patients with cancer.

Methods

Study design

The systematic review was performed according to a pre-specified protocol that was agreed by all authors. We searched the following electronic databases: MEDLINE In-Process & Other Non-Indexed Citations and OVID MEDLINE 1948–present, EMBASE 1980–present and the Cochrane Library. A search of abstract books was also conducted from the annual meetings of the American Society of Clinical Oncology, the American Society of Hematology, the European Hematology Association, the European Society for Medical Oncology, the European Multidisciplinary Cancer Congress, the International Society for Pharmacoeconomics and Outcomes Research and the Multinational Association of Supportive Care in Cancer. Complete search strings are listed in Online Resource 1. The electronic database searches included articles published up to April 2013 and were restricted to English-language studies. Conference abstracts were limited to those published between January 2009 and April 2013. This report follows the PRISMA statement for reporting systematic reviews and meta-analyses [13].

Study selection

Initially, two independent reviewers screened the titles and abstracts of the search results for studies of human adult haematology or oncology patients who were receiving long-acting-G-CSF primary prophylaxis to reduce the risk of CIN during chemotherapy. Studies in which patients received bone marrow transplantation were excluded. Clinical trials and observational studies were included. Editorials, letters, case reports, guidelines, health technology assessment reports, economic evaluations, narrative reviews and research protocols were excluded. Papers were excluded if they did not report neutropenia-related outcomes. Full texts of the remaining articles were then assessed by the reviewers for final inclusion. Additional exclusion criteria were applied at this second stage: studies comparing pegfilgrastim with a daily G-CSF, placebo or no prophylaxis were excluded if fewer than 50 patients received pegfilgrastim; studies with pegfilgrastim alone (which therefore allowed no comparisons) were excluded if fewer than 100 patients received pegfilgrastim. Studies in which pegfilgrastim was used outside of its approved indication were excluded. These additional exclusion criteria were not applied to studies involving new long-acting G-CSFs because we expected to find far fewer papers on these and wanted to ensure that all available data on these other agents were captured. Papers or abstracts reporting results from the same study were indicated as such. If a study included in the form of a congress abstract was published as a peer-reviewed paper after our literature search, we included the paper in place of the congress abstract.

Data extraction

The data collection comprised study and patient characteristics, efficacy (effect of a treatment under controlled, clinical

trial conditions), effectiveness (effect of a treatment under uncontrolled, real-world conditions) and safety. Detailed definitions of outcome measures are listed in Online Resource 2. Studies were classified according to their design: 'RCTs' where patients were randomised to G-CSFs; clinical trials in which patients were not randomly assigned to neutropenia prophylaxis or no treatment were termed 'clinical trials'; and studies of routine clinical practice were termed 'observational studies'. Evidence found in the literature was extracted as presented by the original authors of the study.

Risk of bias assessment

Two independent reviewers assessed risk of bias; disagreements were resolved within the reviewer team by consensus. RCTs were assessed using the Cochrane Collaboration's assessment tool [14]. Non-randomised studies were assessed using the Methods Guide for Comparative Effectiveness Reviews of the US Agency for Healthcare Research and Quality [15]. Six domains of bias (selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias) were assessed. Based on the reviewers' judgments, every article was rated as having a 'low', 'high' or 'unclear' risk of bias. Risk of bias was not assessed for conference abstracts.

Results

Eligible trials and study characteristics

Our search identified 731 full publications and 108 congress abstracts (Fig. 1). After removing duplicates, 700 items were left, of which 482 were excluded on the basis of title and abstract screening, leaving 218 articles (Online Resource 3). Three relevant articles were published after completion of the search: Bondarenko et al. (2013) [16], Almenar-Cubells et al. (2013) [17] and Volovat et al. (2013) [18]; these were included to replace congress abstracts identified by the initial search that described the same studies [19–21]. Finally, 33 publications and 11 congress abstracts representing 41 studies were analysed. Key characteristics of the included studies are presented in Table 1.

Figure 2 illustrates the number of patients exposed to each of the included substances or treatment strategies, the G-CSF interventions used and the study design. The studies included 13 that looked at pegfilgrastim alone, 15 studies in which pegfilgrastim was compared with a daily G-CSF, three studies in which pegfilgrastim was compared with placebo and two studies in which pegfilgrastim primary prophylaxis was compared with no pegfilgrastim primary prophylaxis. We found eight studies that compared other long-acting G-CSFs with daily G-CSFs, pegfilgrastim or placebo. The number of patients who received a long-acting G-CSF was 50,089 (pegfilgrastim=49,207; lipegfilgrastim=505; balugrastim=281; Maxy-G34=27; Ro 25-8315=28; BCD-017=41).

Pegfilgrastim studies included patients with breast, lung, colorectal or gastro-esophageal cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, acute myeloid leukaemia and various other solid tumours. These studies included patients taking 12 standard chemotherapy regimens and numerous non-standard regimens. All studies of newer long-acting G-CSFs except one (which looked at lipegfilgrastim in non-small cell lung cancer [22]) were conducted in patients with breast cancer, most of whom were receiving docetaxel and doxorubicin.

Risk of bias assessment

Risk of bias was typically higher in non-randomised trials and observational studies than in RCTs (Fig. 3). Most studies excluded patients receiving concomitant antibiotic prophylaxis or who had previously received chemotherapy; therefore, risk of performance bias was low. Risk of reporting bias was difficult to assess across all types of studies because the study protocols were not published.

Efficacy and effectiveness of pegfilgrastim

Table 2 shows efficacy and effectiveness endpoints for studies of pegfilgrastim alone or compared with daily G-CSFs, placebo or no treatment.

Incidence of FN

Three RCTs reported a significant reduction in FN for pegfilgrastim versus placebo (1 % vs 17 % [23], 2 % vs 6 % [24, 25] and 2 % vs 8 % [26]) in patients with breast or colorectal cancer receiving chemotherapy regimens associated with various FN risk profiles. One RCT designed to demonstrate non-inferiority in duration of severe neutropenia reported a significant reduction in FN incidence for pegfilgrastim versus filgrastim (9 % vs 18 %) in patients with breast cancer [27]. Another RCT with a similar design found a non-significant trend towards lower FN incidence for pegfilgrastim versus filgrastim (13 % vs 20 %) [28].

Ten clinical trials reported FN incidence across numerous tumour and chemotherapy types, including several dose-dense regimens. In eight of these trials, all patients received pegfilgrastim; FN incidence ranged from 1 to 10 % [29–36]. A study in which FN prophylaxis was changed by protocol amendment in subsequent cohorts of patients with primary breast cancer treated with a high FN-risk regimen (docetaxel, doxorubicin and cyclophosphamide) found a significant reduction in the incidence of FN for pegfilgrastim versus daily G-CSF (7 % vs 18 %) [37]. In contrast, another breast cancer

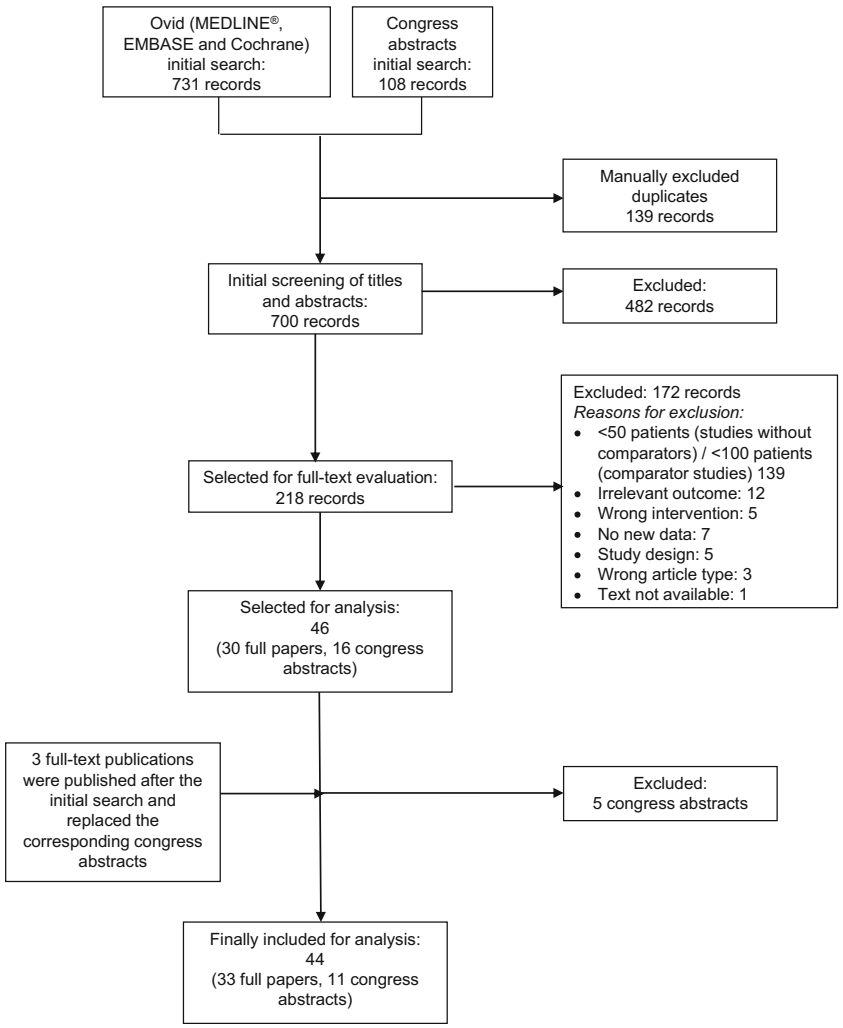

Fig. 1 PRISMA flow diagram

trial in which G-CSF schedules were selected at the physician's discretion reported a higher FN incidence for pegfilgrastim versus filgrastim (11 % vs 4 %) [38].

Observational studies showed FN incidence was higher among patients with haematological malignancies (14–16 %) [39, 40] than in those with solid tumours (4–12 %) [41–43, 17, 44–46]. Five of these observational studies that reported FN incidence compared neutropenia prophylaxis: two studies across various tumour types reported trends towards reduced FN incidence with pegfilgrastim versus daily G-CSF (11 % vs 24 % and 7 % vs 13 %, respectively) [17, 44], one found a significant reduction (5 % vs 7 %) [45] and two did not find a difference for pegfilgrastim versus filgrastim in non-Hodgkin's lymphoma (NHL) [39] and breast cancer [47]. Significant reductions in FN incidence for pegfilgrastim primary prophylaxis versus no pegfilgrastim primary prophylaxis were also seen in observational studies of patients with breast cancer (4 % vs 30 %) and in patients with various tumour types (odds ratio [95 % confidence interval (CI)]= 0.49 [0.34–0.68]) [48, 41].

Incidence of CIN

An RCT in patients with colorectal cancer treated with chemotherapy with a low FN risk (FOLFOX, FOLFIRI or FOIL) found pegfilgrastim significantly reduced CIN incidence compared with placebo (13 % vs 43 %) [26]. RCTs comparing pegfilgrastim with filgrastim in a non-inferiority setting reported no significant difference in CIN incidence in patients with breast cancer receiving chemotherapy associated with a high FN risk [27, 28].

In clinical trials investigating dose-dense regimens, CIN incidence with pegfilgrastim was low and ranged from 3 to 11 % in patients with breast cancer [29, 31, 32] and 34 % in gastro-esophageal cancer [34]. In studies of standard-dose chemotherapy regimens across various tumour types, CIN incidence ranged from 22 to 30 % [36, 35]. One trial reported that pegfilgrastim significantly reduced the incidence of CIN compared with daily G-CSF (37 % vs 58 %) in patients with breast cancer [37].

Table 1 Overview of study and patient characteristics of included studies

Author, year	Study design	Chemotherapy regimen	G-CSF interventions (dose)	Primary endpoint	Tumour type	Mean/median* age± SD (range)	Follow-up (mean)
RCTs							
Bondarenko et al. 2013 [16]	RCT	Doxorubicin/docetaxel	Lipegfilgrastim (6 mg) *n*=101 Pegfilgrastim (6 mg) *n*=101	Duration of SN in cycle 1	Breast cancer	Lipegfilgrastim 49.9±10.1 Pegfilgrastim 51.1±9.4	4 cycles
Buchner et al. 2011 [55] congress abstract	RCT	Doxorubicin/docetaxel	Lipegfilgrastim (3 mg; 4.5 mg; 6 mg) *n*=53; *n*=51; *n*=50 Pegfilgrastim (6 mg) *n*=54	Duration of SN in cycle 1	Primary breast cancer	–	4 cycles
Gladkov et al. 2012 [63] congress abstract	RCT	Doxorubicin/docetaxel	Balugrastim (40 mg; 50 mg) or pegfilgrastim (6 mg) *n*=256	Duration of SN in cycle 1	Breast cancer	–	–
Green et al. 2003 [28]	RCT	Doxorubicin/docetaxel	Pegfilgrastim (6 mg) *n*=77 Filgrastim (5 μg/kg/day) *n*=75	Duration of grade 4 neutropenia in cycle 1	High-risk breast cancer	Pegfilgrastim 52.1 (31–75) Filgrastim 52.8 (30–74)	4 cycles
Holmes et al. 2002 [27]	RCT	Doxorubicin/docetaxel	Pegfilgrastim (100 μg/kg) *n*=150 Filgrastim (5 μg/kg/day) *n*=151	Duration of grade 4 neutropenia in cycle 1	Breast cancer	Pegfilgrastim 50.9± 11.7 Filgrastim 51.9± 11.1	4 cycles
Salafet et al. 2013 [56] congress abstract	RCT	Doxorubicin/docetaxel	BCD-017 (3 mg; 6 mg) *n*=21; *n*=20 Filgrastim (5 mg/kg/day) *n*=19	Incidence of SN	Breast cancer	–	–
Viens et al. 2002 [57]	RCT	Doxorubicin, cyclophosphamide	Ro 25-8315 (20 μg/kg; 60 μg/kg; 100 μg/kg) *n*=9; *n*=9; *n*=10 Filgrastim (5 μg/kg/day) *n*=8	Peak of circulating CD34+ cells and duration of CIN	Advanced breast cancer	Ro 25-8315 50* (39–57) 54* (37–59) 54* (37–61) Filgrastim 52* (32–56)	–
Vogel et al. 2005 [23][a]	RCT	Docetaxel	Pegfilgrastim (6 mg) *n*=463 Placebo *n*=465	Incidence of FN	Breast cancer	Pegfilgrastim 51.9* (21–88) Placebo 52.1* (24–76)	4 cycles
Volovat et al. 2013 [18][b]	RCT	Doxorubicin/docetaxel	Balugrastim (40 mg) *n*=153 Pegfilgrastim (6 mg) *n*=151	Duration of SN in cycle 1	Breast cancer	Balugrastim 51.5± 10.3 Pegfilgrastim 50.8± 9.7	4 cycles
Gladkov et al. 2012 [22] congress abstract	RCT	Cisplatin/etoposide	Lipegfilgrastim (6 mg) *n*=250 Placebo *n*=125	Incidence of FN during cycle 1	NSCLC	–	–
Decaestecker et al. 2013, Pinter et al. 2013 [24, 25] congress abstracts	RCT	FOLFOX/FOLFIRI plus bevacizumab	Pegfilgrastim (6 mg) *n*=422 Placebo *n*=423	Incidence of grade 3/4 neutropenia	Advanced/metastatic colorectal cancer	–	4 cycles
Hecht et al. 2010 [26]	RCT	FOLFOX, FOLFIRI, FOIL	Pegfilgrastim (6 mg) *n*=123		Colorectal cancer	Pegfilgrastim 62.4* (28–85)	17.1 months

Table 1 (continued)

Author, year	Study design	Chemotherapy regimen	G-CSF interventions (dose)	Primary endpoint	Tumour type	Mean/median* age± SD (range)	Follow-up (mean)
			Placebo n=118	Incidence of grade 3/4 neutropenia in first 4 cycles		Placebo 62.9* (18–87)	
Clinical trials							
Braess et al. 2009 [64]	Clinical, non-comparative	S-HAM	Pegfilgrastim (6 mg) n=172	Overall toxicity and early death rate	De novo AML	54* (18–83)	13 months
Burstein et al. 2005 [29]	Clinical, non-comparative	AC followed by paclitaxel	Pegfilgrastim (6 mg) n=135	Incidence of FN	Breast cancer	48* (28–71)	4 cycles AC+4 cycles paclitaxel
Hendler et al. 2011 [38][c]	Clinical, comparative	AC followed by paclitaxel	Pegfilgrastim (6 mg) n=57 Filgrastim (300 μg, days 3–10; days 3–7; days 5, 7, 9, 11) n=174	Incidence of FN, hospitalisation, dose delays	Breast cancer	Pegfilgrastim 52* (27–73) Filgrastim 52* (26–71) 54* (38–69) 48* (28–74)	4 cycles+12 weeks
Loibl et al. 2011 [30][d]	Clinical, non-comparative	Epirubicin, docetaxel, cyclophosphamide	Pegfilgrastim (6 mg) n=174	Grade 4 leukopenia	Breast cancer	49* (29–68)	–
Pippen et al. 2011 [31]	Clinical, non-comparative	Dose-dense AC followed by paclitaxel+ bevacizumab	Pegfilgrastim (6 mg) n=197	Incidence of treatment-related adverse events	Breast cancer	51.2±9.2	4 cycles+4 cycles+ 10 cycles
Schwartzberg et al. 2009 [58] congress abstract	Clinical, comparative	Docetaxel, adriamycine, cyclophosphamide	Maxy-G34 (10; 30; 45; 60; 100 μg/kg) n=6; 6; 6; 6; 3 Pegfilgrastim n=8	Duration of severe, grade 4 neutropenia in cycle 1	High-risk breast cancer	–	6 cycles
von Minckwitz et al. 2008 [37][e]	Clinical, comparative	Docetaxel, doxorubicin, cyclophosphamide	Pegfilgrastim (6 mg) n=303 Filgrastim or lenograstim n=374	Incidence of FN	Primary breast cancer	–	6 or 8 cycles
Yardley et al. 2010 [32]	Clinical, non-comparative	Gemcitibine, epirubicin and paclitaxel	Pegfilgrastim (6 mg) n=123	Pathological complete response rate	Breast cancer	51* (29–82)	35 months
Miller et al. 2008 [33]	Clinical, non-comparative	Docetaxel and cisplatin with or without BNP7787	Pegfilgrastim (6 mg) n=151	Neurotoxicity	NSCLC	62* (30–88)	21.7 months
Toppo et al. 2013 [34] Congress abstract	Clinical, non-comparative	Dose-dense TCF	Pegfilgrastim (6 mg) n=128	–	Gastro-esophageal cancer	65* (31–81)	44 months
Balducci et al. 2007 [36][f]	Clinical, non-comparative	Various	Pegfilgrastim (6 mg) n=343/73 (PP)	Incidence of FN	Solid tumours/NHL	72* (65–88)	–
Ozer et al. 2007 [35] sub-analyses: Noga et al. 2007 [65], Rader et al. 2010 [66]	Clinical, non-comparative	Various	Pegfilgrastim (6 mg) n=2,112 n=325 n=971	Hospitalisation, dose delay/reduction	Various NHL Breast cancer	59*±12.8 65* (24–93) 54* (19–84)	4–8 cycles Up to 8 cycles
Observational studies							
Chan et al. 2011 [39]	Comparative, observational (retrospective)	Various	Pegfilgrastim n=123 Filgrastim n=81	Incidence of FN	NHL	Pegfilgrastim 55.3±14.8 Filgrastim 56.7±13.1	Pegfilgrastim 5.5 cycles Filgrastim 3.9 cycles

Table 1 (continued)

Author, year	Study design	Chemotherapy regimen	G-CSF interventions (dose)	Primary endpoint	Tumour type	Mean/median* age± SD (range)	Follow-up (mean)
Ng et al. 2011 [40]	Non-comparative, observational (retrospective)	CHOP-21 or CHOP-14	Pegfilgrastim (PP/SP) *n*=132	Incidence of breakthrough FN	Various (80 % DLBCL)	55* (49–65)	–
Salar et al. 2009 [49] congress abstract	Comparative, observational (prospective)	Various (76 % CHOP-R)	Pegfilgrastim (PP/SP) *n*=127 (~100 PP) Filgrastim (PP/SP) *n*=118 (~84 PP)	Incidence of grade 3/4 neutropenia	NHL (97 %) HL (3 %)	58* (19–85)	8 cycles or end of chemotherapy
Hamilton et al. 2013 [41] congress abstract	Comparative, observational (retrospective)	Adjuvant docetaxel/ cyclophosphamide	Upfront pegfilgrastim *n*=153 No upfront pegfilgrastim *n*=87	Incidence of FN	Breast cancer	Upfront pegfilgrastim 57[#] No upfront pegfilgrastim 52[#]	–
Jenkins et al. 2012 [42][g]	Non-comparative, observational (retrospective)	Docetaxel, adriamycine, cyclophosphamide	Pegfilgrastim (6 mg) *n*=263	Incidence of FN	Breast cancer	48* (27–66)	6 cycles
Leung et al. 2012 [47] congress abstract	Comparative, observational (prospective)	58 % docetaxel-based chemotherapy	Pegfilgrastim (6 mg) *n*=~93 Filgrastim (300 μg) *n*=~47	Incidence and severity of muscle and/or joint pain	Breast cancer	52	2 cycles
Ngamphaiboon et al. 2012 [43]	Non-comparative, observational (retrospective)	TC	Pegfilgrastim (6 mg) *n*=111	Incidence of FN	Breast cancer	56* (27–79)	19.1 months
Almenar et al. 2009 [44]	Comparative, observational (retrospective)	Various	Pegfilgrastim (PP) *n*=75 Filgrastim/Lenograstim (PP) *n*=99; 12	Incidence of CIN, FN, hospitalisation, antibiotic use	Various	Pegfilgrastim 57.0±14.8 Daily G-CSF 55.4±14.5	–
Almenar-Cubells et al. 2013 [17]	Comparative, observational (retrospective)	Various	Pegfilgrastim *n*=180 (107 PP, 53 SP, 20 reactive) Filgrastim/lenograstim *n*=196; *n*=15 (78 PP, 50 SP, 83 reactive)	Incidence of grade 3/4 neutropenia	Solid tumours, except breast cancer	Pegfilgrastim: 57.9±13.7 Daily G-CSF: 61.7±12.2	–
Heaney et al. 2009 [51]	Comparative, observational (retrospective)	Various	Pegfilgrastim (PP/SP) *n*=982 Sargramostim (PP/SP) *n*=982	Infection-related hospitalisation	Various	Pegfilgrastim 58.6±11.5 Sargramostim 57.5±11.6	–
Henk et al. 2013 [54]	Comparative, observational (retrospective)	Various	Pegfilgrastim (PP/SP) *n*=8,569+6,719 Filgrastim (PP/SP) *n*=621+628 Sargramostim (PP/SP) *n*=140+94	Neutropenia-related and all-cause hospitalisation	Various	Pegfilgrastim 56.1±11.3 Filgrastim 56.6±11.3 Sargramostim 60.0±11.8	–
Hershman et al. 2009 [48]	Comparative, observational (retrospective)	Various	Pegfilgrastim *n*=721 No G-CSF *n*=778	Incidence of FN	Solid tumour, lymphoma	–	1–8 cycles
Jurczak et al. 2013 [46] congress abstract	Non-comparative, observational (prospective)	Various	Pegfilgrastim (PP) *n*=1,006	Incidence of FN and safety	Solid tumour, lymphoma	55* (18–86)	–
		Various				–	1–8 cycles

Table 1 (continued)

Author, year	Study design	Chemotherapy regimen	G-CSF interventions (dose)	Primary endpoint	Tumour type	Mean/median* age± SD (range)	Follow-up (mean)
Morrison et al. 2007 [45]	Comparative, observational (retrospective)		Pegfilgrastim n=1,412 (60 % PP) Filgrastim n=1,451 (59 % PP)	Describe use of G-CSF, incidence of FN	Solid tumour, lymphoma		
Naeim et al. 2013 [50]	Comparative, observational (retrospective)	Various	Pegfilgrastim (PP/SP) n=3,372 Filgrastim (PP/SP) n=163	Risk of hospitalisation	Solid tumour, NHL	Pegfilgrastim 55.1±10.7 Filgrastim 57.5±12.6	–
Tan et al. 2011 [52]	Comparative, observational (retrospective)	Various	Pegfilgrastim (PP/SP) n=4,955 Filgrastim (PP/SP) n=616	–	Various	Pegfilgrastim 57.1±11.6 Filgrastim 58.4±11.0	–
Weycker et al. 2009 [53]	Comparative, observational (retrospective)	Various	Pegfilgrastim (PP/SP) n=14,570 Filgrastim (PP/SP) n=1,193	–	Various	Pegfilgrastim 59* (18–98) Filgrastim 60* (19–90)	1–9 cycles

The study design was reported from the perspective of the granulocyte colony-stimulating factor used, e.g. if the study was a randomised controlled trial and patients were randomised according to the chemotherapy regimen and all patients received pegfilgrastim, it was defined as clinical, non-randomised, non-comparative trial. Blank cells indicate that the information was not available.

AC doxorubicin, cyclophosphamide; *AML* acute myeloid leukaemia; *CHOP* cyclophosphamide, doxorubicin, vincristin and prednisone; *CIN* chemotherapy-induced neutropenia; *DLBCL* diffuse large B-cell lymphoma; *FN* febrile neutropenia; *FOIL* 5-fluorouracil, leucovorin, oxaliplatin, irinotecan; *FOLFIRI* 5-fluorouracil, leucovorin, irinotecan; *FOLFOX* 5-fluorouracil, leucovorin, oxaliplatin; *G-CSF* granulocyte-stimulating factor; *HL* Hodgkin's lymphoma; *NHL* non-Hodgkin's lymphoma; *NSCLC* non-small cell lung cancer; *PP* primary prophylaxis; *R* rituximab; *RCT* randomised controlled trial; *SD* standard deviation; *S-HAM* high-dose cytosine arabinoside and mitoxantrone; *SN* severe neutropenia; *SP* secondary prophylaxis; *TC* docetaxel, cyclophosphamide; *TCF* docetaxel, cisplatin, I-folinic acid, 5-fluorouracil

[#] Not stated in the manuscript if mean or median was reported

[a] Patients with febrile neutropenia received open-label pegfilgrastim

[b] 77 additional patients were enrolled and treated open-label with balugrastim

[c] The three groups receiving different schedules of filgrastim were combined to one 'filgrastim' group

[d] Only the patients randomised to receive pegfilgrastim on day two were included

[e] Patients receiving concomitant ciprofloxacin (n=567) were excluded from this review

[f] Patients receiving pegfilgrastim at physician discretion (n=416) were excluded

[g] 185 patients received prophylactic antibiotics

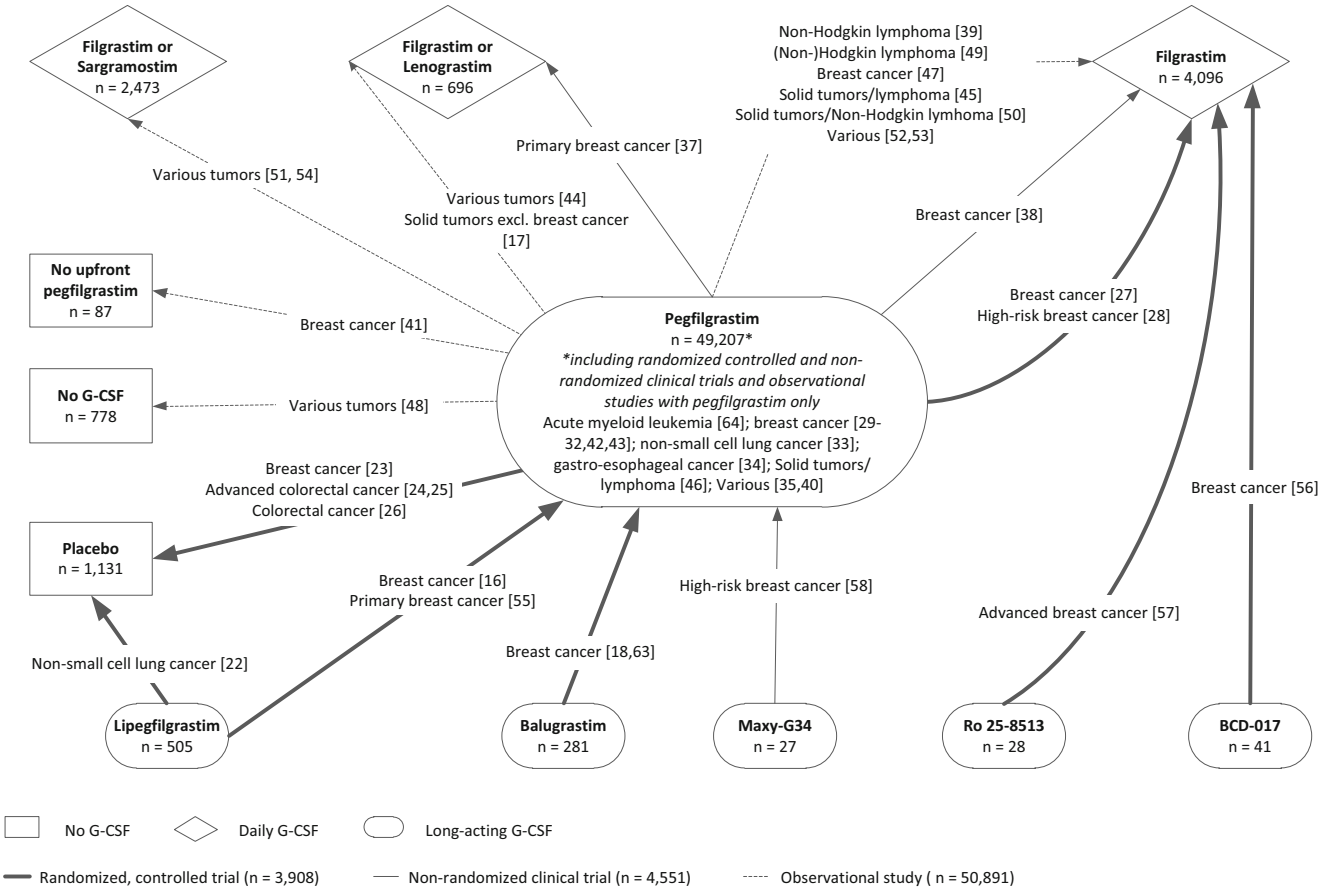

Fig. 2 Network diagram. The total number of patients included in randomised controlled trials, clinical trials and observational studies, and in whom a given granulocyte colony-stimulating factor (G-CSF) has been investigated, is stated below the G-CSF's or comparator's name. Single-arm studies including pegfilgrastim only are reported in the 'Pegfilgrastim' shape. Comparisons between G-CSFs are indicated by *arrows* specifying the type of study. The *arrows* point from the investigated G-CSF to the comparator

Three observational studies reporting CIN incidence compared neutropenia prophylaxis; a difference was not found between pegfilgrastim and filgrastim in patients with breast cancer [47], but in patients with various tumours or NHL CIN incidence was lower in those receiving pegfilgrastim than those receiving daily G-CSF (28 % vs 49 % and 41 % vs 50 %) [17, 49].

Incidence of hospitalisations due to CIN or FN

One RCT reported a significant reduction in FN-related hospitalisations in patients with breast cancer who received pegfilgrastim versus placebo (1 % vs 14 %) [23], while another in patients with colorectal cancer found no significant difference in CIN-related hospitalisations [26].

In a clinical trial including patients with various tumour types receiving pegfilgrastim primary prophylaxis in community-based practices in the USA, the incidence of FN-related hospitalisations was 4 % [35]. A similar study in elderly patients found the incidence of CIN- or FN-related hospitalisations was 5 % [36]. Two clinical trials of patients with breast cancer found no significant difference in incidence and duration of FN-related hospitalisations between pegfilgrastim and daily G-CSFs [37, 38].

Three retrospective observational studies enrolling patients with various tumour types found trends towards reduced incidence of hospitalisations due to FN for pegfilgrastim versus daily G-CSF (9 % vs 20 %, 3 % vs 11 % and 3 % vs 7 %) [17, 44, 50], whereas another found no significant difference between sargramostim and pegfilgrastim [51]. Two other retrospective observational studies [52, 53] reported significant decreases in the risk of CIN-related hospitalisations for pegfilgrastim compared with filgrastim (1 % vs 4 % and 1 % vs 2 %); findings supported by a study of two US databases that found pegfilgrastim reduced the risk of neutropenia-related hospitalisation compared with filgrastim [54].

Incidence of chemotherapy dose reductions and delays

In one RCT in patients with breast cancer receiving pegfilgrastim or placebo, there was no significant difference in the proportion of patients receiving their full chemotherapy

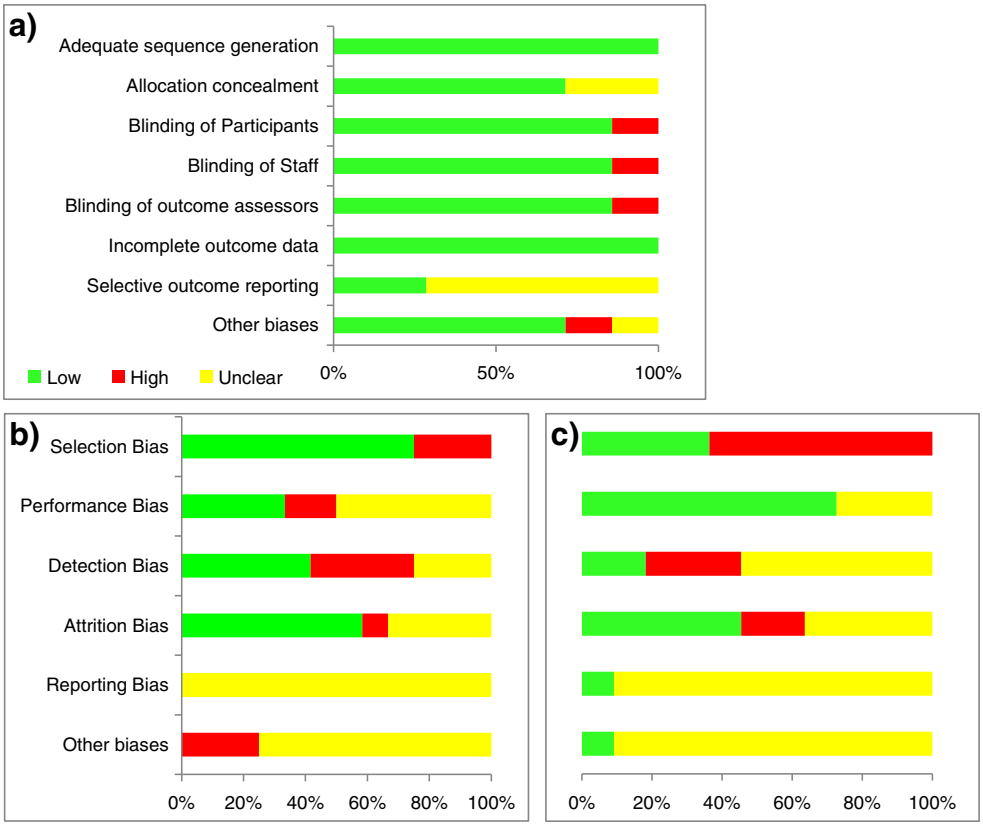

Fig. 3 Risk of bias assessment of included studies. **a** Randomised controlled trials (RCTs) are defined as those studies in which patients were randomised to a granulocyte colony-stimulating factor (G-CSF). Adequate sequence generation and allocation concealment refers to selection bias, blinding of participants and staff to performance bias, blinding of outcome assessors to detection bias, incomplete outcome data to attrition bias and selective outcome reporting refers to reporting bias. **b** Non-randomised clinical trials are those in which patients were not randomised to a G-CSF. The risk of bias assessment includes non-randomised clinical trials and observational studies that included more than one G-CSF. **c** The risk of bias assessment includes non-randomised clinical trials and observational studies that included pegfilgrastim only

dose on schedule [23]; however, cross-over from the placebo to the pegfilgrastim arm was allowed if FN occurred. Another RCT in colorectal cancer reported a significant decrease in dose reductions (3 % vs 11 %) and delays (4 % vs 20 %) due to neutropenia for pegfilgrastim versus placebo [26].

There was a wide range of incidence of dose delays and reductions in the clinical trials (2–77 % and 2–33 %, respectively), but most papers did not specify whether or not the chemotherapy modifications were due to neutropenia [38, 31, 34, 35]. Only one clinical trial compared the incidence of dose delays (due to FN events and non-haematological toxicity) with pegfilgrastim and filgrastim in patients with breast cancer. It found no significant difference between the two arms [38].

Rates of dose delays and reductions in observational studies also varied considerably between trials (5–55 % and 5–42 %, respectively) [39–41, 43, 17, 44]. One study found a significantly lower incidence of delays for pegfilgrastim primary prophylaxis versus no pegfilgrastim primary prophylaxis in patients with breast cancer (5 % vs 12 %), but found no significant difference in dose reductions [41]. In two studies of patients with various tumour types, fewer dose delays (42 % vs 55 %) [17] and dose reductions (32 % vs 38 % and 7 % vs 21 %) [17, 44] due to neutropenia for pegfilgrastim versus daily G-CSF were observed. In a population of Asian patients with NHL, rates of dose reductions and delays were slightly higher in patients who received pegfilgrastim than in those who received filgrastim [39].

Antibiotic use

In one RCT, a non-significant reduction in antibiotic use was reported for pegfilgrastim versus filgrastim (17 % vs 21 %) in patients with breast cancer [28]. Two RCTs reported a significant reduction in the use of antibiotics due to FN for pegfilgrastim versus placebo, one in breast cancer (2 % vs 10 %) [23] and one in colorectal cancer (2 % vs 7 %) [26].

A clinical trial in breast cancer found no significant difference in the use of antibiotics between patients receiving pegfilgrastim and filgrastim (11 % vs 4 %) [38].

An observational study found a significant reduction in the use of antibiotics for pegfilgrastim primary prophylaxis versus no pegfilgrastim primary prophylaxis (28 % vs 46 %) in patients with breast cancer [41]. Two observational studies in patients with various tumour types found lower rates of FN-related antibiotic use in patients who received pegfilgrastim than those receiving daily G-CSF (4 % vs 11 % and 8 % vs 17 %); in the former study, this difference reached significance [17, 44].

Safety of pegfilgrastim

Table 2 shows safety endpoints for studies of pegfilgrastim alone or compared with daily-G-CSFs, placebo or no treatment.

Table 2 Efficacy, effectiveness and safety of pegfilgrastim

Author, year	G-CSF intervention	Tumour type	Incidence of FN % (95 % CI)	Efficacy and effectiveness				Safety
				Incidence/duration of neutropenia %/days (95 % CI)	Incidence/duration of hospitalisations %/days (95 % CI)	Incidence of chemotherapy delivery parameter % (95 % CI)	Incidence of antibiotic use % (95 % CI)	Incidence of AEs (%)
RCTs								
Green et al. 2003 [28]	Pegfilgrastim n=77 Filgrastim n=75	High-risk breast cancer	13 % vs 20 % −7 % (−19 %, 5 %) NS	Grade 4 cycle 1: 84 % vs 83 % 0.2 days (−0.2, 0.6) NS	18 % vs 31 %	Reduction: ~5 % had >25 % Dose on schedule: 90 %	17 % vs 21 %	G-CSF-related: All: 57 % vs 58 % Severe: 1.3 % vs 2.7 % Bone pain: All: 37 % vs 42 % Severe: 1 % vs 8 %
Holmes et al. 2002 [27]	Pegfilgrastim n=147 Filgrastim n=150	Breast cancer	9 % vs 18 % −9 % (−17 %, −1 %) p=0.029	Grade 4 cycle 1: 77 % vs 79 % p>0.500 1.73 days vs. 1.76 days (−0.03 days (−0.4, 0.3)) NS	–	–	–	Skeletal pain: All: 25 % vs 26 % G-CSF-related: Severe: 19 % vs 20 %
Vogel et al. 2005 [23][a]	Pegfilgrastim n=463 Placebo n=465	Breast cancer	1 % vs 17 % −16 % (−19 %, −12 %) OR 15.0 (6.5, 34.6) p<0.001	–	Due to FN: 1 % vs 14 % OR 12 (5.2, 27.8) p<0.001	Full dose on schedule: 80 % vs 78 %	To treat FN: 2 % vs 10 % OR 7.5 (3.4, 16.7) p<0.001	Bone pain: All: 31 % vs 27 % Severe: 2 % vs 1 %
Decaestecker et al. 2013 [24], Pinter et al. 2013 [25] Cong. abstracts	Pegfilgrastim n=422 Placebo n=423	Advanced/metastatic colorectal cancer	2.4 % vs 5.7 % −3.3 % (−6.6 %, 0 %) OR 0.4 (0.2, 0.9) p=0.014	–	–	–	–	–
Hecht et al. 2010 [26]	Pegfilgrastim n=123 Placebo n=118	Colorectal cancer	2 % vs 8 % OR 0.3 (0.1–1.0) p=0.04	Grade 3/4: 13 % vs 43 % OR 0.2 (0.1–0.4) p<0.0001	Due to neutropenia: 6 % vs 8 % p=0.55	Due to neutropenia: Reduction: 3.3 % vs 11 % p=0.02 Delay: 4.1 % vs 19.5 % p<0.001	Due to FN: 2 % vs 7 % OR 0.2 (0.1, 1.1) p=0.046	Bone pain: All: 10.5 % vs 0.9 % Severe: 0.8 % vs 0 %
Clinical trials								
Braess et al. 2009 [64]	Pegfilgrastim n=172	De novo AML	–	Median time to leukocyte recovery (>1,000/μL): 31 days	–	–	–	–
Burstein et al. 2005 [29]	Pegfilgrastim n=135	Breast cancer	1.5 %	Grade 3/4: 3 %	–	Planned dose on time: 88.4 %	–	Musculoskeletal pain: All: 7–26 % Severe: 5 %
Hendler et al. 2011 [38][b]	Pegfilgrastim n=57 Filgrastim n=174	Breast cancer	10.5 % vs 4.0 %	–	Due to FN: 10.5 % vs 4.0 % 3 days (range 1–7)	Delay: 3.0 % vs 16.1 % NS	10.5 % vs 4.0 %	–
Loibl et al. 2011 [30][c]	Pegfilgrastim n=174	Breast cancer	4.7 %	–	–	–	–	–
Pippen et al. 2011 [31]	Pegfilgrastim n=197	Breast cancer	7 %	9 %	–	Due to adverse events: Reduction: 14 %	–	Severe myalgia: 9 % Severe arthralgia: 8 %

Table 2 (continued)

Author, year	G-CSF intervention	Tumour type	Incidence of FN % (95 % CI)	Efficacy and effectiveness				Safety
				Incidence/duration of neutropenia %/days (95 % CI)	Incidence/duration of hospitalisations %/days (95 % CI)	Incidence of chemotherapy delivery parameter % (95 % CI)	Incidence of antibiotic use % (95 % CI)	Incidence of AEs (%)
von Minckwitz et al. 2008 [37][d]	Pegfilgrastim n=303 Daily G-CSF n=374	Primary breast cancer	7 % vs 18 % p<0.001	Grade 4: 37 % vs 58 % p<0.01	Due to FN: <1 % vs 1 % Due to neutropenia: 1 % vs 1 %	Delay: 49.5 % –	–	–
Yardley et al. 2010 [32]	Pegfilgrastim n=123	Breast cancer	Grade 3 FN: 1 %	Grade 3/4: 11 %	–	–	–	Severe myalgia/ arthralgia: 7 %
Miller et al. 2008 [33]	Pegfilgrastim n=151	NSCLC	3.3 %	–	–	–	–	–
Toppo et al. 2013 [34] Cong. abstract	Pegfilgrastim n=128	GEC	Grade 3/4 FN: 10 %	Grade 3/4: 34 %	–	Reduction: 33 % Delay: 77 %	–	–
Balducci et al. 2007 [36][e]	Pegfilgrastim n=343	Solid tumours	4 % (2 %, 6 %)	Grade 3/4: 30 % (25 %, 35 %)	Due to neutropenia/ FN: 5 % (3 %, 7 %)	Due to neutropenia: Reduction: 2 % (1 %, 4 %) Delay: 5 % (3 %, 7 %)	Due to neutropenia: 10 %	Bone pain: All: 12 % Arthralgia was noted related to pegfilgrastim
	n=73	NHL	15 % (8 %, 25 %)	Grade 3/4: 82 % (72 %, 90 %)	Due to neutropenia/ FN: 17 % (10 %, 28 %)	Due to neutropenia: Reduction: 16 % (9 %, 27 %) Delay: 25 % (15 %, 36 %)	Due to neutropenia: 55 %	
Ozer et al. 2007 [35]	Pegfilgrastim n=2,112	Various	5.6 % (4.6 %, 6.7 %)	Grade 3/4: 29.5 % (27.6 %, 31.5 %)	Due to FN: 3.5 % (3.7 %, 4.3 %)	Due to neutropenia: Reduction: 2.9 % Delay: 2.1 %	Due to neutropenia: 5.7 % iv, 12.0 % oral Due to FN: 3.6 % iv	G-CSF-related: Severe: 0.5 % Musculoskeletal pain: Severe: 0.1 %
Observational studies								
Chan et al. 2011 [39]	Pegfilgrastim: n=123 Filgrastim: n=81	NHL	16.3 % vs 13.6 % p=0.69	–	–	Reduction: 10.6 % vs 9.9 %, p=1.0 Delay: 18.7 % vs 16 %, p=0.71	–	–
Ng et al. 2011 [40]	Pegfilgrastim n=132	Various (80.3 % DLBCL)	13.6 %	–	Due to FN: CHOP-14: 11.7 % CHOP-21: 23.6 %	Due to FN: Reduction/delay: CHOP-14: 10 %/ 16.7 % CHOP-21: 41.7 %/ 19.4 %	–	–
Salar et al. 2009 [49] Cong. abstract	Pegfilgrastim n=127 (100 PP) Filgrastim n=119 (84 PP)	NHL (96.6 %), HL (3.4 %)	PP: 15.8 % SP: 21.8 %	Grade 3/4: 41.1 % vs 50.0 %	Due to FN: 12 % 5.9 days vs 12.4 days	Full dose on schedule: 72.1 % vs 61.2 %	–	–
Hamilton et al. 2013 [41]	Upfront pegfilgrastim n=153	Breast cancer	4 % vs 30 % adj. OR 0.10	–	11.1 % vs 38 % adj. OR 0.19	Reduction: 8.5 % vs 9.2 %	28.1 % vs 46 % OR 0.43, p=0.004	–

Table 2 (continued)

Author, year	G-CSF intervention	Tumour type	Incidence of FN % (95 % CI)	Efficacy and effectiveness				Safety
				Incidence/duration of neutropenia %/days (95 % CI)	Incidence/duration of hospitalisations %/days (95 % CI)	Incidence of chemotherapy delivery parameter % (95 % CI)	Incidence of antibiotic use % (95 % CI)	Incidence of AEs (%)
Cong. abstract	No upfront pegfilgrastim n=87		p<0.0001		p<0.0001 2.9 vs 3.8 days	OR 0.83, p=0.71 Delay: 4.6 % vs 11.5 % OR 0.33, p=0.046		
Jenkins et al. 2012 [42][f]	Pegfilgrastim n=263	Breast cancer	12 %	–	–	–	–	–
Leung et al. 2012 [47] Cong. abstract	Pegfilgrastim n=93 Filgrastim n=47	Breast cancer	No difference between groups	No difference between groups	–	–	–	Over 50 % of the patients reported muscle and/or joint pain
Ngamphaiboon et al. 2012 [43]	Pegfilgrastim n=111	Breast cancer	7 %	Grade 3/4: 9 %	Due to FN: 6.3 %	Reduction: 5 % Delay: 5 %	0.9 % oral	–
Almenar et al. 2009 [44]	Pegfilgrastim n=75 (29 PP) Daily G-CSF n=111 (44 PP)	Various	10.7 % (5.3 %, 19.9 %) vs 24.3 % (17.2 %, 33.1 %)	–	Due to FN: 9.3 % (4.3 %, 18.3 %) vs 19.8 % (13.4 %, 28.3 %)	Due to neutropenia: Reduction: 6.7 % (2.5 %, 15 %) vs 20.7 % (14.1 %, 29.2 %)	Due to FN: 8 % (3.4 %, 16.7 %) vs 17.1 % (11.2 %, 25.3 %)	G-CSF-related: All: 1.3 % vs 5.4 % Bone pain: All: 1.3 % vs 2.7 %
Almenar-Cubells et al. 2013 [17]	Pegfilgrastim n=180 (107 PP) Daily G-CSF n=211 (78 PP)	Solid tumours except breast cancer	6.7 % vs 13.3 % p=0.032	Grade 3/4: 28.3 % vs 49.3 % p<0.0005	Due to neutropenia: 3.9 % vs 14.7 % p<0.0005 Due to FN: 2.8 % vs 10.9 % p=0.002	Reduction: 31.6 % vs 38.4 % p=0.116 Delay: 41.7 % vs 54.7 % p=0.013	Due to neutropenia: 9.4 % vs 23.7 % p=0.002 Due to FN: 4.4 % vs 11.4 % p=0.013	G-CSF-related: All: 6.1 % vs 9.5 % p=0.219 Bone/muscle pain: All: 1.7 % vs 6.2 % p=0.025
Heaney et al. 2009 [51]	Pegfilgrastim n=982 Sargramostim n=982	Various	–	–	Due to FN: 9 vs 4 events p=0.624	–	–	–
Henk et al. 2013 [54]	Pegfilgrastim (reference) n=8,569/6,719 Filgrastim n=621/628	Various	–	–	Due to neutropenia: HIRD^{SM} database OR 1.8 (1.3, 2.5)/ OptumInsight database OR 2.4 (1.8, 3.1)	–	–	–
Hershman et al. 2009 [48]	Pegfilgrastim n=721 no G-CSF n=778	Various	OR 0.46 (0.31, 0.68) p<0.001	–	–	–	–	–
Jurczak et al. 2013 [46] Cong. abstract	Pegfilgrastim n=1,006	Various	4 %	–	–	–	–	Bone/muscle/joint pain: 6 % No serious pain
Morrison et al. 2007 [45]	(PP/SP) Pegfilgrastim n=1,412 Filgrastim n=1,451	Various	4.7 % vs 6.5 % adj. OR 1.4 (1.0, 2.0) p=0.044	–	–	–	–	–
Naeim et al. 2013 [50]	(PP/SP) Pegfilgrastim	Various	–	–	Due to neutropenia: 2.4 % (2.1 %, 2.7 %) vs	–	–	–

Table 2 (continued)

Author, year	G-CSF intervention	Tumour type	Incidence of FN % (95 % CI)	Efficacy and effectiveness				Safety
				Incidence/duration of neutropenia %/days (95 % CI)	Incidence/duration of hospitalisations %/days (95 % CI)	Incidence of chemotherapy delivery parameter % (95 % CI)	Incidence of antibiotic use % (95 % CI)	Incidence of AEs (%)
	n=3,372				6.7 % (4.4 %, 9.7 %)			
	Filgrastim *n*=163				*p*<0.001			
Tan et al. 2011 [52]	(PP/SP)	Various	–	–	Due to neutropenia:	–	–	–
	Pegfilgrastim				1.1 % vs 3.5 % adj.			
	n=4,955				OR 0.4 (0.2, 0.8)			
	Filgrastim				*p*=0.016			
	n=616							
Weycker et al. 2009 [53]	(PP/SP)	Various	–	–	Due to neutropenia:	–	–	–
	Pegfilgrastim				1.2 % vs 2.1 %			
	n=14,570				adj. OR 0.6 (0.4,			
	Filgrastim				1.0)			
	n=1,193				*p*=0.043			

In the table, the first number corresponds to the upper G-CSF mentioned and the second number corresponds to the lower G-CSF mentioned in the G-CSF intervention column. If available and not otherwise specified, numbers are given in percentages of the patients across all cycles. We also included differences with a 95 % CI and/or OR with a 95 % CI and/or *p* values, if available in the original study. Differences and ORs refer to the upper G-CSF mentioned compared to the lower G-CSF mentioned in the G-CSF intervention column. – indicates that the data was not available.

Adj. Adjusted, *Adv*. advanced, *AEs* adverse events, *CI* confidence interval, *Cong*. Congress, *FN* febrile neutropenia, *G-CSF* granulocyte colony-stimulating factor, *GEC* gastro-esophageal cancer, *DLBCL* diffuse large B-cell lymphoma, *HL* Hodgkin's lymphoma, *iv* intravenous, *meta*. metastatic, *NHL* non-Hodgkin's lymphoma, *NS* not statistically significant, *NSCLC* non-small cell lung cancer, *OR* odds ratio, *PP* primary prophylaxis, *SP* secondary prophylaxis, *RCT* randomised controlled trial

[a] Patients with FN received open-label pegfilgrastim

[b] The three groups receiving different schedules of filgrastim were combined to one 'filgrastim' group

[c] Only the patients randomised to receive pegfilgrastim on day 2 were included

[d] Patients receiving concomitant ciprofloxacin (*n*=567) were excluded from this review

[e] Patients receiving pegfilgrastim at physician discretion (*n*=416) were excluded

[f] 185 patients received prophylactic antibiotics

All G-CSF-related adverse events

Two RCTs in patients with breast cancer reported that G-CSF-related adverse events (AEs) were similar for pegfilgrastim and filgrastim [27, 28]. Another RCT found a non-significant increase in G-CSF-related AEs for pegfilgrastim compared with placebo (11 % vs 1 %) in patients with colorectal cancer, primarily due to increased bone pain [26]. Pegfilgrastim-related serious AEs were also infrequent (0.5 %) in patients with various tumours in a clinical trial [35]. Two observational studies in patients with various tumours reported a non-significant decrease in G-CSF-related AEs for pegfilgrastim versus daily G-CSF (6 % vs 10 % and 1 % vs 5 %) [17, 44]. None of the studies reported any fatal AEs that were attributed to G-CSF prophylaxis.

Musculoskeletal pain

In two placebo-controlled RCTs including patients with breast or colorectal cancer, occurrence of any-grade musculoskeletal pain was higher in the pegfilgrastim arms than the placebo arms (31 % vs 27 % and 11 % vs 1 %) [23, 26]. In two further RCTs of patients with breast cancer randomised to pegfilgrastim or filgrastim, overall rates of bone pain were comparable between arms [27, 28], and severe bone pain appeared reduced for pegfilgrastim versus filgrastim (1 % vs 8 %) [28].

In five non-comparative clinical trials, the incidence of any-grade musculoskeletal pain with pegfilgrastim reported ranged from 7 to 26 % [29, 36] and the incidence of severe musculoskeletal pain ranged from 0 to 9 % [29, 31, 32, 35] across patients with breast cancer and various tumour types.

In general, the reported incidence of musculoskeletal pain was lower in observational studies than in clinical trials. The incidence of any-grade musculoskeletal pain with pegfilgrastim in observational studies varied, from 6 % in one study where all patients received pegfilgrastim (with no patients experiencing serious bone or muscle pain) [46] to 50 % in patients receiving either pegfilgrastim or filgrastim [47]. In two other observational studies of patients with various tumour types that compared pegfilgrastim with daily G-CSF, bone pain was less common in the pegfilgrastim arms (2 % vs 6 % and 1 % vs 3 %) [17, 44].

Other long-acting G-CSFs

Table 3 shows the efficacy and safety endpoints for studies involving other long-acting G-CSFs.

Lipegfilgrastim

Lipegfilgrastim is pegylated at a different site from pegfilgrastim (threonine 134) using a carbohydrate linker involving two enzymatic steps. In a placebo-controlled RCT in patients with lung cancer, there was no statistically significant reduction in the first-cycle incidence of FN compared to placebo (2 % vs 6 %) and a significant reduction in the first-cycle incidence of severe neutropenia (32 % vs 59 %) [22]. G-CSF-related AEs were more common in the lipegfilgrastim arm (14 % vs 10 %) [22]. In a non-inferiority RCT comparing lipegfilgrastim with pegfilgrastim in patients with breast cancer, there was no significant difference in FN incidence (1 % vs 3 %) and a non-significant reduction in severe neutropenia incidence (44 % vs 51 %) [16]. Rates of FN-related hospitalisations and antibiotic use were also comparable between the two study arms (1 % vs 2 % and 1 % vs 3 %, respectively) [16]. AEs, including bone pain (14 % vs 10 %), myalgia (9 % vs 6 %) and arthralgia (5 % vs 2 %), were slightly more common with lipegfilgrastim than with pegfilgrastim, but the difference was not significant [16]. In a second RCT in breast cancer, duration of severe neutropenia for lipegfilgrastim and pegfilgrastim was reported to be similar [55].

Balugrastim

Balugrastim is a non-pegylated recombinant fusion protein composed of human serum albumin and G-CSF harvested from yeast. It has been investigated at a dose of 40 mg in two RCTs in patients with breast cancer treated with doxorubicin and docetaxel. In one, incidence (58 % vs 59 %) and duration (1.1 days vs 1 day) of severe neutropenia in cycle 1 were similar for balugrastim and pegfilgrastim [18]. There was no significant difference in FN incidence in cycle 1 between balugrastim and pegfilgrastim (1 % vs 3 %) [18]. The frequency of treatment-related AEs was similar for balugrastim and pegfilgrastim (20 % vs 19 %) [18]. The second RCT found similar durations of severe neutropenia for balugrastim and pegfilgrastim (1.3 days vs 1.2 days) [19].

BCD-017, Maxy-G34 and Ro 25-8315

BCD-017 (empegfilgrastim), Maxy-G34 and Ro 25-8315 are all covalent conjugates of recombinant human G-CSF and polyethylene glycol. Small RCTs compared BCD-017 and Ro 25-8315 with filgrastim in patients with breast cancer but found that neutropenia-related outcomes, including rates of FN, were generally lower in the filgrastim arms [56, 57]. Safety data were reported in the Ro 25-8315 study and suggest G-CSF-related AEs are more common with Ro 25-8315 than with filgrastim [57]. Maxy-G34 was compared with pegfilgrastim in a clinical trial. The incidence of FN and duration of CIN were similar in the two study arms [58]. No safety data were reported.

Discussion

To our knowledge, this is the only systematic review of long-acting G-CSFs that includes newly developed agents and data

Table 3 Efficacy and safety of other long-acting granulocyte colony-stimulating factors

Author, year	G-CSF intervention	Tumour type	Efficacy			Safety
			Incidence of febrile neutropenia % (95 % CI)	Incidence/duration of severe neutropenia %/ days (95 % CI)	Incidence of other efficacy outcomes % (95 % CI)	Incidence of all treatment-related AEs %
RCTs						
Bondarenko et al. 2013 [16]	Lipegfilgrastim n=101 (94 PP) Pegfilgrastim n=101 (94 PP)	Breast cancer	Cycle 1: 1 % vs 3 % NS	Cycle 1: 43.6 % vs 51.1 % p=0.341 0.7 vs 0.8 days p=0.126	Hospitalisation due to FN/ infection: 1 % for 1 day vs 2 % for 5–6 days Antibiotic use 1 % vs 3 % Chemotherapy dose delivery cycles 2–4: Delay: 30.7 % vs 35.6 % Reduction: 0 % vs 7.9 %	27.7 % vs 25.7 % Bone pain-related: 23.8 % vs 16.8 % Bone pain: 13.9 % vs 9.9 % Myalgia: 8.9 % vs 5.9 % Arthralgia: 5 % vs 2 % Serious AEs: 1 % vs 1 % Severe AEs: 2 % vs 1 %
Buchner et al. 2011 [55] Congress abstract	Lipegfilgrastim (3; 4.5; 6 mg) n=53; 51; 50 Pegfilgrastim (6 mg) n=54	Primary breast cancer	–	Cycle 1: 1.1 days vs 0.8 days vs 0.8 days vs 0.9 days	–	–
Gladkov et al. 2012 [63] congress abstract	Balugrastim (40 mg; 50 mg) Pegfilgrastim (6 mg) n=256	Breast cancer	–	Cycle 1: 1.3 days vs 1.0 days vs 1.2 days NS	–	–
Salafet et al. 2013 [56] congress abstract	BCD-017 (3 mg; 6 mg) n=21; n=20 Filgrastim (5 mg/kg/day) n=19	Breast cancer	5 % vs 5 % vs 0 %	Cycle 1: 85.7 % vs 65.0 % vs 61.1 % 0.43 days vs 0.40 days vs 0.33 days NS	–	–
Viens et al. 2002 [57]	Ro 25-8315 (20; 60; 100 μg/kg) n=9; 9; 10 Filgrastim (5 μg/kg/day) n=8	Advanced breast cancer	0 % vs 11 % vs 10 % vs 0 %	–	Hospitalisations: 55.6 % vs 44.4 % vs 60 % vs 37.5 % Antibiotic use: 75 % vs 50 % vs 60 % vs 50 % Chemotherapy dose delay: 1 day	4 vs 4 vs 11 vs 2 events Bone pain: 20 % Two episodes of severe bone pain with Ro 25-8315 100 μg/kg
Volovat et al. 2013 [18]	Balugrastim (40 mg) n=153 (150 PP) Pegfilgrastim n=151 (149 PP) Balugrastim (40 mg, open-label) n=77	Breast cancer	Cycle 1: 1.3 % vs 2.7 % p=0.446	Cycle 1: 58 % vs 58.8 % 1.1 days vs 1.0 days NS	–	20 % vs 19 % Bone pain: 11.8 % vs 10.7 % vs 18.2 % Severe AEs: 19.6 % vs 18.7 % vs 15.6 %
Gladkov et al. 2012 [22]	Lipegfilgrastim n=250 Placebo n=125	Lung cancer	Cycle 1: 2.4 % vs 5.6 % OR 0.39 (0.12–1.26) p=0.1151	Cycle 1: 32 % vs 59 % OR 0.33 (0.21–0.51) p<0.0001 0.6 days vs 2.3 days p<0.0001	–	G-CSF-related: 14 % vs 10 % Severe AEs: 23 % vs 18 %

Table 3 (continued)

Author, year	G-CSF intervention	Tumour type	Efficacy			Safety
			Incidence of febrile neutropenia % (95 % CI)	Incidence/duration of severe neutropenia %/ days (95 % CI)	Incidence of other efficacy outcomes % (95 % CI)	Incidence of all treatment-related AEs %
Clinical trials						
Schwartzberg et al. 2009 [58] congress abstract	Maxy-G34 (10; 30; 45; 60; 100 μg/kg) n=6; 6; 6; 6; 3 Pegfilgrastim n=8	High-risk breast cancer	2.6 % vs 4.2 %	Cycle 1: 2.2 days vs 1.8 days vs 0.8 days vs 2.2 days vs 1.7 days vs 2.0 days	–	–

In the table, the first number corresponds to the upper G-CSF mentioned and the second number corresponds to the lower G-CSF intervention column. If not otherwise specified, numbers are given in percentages of the patients across all cycles. – indicates that the data was not available.

AE adverse event, *CI* confidence interval, *G-CSF* granulocyte colony-stimulating factor, *FN* febrile neutropenia, *NS* not statistically significant, *OR* odds ratio, *PP* per protocol, *RCT* randomised controlled trial

from both clinical trials and observational studies. We identified 12 RCTs, 12 clinical trials and 17 observational studies, including 58,342 patients in total. Studies in patients with breast cancer were dominant, partly because these were the registration studies for the G-CSFs.

Pegfilgrastim studies included a range of patient populations, cancer types and stages, and chemotherapy regimens. Efficacy and effectiveness results were generally consistent. Although pegfilgrastim did not uniformly show better efficacy or effectiveness in all studies, the vast majority showed better efficacy or effectiveness compared to daily G-CSF, no upfront pegfilgrastim, no G-CSF or placebo in terms of reduction of the incidence of CIN (4/7 studies), FN (11/14 studies), chemotherapy dose delays and reductions (6/8 studies), antibiotic use (6/7 studies) and neutropenia-related hospitalisations (9/13 studies). The observed variation may be partly explained by differences in patient populations and cancer types, or in the way G-CSF was administered. Thirteen (35 %) studies of pegfilgrastim reported safety data and most of these focused on musculoskeletal pain; only three studies reported other G-CSF-related AEs. This suggests that the safety profile of G-CSFs may be generally accepted and studies now investigate only specific AEs known to be associated with their use. The incidence of G-CSF-related AEs was similar between pegfilgrastim and filgrastim. The incidence of bone pain and severe bone pain was lower or no different for pegfilgrastim than filgrastim in most RCTs and observational studies (4/6 studies).

Previously published systematic reviews and meta-analyses of RCTs comparing pegfilgrastim with daily G-CSF or placebo by Cooper et al. and Pinto et al. found that pegfilgrastim more effectively reduced the incidence of FN [59, 60]. The RCT reported by Decaestecker et al. and Pinter et al. [24, 25], showing better efficacy for pegfilgrastim than placebo in reducing the incidence of neutropenia in colorectal cancer patients, reported in this systematic review was not included in these previous systematic reviews. We additionally included non-randomised clinical trials and observational studies that have not been included in former systematic reviews [59, 60]. Nevertheless, the results of our systematic review are generally consistent with these studies. However, while well-designed RCTs have a low risk of bias, inclusion criteria can be restrictive. The observational studies included in our review indicate an advantage for pegfilgrastim over daily G-CSFs or no treatment, suggesting that the efficacy of pegfilgrastim demonstrated in clinical trials has been translated into clinical practice. In fact, we found a greater magnitude of reduction in CIN incidence with pegfilgrastim versus filgrastim in observational studies than RCTs; this could be due to a shorter duration of G-CSF use in current practice (e.g. 5–6 days in clinical practice vs 10–11 days in clinical trials) [7]. Importantly, the safety data from observational studies were consistent with data from RCTs, suggesting that the

pegfilgrastim safety profile can be used to guide treatment in a broad patient population. However, care should be taken when interpreting the results of observational studies, owing to the higher risk of bias and confounding factors.

Almost all the studies including other long-acting G-CSFs were RCTs of patients with breast cancer (7/8 studies) receiving doxorubicin and docetaxel (5/8 studies). Lipegfilgrastim has been the most extensively tested (3/8 studies) and appears to be similar to pegfilgrastim regarding the reduction in duration of severe neutropenia in patients with breast cancer. Efficacy of lipegfilgrastim in reducing the incidence of FN was not statistically superior to placebo in a congress abstract describing an RCT in patients with lung cancer [22]. Lipegfilgrastim has now been approved in Europe for reducing the incidence and duration of FN in adults with cancer who are receiving cytotoxic chemotherapy [11]. Further clinical and observational studies in a wider range of tumour types and chemotherapy regimens will confirm whether its efficacy and safety are maintained across a broader patient population in real-world clinical practice. Balugrastim has also been investigated in two phase 3 RCTs of patients with breast cancer and has an efficacy and safety profile comparable to that of pegfilgrastim. Again, further studies will determine whether this translates to other patient populations. Notably, the incidence of FN in the pegfilgrastim arms of the lipegfilgrastim and balugrastim studies (3 % in cycle 1 for both studies [16, 18]) was lower than in the registrational pegfilgrastim studies (9 % and 7 % in cycle 1 [27, 28]), despite a similar study design and patient population. Maxy-G34 also appears to be non-inferior to pegfilgrastim; however, it was tested in only a very small number of patients (n=35) [58]. BCD-017 and Ro 25-8315 did not appear to be as effective at reducing the incidence of FN as filgrastim [56, 57].

Because very few studies reported long-term outcomes of G-CSF use and two systematic reviews by Kuderer and Lyman et al. [61, 62] looking at survival have previously been published, we did not include overall survival as an endpoint. In 2007, Kuderer et al. [61] published a systematic review of infection-related and early mortality during chemotherapy by type of G-CSF. They reported that there is insufficient data to draw conclusions. An updated analysis in 2013 by Lyman et al. [62] concluded that all-cause mortality is reduced in patients receiving chemotherapy with primary G-CSF support. However, Lyman et al. did not report results by type of G-CSF. We are still awaiting long-term survival data for the newer long-acting G-CSFs. Future research should examine in more detail the effects of long-acting G-CSFs on survival outcomes.

As is true for all systematic reviews, the validity of our findings is limited by the quality of its underlying studies. Another limitation is that some studies did not report how many patients received primary prophylaxis versus secondary prophylaxis. This may have led to an underestimation of effectiveness. Furthermore, the studies were not all consistent in their definitions of FN and CIN and the number of chemotherapy cycles over which they reported data. Finally, combined measures of effect are missing in our analysis.

It is clear that pegfilgrastim is widely used in clinical practice across a broad patient population. Lipegfilgrastim and balugrastim were similar to pegfilgrastim in reducing the duration and incidence of CIN and FN in five studies. Furthermore, the safety profiles of the recently developed long-acting G-CSFs were comparable to pegfilgrastim based on the phase 3 studies identified by this systematic review. These G-CSFs may prove to be valuable therapeutic options; however, there is a need for further studies in broader patient populations to confirm their effectiveness and safety in real-world clinical practice. New biosimilar G-CSFs and next-generation drugs targeting the G-CSF receptor are also in the early stages of development [12] and should be assessed against the current standard of care.

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Authors' contributions All authors were involved in the design of the study. KA was responsible for the first draft of the protocol, which was critically reviewed, further developed and approved by all authors. KA performed the literature search, and collected and extracted the data. AMP was responsible for the risk of bias assessment and the first draft of the manuscript. KA and AMP were responsible for the second draft. All authors contributed to data interpretation, critically reviewed all manuscript versions and approved the final version.

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