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REVIEW ARTICLE

A systematic literature review of the efficacy, effectiveness, and safety of filgrastim

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Abstract
Purpose Filgrastim (NEUPOGEN®) is the originator recombinant human granulocyte colony-stimulating factor widely used for preventing neutropenia-related infections and mobilizing hematopoietic stem cells. This report presents findings of a systematic literature review and meta-analysis of efficacy and safety of originator filgrastim to update previous reports.
Methods A literature search of electronic databases, congress abstracts, and bibliographies of recent reviews was conducted to identify English-language reports of clinical trials and observational studies evaluating filgrastim in its US-approved indications up to February 2015. Two independent reviewers assessed titles/abstracts and full texts of publications, and extracted data from studies that compared originator filgrastim vs placebo or no treatment. For outcomes with sufficient homogeneous data reported across studies, meta-analysis was performed and relative risk (RR) determined. Data were summarized descriptively for all other evaluated outcomes.
Results A total of 1194 unique articles evaluating originator filgrastim were identified, with 25 meeting eligibility criteria for data extraction: 18 randomized controlled trials, 2 nonrandomized clinical trials, and 5 observational studies. In chemotherapy-induced neutropenia (CIN), filgrastim vs placebo or no treatment significantly reduced febrile neutropenia incidence (RR 0.63, 95% CI 0.53–0.75) and grade 3 or 4 neutropenia incidence (RR 0.50, 95% CI 0.37–0.68). The most commonly reported adverse event (AE) with filgrastim was bone pain (RR 2.61, 95% CI 1.29–5.27 in CIN). Additional efficacy and safety outcomes are described within indications.
Conclusions This systematic literature review and meta-analysis confirms and updates previous reports on the efficacy and safety of originator filgrastim. Bone pain was the commonly reported AE associated with filgrastim use.

Keywords Absolute neutrophil count · Granulocyte colony-stimulating factor · Meta-analysis · NEUPOGEN® · Neutropenia · Systematic review

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Introduction

Neutropenia increases risk of bacterial and fungal infections [1–4]. Before the late 1980s, there was no effective primary treatment for neutropenia; patients were treated with antibiotics, fluid replacement, and general supportive measures [4, 5]. For

patients with severe chronic neutropenia (SCN), lack of treatment options led to repeated hospitalizations and recurrent and sometimes fatal infections [5, 6]. Cancer patients receiving myelosuppressive chemotherapy frequently developed chemotherapy-induced neutropenia (CIN), with longer CIN duration associated with febrile neutropenia (FN), often necessitating dose delays and dose reductions in subsequent chemotherapy cycles, affecting clinical outcomes [7, 8]. Repeated bone marrow aspiration was the only available method for hematopoietic progenitor cell collection.

Granulocyte colony-stimulating factor (G-CSF) stimulates proliferation and differentiation of neutrophil progenitors and release of neutrophils from bone marrow into blood [9, 10]. Filgrastim (NEUPOGEN®, Amgen Inc., CA, USA) [11], the originator short-acting recombinant human G-CSF, was first approved in the US in 1991 and has been used to treat patients worldwide for over two decades. The pivotal trial leading to approval showed filgrastim administration decreased FN incidence; reduced grade 4 neutropenia incidence, duration, and severity; and decreased infection rates, duration of antibiotic treatment, and hospitalization in patients with small cell lung cancer (SCLC) receiving myelosuppressive chemotherapy [4]. Similar observations were made in a study of patients with SCN [6].

As of 2016, originator filgrastim has 6 US-approved indications [11]. These include the following: (1) preventing FN in CIN, (2) reducing time to neutrophil recovery and duration of fever in patients with acute myeloid leukemia (AML) receiving induction or consolidation chemotherapy, (3) reducing incidence and duration of sequelae of severe neutropenia in patients with SCN, (4) mobilizing autologous hematopoietic progenitor cells in patients undergoing peripheral blood progenitor cell (PBPC) collection and therapy, (5) reducing duration of neutropenia and neutropenia-related clinical sequelae in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation (BMT), and (6) increasing survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome [ARS]).

Numerous trials have evaluated efficacy and safety of originator filgrastim, which has a long history of use in real-world settings across diverse indications and populations. However, a systematic review of data from randomized controlled trials (RCTs), nonrandomized clinical trials (NCTs), and observational studies evaluating use of originator filgrastim in all its US-approved indications has not been undertaken.

To date, several biosimilar filgrastims have been approved by European and US regulatory agencies, often on the basis of clinical safety and efficacy data in one indication. To obtain approval in other indications, biosimilar filgrastim applicants have relied on extrapolation of data from originator filgrastim. A report summarizing the long history of clinical trial and real-world data for originator filgrastim across indications could be useful for the field.

This systematic review and meta-analysis summarizes efficacy, effectiveness, and safety of originator filgrastim in studies comparing filgrastim with placebo or no treatment in any of its US-approved indications. Overall results from the literature search are presented. Summary data are provided for the CIN, AML, SCN, and BMT indications. Within each indication, data on neutropenia-related complications, overall survival (OS), adverse events (AEs), and other relevant outcomes are presented. Meta-analysis results are presented for FN, grade 3 or 4 neutropenia, and bone pain incidence for data from RCTs in CIN. Data for all other outcomes are summarized descriptively.

Methods

Study design

This study was performed in accordance with the PRISMA guidelines [12], following a prespecified protocol. MEDLINE In-Process & Other Non-Indexed Citations, OVID MEDLINE EMBASE, and Cochrane Library databases were searched for English-language publications of studies including patients treated with originator filgrastim (NEUPOGEN®) in accordance with US prescribing instructions [11] (see Online Resource 1). The search cutoff date was 26 February 2015. No start date was specified as each database was searched from its start date. Congress abstracts from meetings of 16 relevant organizations (see Online Resource 1) published from January 2012 to February 2015 plus abstracts from the 2015 Annual Meeting of the American Society of Clinical Oncology were also searched. A hand search of bibliographies was also performed for 3 systematic reviews—Cooper et al. [13], Renner et al. [14], and Sheppard et al. [15]—identified as containing relevant information in the initial search.

Study selection

Pre-defined eligibility criteria (Table 1) were used for study selection in a two-part process. In part 1, two independent reviewers screened titles/abstracts and then full texts of identified reports for eligibility. In part 2, two independent reviewers assessed titles/abstracts and full texts of publications identified in part 1 to find relevant studies comparing originator filgrastim to placebo or no treatment. Further excluded at this stage were studies in which < 50 patients received filgrastim for all indications except SCN. Due to generally low patient numbers in studies evaluating filgrastim in SCN, a protocol amendment was made to allow for inclusion of studies with ≥ 10 patients.

Table 1 Inclusion and exclusion criteria

Parameter	Inclusion criteria	Exclusion criteria
Study type: Parts 1 and 2	Published English-language studies including: • RCTs • NCTs • Observational studies (longitudinal studies, registry studies, open-label studies) • Systematic reviews[a]	Studies in animals but not humans Comments, editorials, letters, case reports, guidelines, health technology assessment reports, economic evaluations, narrative reviews, cancer registry reports, legal cases, debates, newspaper articles, opinions, research protocols, workshops, and patient education brochures
Population: Parts 1 and 2	Patients receiving filgrastim for one of its 6 US indications listed below: • Prophylaxis of CIN • Reducing time to neutrophil recovery and duration of fever in patients with AML receiving induction or consolidation chemotherapy • Reducing incidence and duration of sequelae of SN in patients with SCN • Mobilizing autologous hematopoietic progenitor cells in patients undergoing PBPC collection and therapy • Reducing duration of neutropenia and neutropenia-related clinical sequelae in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by BMT • Increasing survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of ARS) No limits on age, gender, or geographic region	Patients receiving filgrastim outside of its six currently approved US indications Patients with existing FN receiving G-CSF treatment Studies in which the tumor type studied, if applicable, was not clear
Interventions and comparators: Part 1	Comparative studies of originator filgrastim (NEUPOGEN®) vs placebo, no treatment, or the following G-CSFs: • Granocyte (lenograstim) • Leridistim • Other short-acting G-CSFs • Neulasta® (pegfilgrastim) • Balugrastim (CG-10639, Neugranin™, albugranin) • Lipegfilgrastim (XM-22, Lonquex®) • Empegfilgrastim (Extimia®, BCD-017, metpegfilgrastim) • LAPS-G-CSF (SPI-2012, HM10460A) • Other long-acting G-CSF The above interventions (as either primary or secondary prophylaxis) were included	Studies specifying the use of filgrastim but not reporting filgrastim efficacy or safety data or outcomes of interest Studies in which filgrastim use was not prophylactic G-CSF-related outcomes not clear Studies in which the short-acting form of G-CSF was not specified to be filgrastim (NEUPOGEN®) Studies in which data for filgrastim were pooled with data for other short-acting G-CSFs Studies in which fewer than 50 patients received filgrastim for all other indications except SCN; in SCN studies with ≥ 10 patients were included
Interventions and comparators: Part 2	Comparative studies of originator filgrastim (NEUPOGEN®) vs placebo or no treatment	Data for any other short- or long-acting G-CSFs, including biosimilar filgrastims
Outcomes: Parts 1 and 2	Studies that reported neutropenia, ANC, neutropenia-related infection, or CD34+ cell mobilization and additional outcomes including: • Efficacy (data from RCTs and NCTs) and effectiveness (data from observational studies) that reported - Rate and duration of FN or grade 3 or 4 neutropenia - ANC nadir and white blood cell count - Survival - Rate and duration of hospitalization - Need for antibiotic prophylaxis or treatment - Chemotherapy dose reductions/delays, reduced dose intensity, and number of patients receiving full dose on schedule - CD34+ cell yield - Number of apheresis sessions required - Time to neutrophil and platelet recovery • Safety - AEs related to G-CSF, including bone pain, nausea/vomiting, diarrhea, leukocytosis, thrombocytopenia, allergic reactions, splenic rupture, acute respiratory distress syndrome, dyspnea, and alveolar hemorrhage and hemoptysis	Not applicable

[a] Systematic reviews were used for identification of primary studies but were not included in this review

AE = adverse event; AML = acute amyloid leukemia; ANC = absolute neutrophil count; ARS = acute radiation syndrome; BMT = bone marrow transplantation; CIN = chemotherapy-induced neutropenia; FN = febrile neutropenia; G-CSF = granulocyte colony-stimulating factor; NCT = nonrandomized clinical trial; PBPC = peripheral blood progenitor cell; RCT = randomized controlled trial; SCN = severe chronic neutropenia; SN = severe neutropenia

Data extraction and analysis

Data on efficacy, effectiveness, and safety were extracted from publications identified in part 2. Data were extracted from each selected full-text publication, where available; if data were extracted from alternative sources, such as congress abstract or poster, this was noted. Studies were classified according to filgrastim indication [11] and study design. Studies were classified into three categories: RCTs (patients randomized to filgrastim or its comparators [placebo or no treatment]); NCTs (patients not randomly assigned to filgrastim or its comparators); and observational studies (i.e., routine clinical practice under real-world conditions, including longitudinal and registry studies).

Data collected include study and patient characteristics, efficacy (treatment effect in RCTs and NCTs), effectiveness (treatment effect in observational studies), and safety (Table 1). Data were extracted and reported as presented by the authors of each publication reviewed. Statistical significance, where stated, is based on data provided in the original publication, using the standard $P < 0.05$ boundary to denote significance. Study quality was assessed and reported qualitatively by two independent reviewers; any disagreements were resolved by a third reviewer. Reviewers assessed study design on criteria including size of patient population, phase of study, strength of study design, and appropriateness of study design to reach the objective; filgrastim dose, timing, and treatment duration; risk bias; choice of outcome measures; statistical issues; quality of reporting; quality of the intervention; and generalizability of findings.

For safety outcomes, incidence of pre-specified G-CSF-related AEs was collected (Table 1). Additionally, any AEs that were compared for filgrastim vs no filgrastim in any of the studies were collected, as these AEs were presumed to be filgrastim-related. For each AE, the proportion of patients experiencing the AE overall and, where available, the proportion experiencing events classified as severe or grade 3/4 were collected.

Statistical analysis

Meta-analysis was performed using the random effects model [16, 17] for FN, grade 3 or 4 neutropenia, and bone pain incidence in CIN to compare results from clinical trials (RCTs and NCTs only) for filgrastim vs placebo or no treatment, and relative risks (RRs) were determined. Details for studies included in the meta-analysis are provided in Online Resource 2. Due to limited and heterogeneous data available for other outcomes and indications, mean or median values were summarized, and no meta-analysis was performed.

Results

Search results

Results of the literature search are summarized in Fig. 1 and Online Resource 3. Of 6588 unique records initially identified, 1194 articles were English-language publications reporting RCTs, NCTs, or observational studies that included patients treated with originator filgrastim (NEUPOGEN®) in its 6 US-approved indications and met eligibility criteria for part 1 of the search. Of these, 26 compared filgrastim efficacy, effectiveness, and safety to placebo or no treatment and met eligibility criteria for part 2, qualifying for data extraction. These 26 records were from 25 separate studies published between 1991 [4] and 2013 [18] and represent data from 9018 patients, with filgrastim administered to 4088 patients (Fig. 1, Online Resource 3, and Online Resource 4): 15 were in CIN (11 RCTs, 1 NCT, and 3 observational studies), 6 in AML (5 RCTs and 1 NCT), 2 in SCN (1 RCT and 1 observational study), and 2 in BMT (1 RCT and 1 observational study), for a total of 18 RCTs, 2 NCTs, and 5 observational studies. No studies evaluating filgrastim compared with placebo or no treatment in the PBPC or ARS indications met eligibility criteria for data extraction. Data on filgrastim dose, timing, and duration were provided in most studies and varied across studies, even within indication (Online Resource 4 and Online Resource 5).

Outcomes for filgrastim vs placebo or no treatment by indication

CIN

The 15 studies evaluating filgrastim vs placebo or no treatment in CIN enrolled 6521 patients in total, with filgrastim administered to 2691 patients (Online Resource 4 and Online Resource 6). Eleven studies were RCTs (10 full articles and 1 [19] abstract). Six RCTs were in solid tumors (breast cancer [20–22], SCLC [4, 23], and germ cell tumors [24]), 3 were in non-Hodgkin's lymphoma (NHL) [25–27], and 2 were in acute lymphoblastic leukemia (ALL) [28, 29]. One study [30] was an NCT in non-small cell lung cancer (NSCLC) and NHL. The remaining 3 [18, 31, 32] were observational studies conducted in mixed tumor types.

Several studies reported data on FN, grade 3 or 4 neutropenia, and bone pain incidence for filgrastim vs placebo or no treatment in CIN (Online Resource 6), and RRs for these outcomes were determined by meta-analysis (Fig. 2 and Fig. 3). Limited data were reported for the remaining outcomes; therefore, data for these additional outcomes were summarized descriptively.

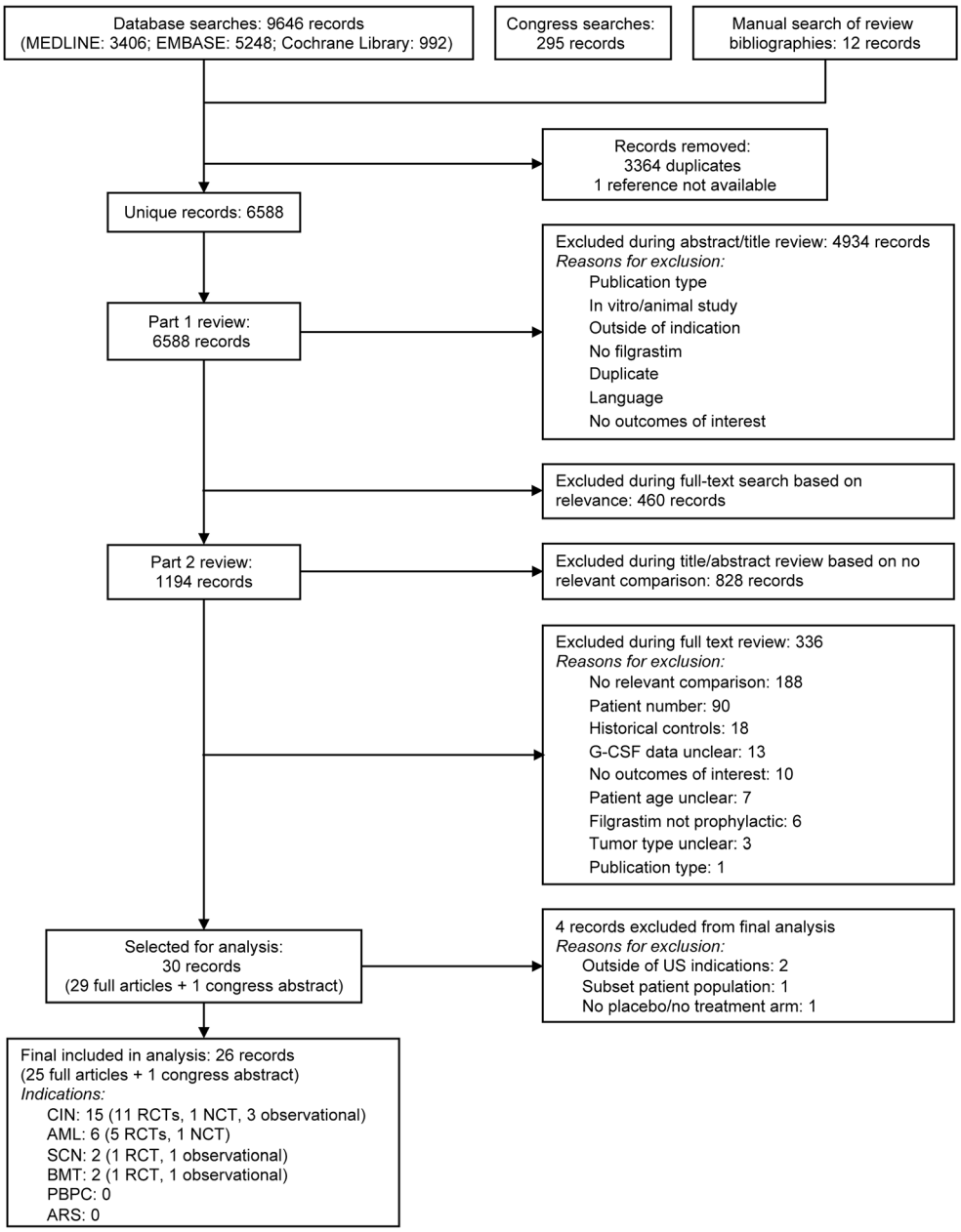

Fig. 1 PRISMA flow diagram. AML = acute myeloid leukemia; ARS = acute radiation syndrome; BMT = bone marrow transplantation; CIN = chemotherapy-induced neutropenia; G-CSF = granulocyte colony-stimulating factor; NCT = nonrandomized clinical trial; PBPC = peripheral blood progenitor cell; RCT = randomized controlled trial; SCN = severe chronic neutropenia

FN incidence Nine of the 11 RCTs in CIN [4, 19–21, 23, 24, 26, 27, 29] reported FN incidence (Online Resource 6) and were included in the meta-analysis (Fig. 2a). Data analyzed were from 2197 total patients (filgrastim, n = 1130; placebo or no treatment, n = 1067). The risk of developing FN was much lower with filgrastim vs placebo or no treatment (RR 0.63, 95% CI 0.53–0.75). In addition, 3 observational studies [18, 31, 32] reported FN incidence, and statistical comparisons were provided in all 3 studies. Two [18, 32] reported significant reductions in FN risk with filgrastim; the other [31] reported no difference in FN risk for filgrastim vs placebo or no treatment.

Grade 3 or 4 neutropenia incidence Five RCTs [4, 19, 20, 25, 27] and 1 NCT [30] reported grade 3 or 4 neutropenia incidence (Table 2 and Online Resource 6) and were included in the meta-analysis (Fig. 2b). Data analyzed were from 1409 total patients (filgrastim, n = 714; placebo or no treatment, n = 695). The risk of developing grade 3 or 4 neutropenia was significantly lower with filgrastim vs placebo or no filgrastim (RR 0.50, 95% CI 0.37–0.68).

Duration of grade 3 or 4 neutropenia Four RCTs [4, 21, 23, 28] and 1 NCT [30] reported duration of grade 3 or 4 neutropenia (Table 3 and Online Resource 6), with statistical comparisons

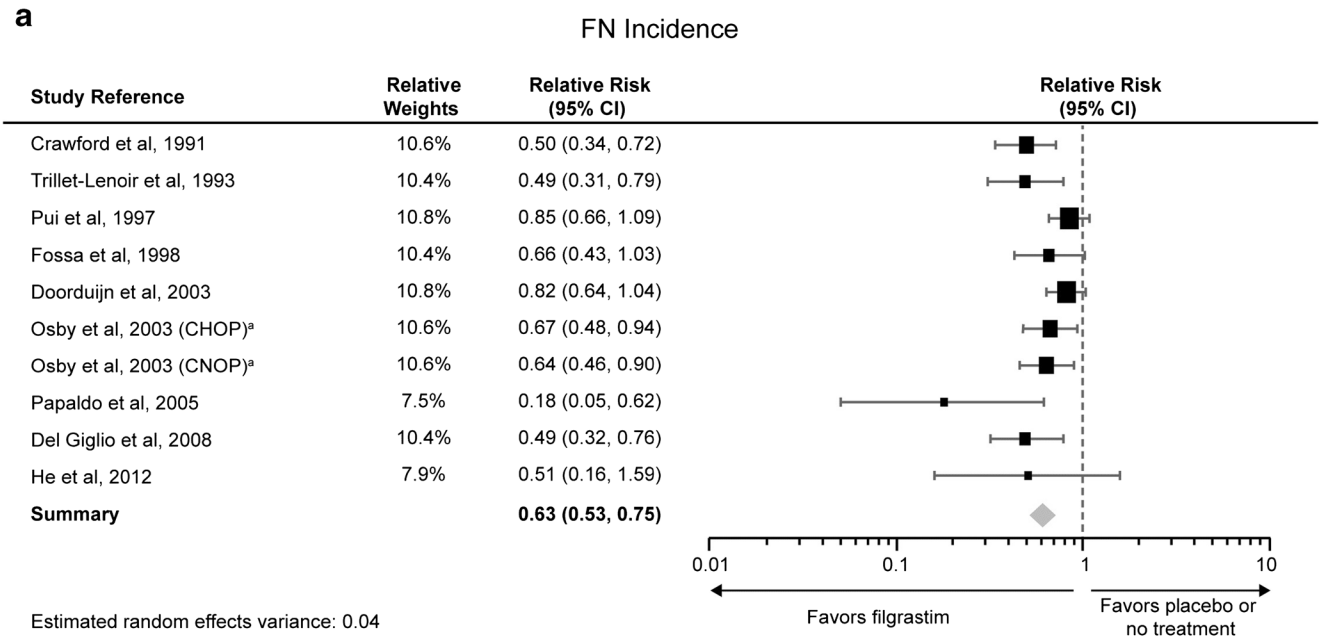

Fig. 2 Risk estimates in CIN for (**a**) FN incidence (2197 total patients; filgrastim, $n = 1130$; placebo or no treatment, $n = 1067$) and (**b**) grade 3 or 4 neutropenia incidence (1409 total patients; filgrastim, $n = 714$; placebo or no treatment, $n = 695$). Random effects meta-analysis was performed for the outcomes to compare data from clinical trials for filgrastim vs placebo or no treatment and relative risk determined. Note: filgrastim = originator filgrastim (NEUPOGEN®). [a]Data for patients who received CHOP (filgrastim, $n = 101$; no filgrastim, $n = 104$) and those who received CNOP (filgrastim, $n = 103$; no filgrastim, $n = 100$) in the Osby et al. [27] study were analyzed separately. [b]Data for patients with NSCLC (filgrastim, $n = 24$; no filgrastim, $n = 9$) and those with NHL (filgrastim, $n = 10$; no filgrastim, $n = 5$) in the Blayney et al. [30] study were analyzed separately. Chemotherapy regimens: CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CNOP = cyclophosphamide, mitoxantrone, vincristine, prednisone. CIN = chemotherapy-induced neutropenia; FN = febrile neutropenia; NSCLC = non-small cell lung cancer; NHL = non-Hodgkin's lymphoma

provided in 2 RCTs [4, 28]. In both studies, median duration of grade 3 or 4 neutropenia was significantly shorter with filgrastim vs placebo [4, 28]. Duration of grade 3 or 4 neutropenia was numerically lower with filgrastim in the other 2 RCTs [21, 23] and the 1 NCT [30].

Infection rates Seven RCTs [4, 23–26, 28, 29] and 1 observational study [31] reported infection rates, with statistical comparisons provided in 5 RCTs [23, 25, 26, 28, 29] and the observational study [31]. Three RCTs reported significantly lower overall infection rates with filgrastim vs placebo [25, 26, 29], whereas 2 [23, 28] reported nonsignificantly lower infection rates with filgrastim. Infection incidence was numerically lower with filgrastim in 1 of the remaining RCTs [4], but not different in the other RCT [24]. The observational study [31] reported no significant difference in

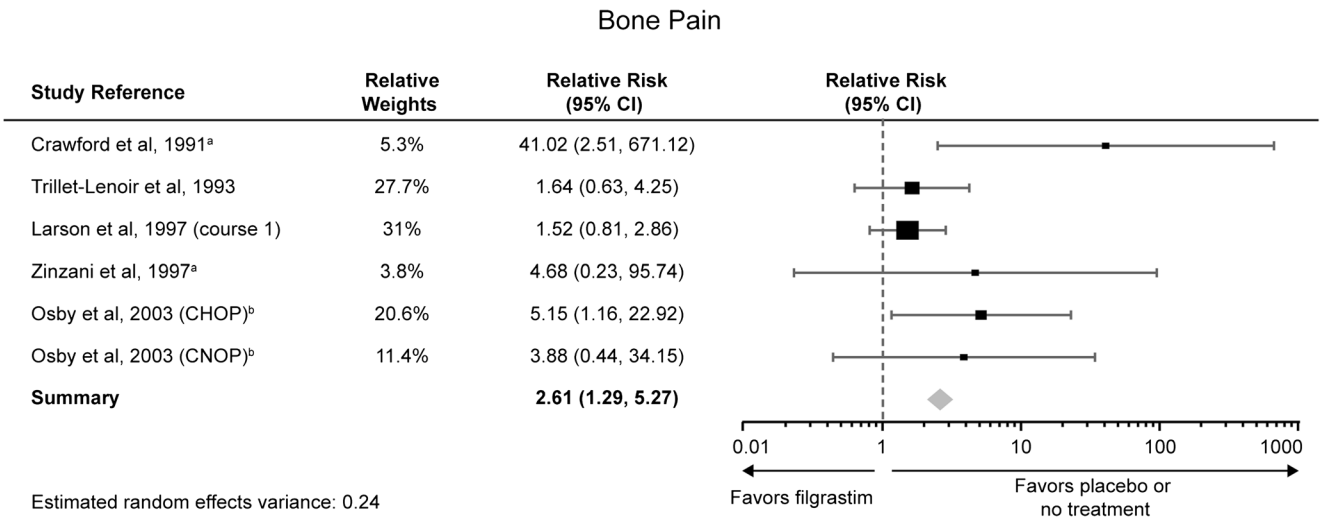

Fig. 3 Risk estimates for bone pain incidence in CIN (1078 total patients; filgrastim, n = 540; placebo or no treatment, n = 538). Random effects meta-analysis was performed and relative risk determined. Note: filgrastim = originator filgrastim (NEUPOGEN®). Studies with missing reports of events for the placebo or no treatment arm (therefore, events not assumed to be 0) were not included in the analysis. [a]Reported 0 events in the placebo or no treatment arm; 0.5 events added to each arm for an adjusted event rate. [b]Data for patients who received CHOP (filgrastim, n = 101; no filgrastim, n = 104) and those who received CNOP (filgrastim, n = 103; no filgrastim, n = 100) in the Osby et al. [27] study were analyzed separately. Chemotherapy regimens: CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CNOP = cyclophosphamide, mitoxantrone, vincristine, prednisone. CIN = chemotherapy-induced neutropenia

infection rates with filgrastim primary prophylaxis vs no filgrastim primary prophylaxis.

Antibiotic use Five RCTs [4, 23, 25, 26, 29] reported antibiotic use, with statistical comparisons provided in 2 [23, 26]. One [23] reported significantly lower incidence of antibiotic use with filgrastim vs placebo or no filgrastim; the other reported significantly reduced days of antibiotic use with filgrastim vs placebo or no filgrastim [26]. Although statistical significance was not reported in the remaining 3 studies, days of antibiotic use were numerically less with filgrastim in one study [4], fewer patients required parenteral antibiotics in another study [25], and fewer patients received intravenous (IV) antibiotics and median days of antibiotic use were less in the other study [29].

Hospitalizations Six RCTs [4, 23, 26–29], 1 NCT [30], and 1 observational study [31] reported hospitalizations, with statistical comparisons provided in 6 RCTs and the observational study [31]. Four RCTs [23, 27–29] demonstrated significantly improved hospital outcomes with filgrastim vs placebo or no filgrastim. Significant improvements were observed in infection-related hospitalization in 1 study [23], granulocytopenic fever requiring hospitalization in 1 study [27], and median days of hospitalization in 2 studies [28, 29]; however, hospitalization rates were not significantly different between filgrastim and no filgrastim in one of the studies [29]. For the 2 remaining RCTs, days of hospitalization were numerically lower with filgrastim in one study [4] and not significantly different in the other [26]. In the NCT [30], mean days of hospitalization were numerically lower with filgrastim in NSCLC but were numerically higher in NHL. The observational study [31] reported no significant difference in hospitalization rates with filgrastim primary prophylaxis vs no filgrastim primary prophylaxis.

Chemotherapy relative dose intensity (RDI), dose reductions, and/or delays Six RCTs [20, 23–27] and 1 observational study [18] reported on chemotherapy dosing. Five RCTs [20, 24–27] reported RDI, with statistical comparisons provided in all 5 studies. RDI was significantly improved with filgrastim vs no filgrastim in germ cell tumor [24] and NHL [27], and was improved, but not significantly different, in breast cancer [20] and NHL [25, 26]. In the observational study [18], RDI was significantly higher with filgrastim vs no filgrastim in the subset of patients who received fluorouracil, epirubicin, cyclophosphamide, and docetaxel (FEC/D), and the proportions of patients who achieved RDI > 85% in this population was numerically higher, but not significantly different, with filgrastim vs no filgrastim. Two RCTs [20, 23], 1 NCT [30], and 1 observational study [18] reported chemotherapy dose delays and dose reductions, with statistical comparisons provided in 2 RCTs and 1 observational study. In the RCTs, dose reduction was significantly reduced with filgrastim vs placebo or no filgrastim in SCLC [23] and breast cancer [20]. Dose delay was significantly reduced in breast cancer [20] and numerically reduced in SCLC [23], although the statistical significance of this difference was not reported. In the observational study, both dose delays and dose

Table 2 Incidence of grade 3 or 4 neutropenia in CIN

Author	Disease type	Filgrastim intervention and patient numbers	Incidence of grade 3 or 4 neutropenia	*P* value
Randomized controlled trials				
Crawford et al. [4]	SCLC	*N* = 199 Filgrastim = 95 Placebo = 104	Grade 4 neutropenia in cycle 1: 84 vs 98%	*P* = 0.001
Papaldo et al. [20]	Breast cancer	*N* = 503 Filgrastim = 254 No filgrastim = 249	Grade 3/4 neutropenia: 28.6 vs 81.6%	*P* < 0.00001
He et al. [19]	Breast cancer	*N* = 107 PP filgrastim = 53 No PP filgrastim = 54	Grade 3/4 neutropenia: 12.2 vs 52.3%	*P* < 0.001
Zinzani et al. [25]	High-grade NHL	*N* = 149 Filgrastim = 77 No filgrastim = 72	Grade 4 neutropenia: 23.0 vs 55.5%	*P* = 0.00005
Osby et al. [27]	NHL	*N* = 455 Filgrastim = 226 No filgrastim = 229	Granulocytopenia (< 0.5×10^9/L): CHOP arms 55 vs 89% CNOP arms 64 vs 86%	Not reported
Nonrandomized clinical trial				
Blayney et al. [30]	NSCLC and NHL	NSCLC (*n* = 33):[a] Filgrastim = 24 No filgrastim = 9 NHL (*n* = 15):[b] Filgrastim = 10 No filgrastim = 5	Grade 3 and grade 4 neutropenia: 62 and 77% lower with filgrastim compared to control arm	Not reported

Note: filgrastim = originator filgrastim (NEUPOGEN®)

[a] Data reported are for the subgroup of 33 patients with NSCLC who received the standard 21-day chemotherapy regimen

[b] Data reported are for the subgroup of 15 patients with NHL who received the standard 21-day chemotherapy regimen

Chemotherapy regimens: CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; CNOP = cyclophosphamide, mitoxantrone, vincristine, prednisone

CIN = chemotherapy-induced neutropenia; NHL = non-Hodgkin's lymphoma; NSCLC = non-small cell lung cancer; PP = primary prophylaxis; SCLC = small cell lung cancer

reductions were reduced with filgrastim vs no filgrastim, but differences did not reach statistical significance [18]. In the NCT [30], filgrastim numerically reduced both dose delays and dose reductions in NSCLC and also reduced dose delays in NHL. Of interest, dose reductions were higher with filgrastim vs no filgrastim in NHL [30] (12 vs 0%).

OS OS was reported in 8 RCTs [4, 20, 23, 25–29]. Reported median follow-up times were 30 months [25], 33 months [26], 55 months [20], 57 months [27], and 4.7 years [28]. Event-free survival at 3 years was reported to be 83% in both filgrastim and placebo arms in one study [29]; whereas follow-up times were not specified in the remaining 2 studies [4, 23]. No statistical comparisons were shown, and none of the studies reported a difference in survival for filgrastim vs placebo or no filgrastim.

AEs Five of 11 RCTs [4, 23, 25, 27, 28] reported sufficient homogeneous data on bone pain incidence to allow for meta-analysis (Fig. 3). Data analyzed were from 1078 total patients (filgrastim, *n* = 540; placebo or no treatment, *n* = 538). The risk of developing bone pain was higher with filgrastim vs placebo or no treatment (RR 2.61, 95% CI 1.29–5.27). Five additional studies [4, 20, 21, 23, 26] reported data on bone pain and/or musculoskeletal pain, with overall rates reported ranging from < 1.0 to 42.5%. Other AEs reported in CIN include hematological, gastrointestinal, and general toxicities, most likely related to chemotherapy (Online Resource 6). Incidences of other nonhematological AEs were similar or lower with filgrastim vs placebo or no treatment, except in two instances. The first exception was grade 1/2 pulmonary toxicity reported in 1 RCT [24]. Higher proportions of patients administered filgrastim vs no filgrastim experienced grade 1/2 pulmonary toxicity after receiving cisplatin, etoposide, bleomycin/etoposide, bleomycin (BEP/EP) (25 vs 16%) or bleomycin, vincristine, cisplatin/cisplatin, ifosfamide, etoposide, bleomycin (BOP/VIP-B) (17 vs 14%). However, no differences were observed in the proportions of patients who experienced grade 3 or grade 4

Table 3 Duration of grade 3 or 4 neutropenia in CIN

Author	Disease type	Filgrastim intervention and patient numbers	Median duration of grade 3 or 4 neutropenia	*P* value	Mean duration of severe neutropenia	*P* value
Randomized controlled trials						
Crawford et al. [4]	SCLC	*N* = 199 Filgrastim = 95 Placebo = 104	Grade 4 neutropenia in cycle 1 (days): 3 vs 6 Grade 4 neutropenia over 6 cycles (days): 1 vs 6	*P* < 0.001 *P* < 0.001		
Trillet-Lenoir et al. [23]	SCLC	*N* = 129 Filgrastim = 65 Placebo = 64	Neutropenia (ANC < 1×10^9/L) over 6 cycles (days): 6 vs 15			
Del Giglio et al. [21]	Breast cancer	*N* = 348 Filgrastim = 136 XM02 = 140 Placebo/XM02 = 72			Severe neutropenia (days): cycle 1 1.1 vs 1.1 vs 3.8 cycle 4 0.7 vs 0.7 vs 0.6	NR
Larson et al. [28]	ALL	*N* = 198 Filgrastim = 102 Placebo = 96	Median (IQR) Neutropenia (ANC < 1000/μL) (days): Course I 13 (10–16) vs 20 (15–27) Course IIA 5 (0–12) vs 13 (6–18) Course IIB 11 (4–17) vs 14 (10–25)	 *P* < 0.001 *P* < 0.001 *P* = 0.001		
Nonrandomized clinical trial						
Blayney et al. [30]	NSCLC and NHL	NSCLC (*n* = 33):[a] Filgrastim = 24 No filgrastim = 9 NHL (*n* = 15):[b] Filgrastim = 10 No filgrastim = 5	Median duration of grade 3 and grade 4 neutropenia: 81 and 94% lower compared to control arm			

Note: filgrastim = originator filgrastim (NEUPOGEN®)

[a] Data reported are for the subgroup of 33 patients with NSCLC who received the standard 21-day chemotherapy regimen

[b] Data reported are for the subgroup of 15 patients with NHL who received the standard 21-day chemotherapy regimen

ALL = acute lymphoblastic leukemia; ANC = absolute neutrophil count; CIN = chemotherapy-induced neutropenia; IQR = interquartile range; NHL = non-Hodgkin's lymphoma; NR = not reported; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer

pulmonary toxicity with or without filgrastim. The other exception was significantly increased grade 3/4/5 pain with filgrastim vs placebo (21 vs 14%, $P = 0.026$) in ALL patients [28]. The 2 RCTs in ALL identified in this search did not report differences in subsequent development of AML for filgrastim vs placebo, with a follow-up of 3 years in one study [29] and 4.7 years in the other [28].

AML

The 6 studies evaluating filgrastim vs placebo or no treatment in AML enrolled 1554 patients in total, with 769 receiving filgrastim (Online Resources 4 and 7). One RCT [33] reported the effect of filgrastim on outcomes following both induction and consolidation chemotherapy, 3 RCTs [34–36] reported the effect of filgrastim following induction chemotherapy, and 1 RCT [37] and 1 NCT [38] reported the effect of filgrastim following consolidation chemotherapy.

Absolute neutrophil count (ANC) recovery Three RCTs [33, 35, 36] reported time to ANC recovery following induction chemotherapy, with statistical comparisons provided in 2 studies [33, 36]. Both reported significantly shorter times to ANC recovery with filgrastim vs no filgrastim [33, 36]. In the remaining RCT [35], time to ANC recovery was also numerically shorter with filgrastim. Time to ANC recovery following consolidation chemotherapy was reported in the 1 NCT [38] and was significantly shorter with filgrastim vs no filgrastim.

Infection rates Three RCTs [33, 35, 36] reported infection rates following induction chemotherapy, with statistical comparisons provided in all 3. Overall, infection rates were not significantly different for filgrastim vs no filgrastim. Infection rates for filgrastim vs no filgrastim following consolidation chemotherapy were reported in 1 RCT [37] and 1 NCT [38], with statistical comparisons provided in the RCT. No

significant differences were seen in the RCT [37], and no numerical differences were seen in the NCT [38].

Antibiotic use Four RCTs [33–36] reported antibiotic use during the induction phase, and statistical comparisons are provided in all 4. All 4 reported no significant differences between treatment groups. Antibiotic use during the consolidation phase was reported in 1 RCT [37], with the study reporting significantly less antibiotic use with filgrastim in both consolidation cycles.

Hospitalizations Three RCTs [33–35] reported hospitalization outcomes during the induction phase, with statistical comparisons provided in 2 RCTs [33, 34]. Duration of hospitalization was significantly shorter with filgrastim vs no filgrastim in 1 RCT [33] and nonsignificantly shorter in the other RCT [34]. Duration of hospitalization was not numerically different in the other RCT [35]. Two RCTs [33, 37] and 1 NCT [38] reported hospitalization outcomes during the consolidation phase, with statistical comparisons provided in all 3 studies. Duration of hospitalization was significantly shorter with filgrastim vs no filgrastim for the cumulative induction and consolidation phases in 1 RCT [33] and the consolidation phase in the other RCT [37]. In the NCT [38], incidence of hospitalization was significantly lower and duration of hospitalization was numerically lower with filgrastim vs no filgrastim.

OS OS was reported in 4 RCTs in which patients received induction chemotherapy [33–36], with statistical comparisons provided in 3 RCTs [33–35]. No significant difference in OS was observed for filgrastim vs no filgrastim in the 3 RCTs. Similarly, the other RCT did not show a numerical difference in OS with filgrastim use [36]. Median follow-up times ranged from 20 months [36] to 7 years [33]. OS was reported in 1 RCT [37] and 1 NCT [38] in which patients received consolidation chemotherapy. In the RCT [37], 2-year OS (standard deviation) was 64% (6%) vs 63% (6%) for filgrastim vs no filgrastim. In the NCT [38], median survival of patients who received the third intensification chemotherapy course was 3.4 years for filgrastim vs 2.4 years for no filgrastim. Long-term follow-up in the study in which patients received both induction and consolidation chemotherapy [33], reported as a separate study [39], confirmed no detrimental effect of filgrastim use on OS in patients with AML at a median follow-up of 7 years.

AEs Among AEs reported, incidence of bone pain and/or musculoskeletal pain for filgrastim vs no filgrastim was reported in 2 studies: 1 vs 5% [35] and 2 vs 1% [33]. Musculoskeletal pain was also mentioned, but incidence not provided, in 1 RCT [34], and 3 patients were reported to experience mild filgrastim-related musculoskeletal pain in another RCT [36].

SCN

One RCT [6] and 1 observational study [40] met eligibility criteria for data extraction in SCN (Online Resource 8). The two studies enrolled 162 patients in total, with 79 receiving filgrastim.

The pivotal RCT leading to filgrastim approval in the US [6] reported a significant increase in median ANC in patients who received filgrastim vs those who were observed for 4 months with no filgrastim ($N = 123$). There were also significantly fewer infections (~50% reduction) and less IV antibiotic use (~70% reduction) with filgrastim. Overall, median incidence and median duration of hospitalization were low. Exposure-adjusted AEs (total number of events divided by total study exposure in patient months) in patients after receiving filgrastim vs before receiving filgrastim were as follows: headache, 35 vs 24%; general musculoskeletal pain, 25 vs 10%; transient bone pain, 17 vs 6%; and rash, 10 vs 4% [6]. Asymptomatic palpable splenomegaly was reported in 18/123 patients (14%) before filgrastim and 29/120 patients (24%) who received filgrastim.

The observational study [40] compared 16 pediatric patients with chronic neutropenia who received filgrastim with 23 who did not receive filgrastim. Groups were heterogeneous, and criteria for filgrastim administration were not specified. In the no filgrastim group, 16 of 23 patients recovered spontaneously, whereas 11 of 16 patients in the filgrastim group remained on filgrastim throughout the study period. For patients with idiopathic severe neutropenia, the largest group ($n = 31$), those selected for treatment with filgrastim had histories of significantly more infections and hospitalizations than those not treated with filgrastim. With filgrastim treatment, rate of infections in the treatment group decreased to that of the comparison group, suggesting a benefit of filgrastim treatment. Of note, the schedule of filgrastim administration in this observation study [40] was different from the RCT [6] (Online Resource 4), and timing of blood count observations was not specified.

BMT

One RCT [41] and 1 observational study [42] that assessed filgrastim's effect on hematopoietic recovery following high-dose chemotherapy with PBPC support met eligibility criteria for data extraction (Online Resource 9). The 2 studies enrolled 781 patients in total, with 549 patients receiving filgrastim.

In the RCT in ALL or solid tumors (filgrastim, $n = 51$; no filgrastim, $n = 66$) [41], median (range) time to achieve ANC $> 0.5 \times 10^9$/L was 10 (7–14) days with filgrastim and 11 (8–21) days with no filgrastim ($P < 0.009$). Median time (range) to platelet engraftment was 15 (9–100) days with filgrastim and 14 (11–71) days with no filgrastim ($P < 0.005$). Duration

of antibiotic use and hospitalization were not significantly different between treatment arms [41].

The single-institution observational study [42] analyzed patients who underwent autologous transplant for multiple myeloma with or without filgrastim (filgrastim, $n = 498$; no filgrastim, $n = 166$), starting on day 6 after transplantation. Median time to ANC recovery was 12.5 days with filgrastim and 13.5 days with no filgrastim ($P < 0.001$). Median time to platelet engraftment was 14.5 days in both groups. Incidence of bacteremia was significantly higher with filgrastim, incidence and duration of hospitalization were significantly higher with filgrastim, and all-cause mortality was similar between treatment groups.

Discussion

This systematic review examined medical literature on originator filgrastim in all its US-approved indications based on pre-specified criteria and identified 1194 unique reports published in a period spanning > 29 years (1987–2015). This is the first study to systematically review and perform a meta-analysis of the efficacy, effectiveness, and safety of filgrastim in clinical trials and real-world settings. The 18 RCTs, 2 NCTs, and 5 observational studies in CIN, AML, SCN, and BMT identified in this search span from 1991 [4] to 2013 [18]; 21/25 studies (84%) were published between 1991 and 2010. The 2 registration studies for the BMT indication did not meet the inclusion criteria for the present analysis as they enrolled < 50 patients in the filgrastim arm [43, 44]. No studies evaluating filgrastim vs placebo or no treatment in PBPC met the inclusion criteria for the present analysis. Similarly, no eligible studies that evaluated filgrastim in patients with ARS were identified in this search. Filgrastim's approval for ARS was based on efficacy studies in animals and filgrastim data from other approved indications [11].

Filgrastim dose, timing, and duration were provided in most studies in CIN [4, 19–21, 23–31], AML [33–38], SCN [6, 40], and BMT [41, 42] but varied across studies (Online Resources 4 and 5). Further evaluation is needed to understand effects of modifications on dose, timing, and duration of filgrastim in different indications.

Overall, the common filgrastim benefit across indications was decreasing incidence and/or duration of severe neutropenia, assessed as the outcomes of FN or fever incidence and/or duration, grade 3 or grade 4 neutropenia incidence and/or duration, and time to ANC recovery. All 25 studies reported at least one of these outcomes, and 21 (84%) provided statistical comparisons for filgrastim vs placebo or no treatment in at least one of the outcomes (11 of 15 CIN studies, all AML studies, all SCN studies, and all BMT studies) (Online Resources 6, 7, 8, 9). Sixteen of 21 studies (76%) demonstrated significant improvement with filgrastim in at least one of the outcomes (9 of 15 CIN studies, 4 of 6 AML studies, 1 of 2 SCN studies, and all BMT studies). The observational study in SCN by Yilmaz et al. [40] showed a nonsignificant reduction in median duration of neutropenia that resolved.

CIN was the indication with the most evidence of improved efficacy with filgrastim vs placebo or no treatment. Meta-analysis of data from 9 RCTs [4, 19–21, 23, 24, 26, 27, 29] with 2197 patients in total (filgrastim, $n = 1130$; placebo or no treatment, $n = 1067$) demonstrated decreased FN incidence with filgrastim (RR 0.63, 95% CI 0.53–0.75), with data from the additional 2 observational studies [18, 32] also showing significantly decreased FN incidence with filgrastim. Meta-analysis of data from 5 RCTs and 1 NCT with 1409 patients in total (filgrastim, $n = 714$; placebo or no treatment, $n = 695$) demonstrated decreased grade 3 or 4 neutropenia incidence with filgrastim (RR 0.50, 95% CI 0.37–0.68).

A recent retrospective study suggested that OS might be greater among patients receiving filgrastim vs placebo [45], but differences were not statistically significant. In our analysis, none of the evaluated studies reported a difference in OS for filgrastim vs placebo or no treatment, suggesting that filgrastim does not appear to have a detrimental effect on long-term outcomes in oncology patients. Cancer treatment is complex; though FN and infection are critical, they are not the only factors determining patient outcomes. Of note, follow-up times were not consistently reported across the evaluated studies.

Chemotherapy dosing outcomes were mostly reported in CIN, with improvements observed with filgrastim use. Significant improvements in RDI were reported in germ cell tumor [24] and NHL [27], significantly fewer dose reductions in SCLC [23] and breast cancer [20], and significantly fewer dose delays in breast cancer [20]. These reports are consistent with recent reports of G-CSF use to maintain planned RDI of chemotherapy in various tumor types [46–49].

In AML, filgrastim shortened time to ANC recovery during induction chemotherapy in 3 RCTs [33, 35, 36] and during consolidation therapy in 1 NCT [38], but no corresponding improvements in infection rates were observed. A possible explanation is that the myeloablative nature of chemotherapy used for acute leukemias results in a period of neutropenia with high infection rates that may not be impacted by filgrastim.

In a pivotal SCN RCT, filgrastim reduced the severity and duration of neutropenia with > 16-fold increase in ANC compared to the control [6]. The study also showed a significant increase in marrow neutrophils and a significant reduction in infection-related events and antibiotic use with filgrastim [6]. Long-term follow-up of this population and nearly 800 other patients affirmed these benefits [50]. As noted earlier, in the observational study by Yilmaz et al. [40] in which the more severely ill patients were treated with filgrastim, ANC was reported to increase with only one patient responding poorly.

Other outcomes such as infections and hospitalizations could not be meaningfully evaluated because of the nature of the study.

In patients undergoing hematopoietic recovery following high-dose chemotherapy with PBPC support, median time to ANC recovery was shorter with filgrastim vs no filgrastim in the RCT (10 vs 11 days, $P < 0.009$) [41] and the observational study (12.5 vs 13.5 days, $P < 0.001$) [42]. Filgrastim did not reduce time to platelet engraftment in either study. Also, filgrastim did not improve other outcomes such as incidence of infection [42], duration of antibiotic use [41], incidence or duration of hospitalization [41, 42], or all-cause mortality [42]. For the observational study [42], incidence of infection and incidence and duration of hospitalization were higher with filgrastim. Of note, the cases reported in this observational study [42] ranged from March 2008 to December 2009. Lack of improvement in patient outcomes might be partially explained by the overall improvement in stem cell transplantation in the past decade [51].

The most commonly reported filgrastim-related AE was bone pain. In the meta-analysis of data from 5 RCTs in CIN [4, 23, 25, 27, 28] with 1078 patients (filgrastim, $n = 540$; no filgrastim, $n = 538$), risk of bone pain was higher with filgrastim (RR 2.61, 95% CI 1.29–5.27). In the remaining CIN studies [4, 20, 21, 23, 26], bone pain rates ranged from < 1.0 to 42.5%. Increased bone pain with filgrastim vs placebo or no treatment was also reported in SCN (general musculoskeletal pain, 25 vs 10%; transient bone pain, 17 vs 6% [6]).

Other salient AEs include pulmonary toxicity in patients with germ cell tumors [24] and splenomegaly in patients with SCN [6]. In Fossa et al. [24], higher proportions of patients receiving filgrastim vs not receiving filgrastim experienced grade 1/2 pulmonary toxicity after BEP/EP (25 vs 16%) or BOP/VIP-B (17 vs 14%) chemotherapy; however, these differences were not observed in the proportions of patients who experienced grade 3 or 4 pulmonary toxicity. Overall, chemotherapy dose intensities were similar across arms in that study [24]. Dale et al. [6] reported asymptomatic palpable splenomegaly in 29 of 120 patients (24%) after receiving filgrastim vs 18 of 123 patients (14%) before receiving filgrastim.

Several limitations should be noted. Firstly, definitions of efficacy outcomes, baseline characteristics and disease history, dose and timing of filgrastim, and the power to detect significant differences in evaluated outcomes varied among studies. Secondly, data from observational studies are likely to be subject to confounding by indication. Lastly, pre-determined inclusion criteria excluded pivotal BMT and PBPC studies due to sample size. However, the advantage of the current systematic review and meta-analysis is that it allowed a comparison of outcomes with filgrastim vs placebo or no treatment in the absence of data from recent clinical trials.

In conclusion, a large dataset evaluating originator filgrastim in US-approved indications exists in the literature. Findings from this study confirmed previous reports on the efficacy and effectiveness of filgrastim, with the most evidence demonstrated in decreased FN and grade 3 or 4 neutropenia incidence in CIN, with a similar trend of improvement in other outcomes in CIN and in other indications. Bone pain was the most commonly reported AE associated with filgrastim use across studies and indications.

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Compliance with ethical standards

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