Meta-analysis of Pegfilgrastim over Filgrastim in the Treatment of Chemotherapy-induced Neutropenia

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Abstract

Introduction: Neutropenia is a major common complication in patients who are treated with myelosuppressive chemotherapy. Prophylaxis with granulocyte colony-stimulating factors (G-CSFs) has been used to reduce the incidence, duration, and severity of chemotherapy-induced neutropenia (CIN).

Methods: This study aimed to examine the efficacy and safety of pegfilgrastim compared with filgrastim in treating chemotherapy-induced febrile neutropenia. PubMed/MEDLINE, Cochrane Library, Scopus, Embase, and Web of science were searched until December 2015. The search was updated in January 2018. Also, the reference lists of included studies were screened for additional citations. The quality of studies was evaluated using the Cochrane risk of bias tools and the random effect model was applied for analyzing the result.

Results: Eleven studies with 1,578 participants (799 in pegfilgrastim arm and 779 in filgrastim arm) fulfilled the inclusion criteria. The incidence of grade 4 neutropenia and febrile neutropenia, the duration of grade 4 neutropenia, and recovery of the absolute neutrophil count were slightly reduced in the pegfilgrastim group, though this difference was not statistically significant. For bone pain, despite the observed superiority in the pegfilgrastim group, there was no significant difference between the two drugs.

Conclusion: The results of our review suggest that there is no overall treatment benefit for a median 10–14 days of filgrastim compared to a single dose of pegfilgrastim in the incidence of grade 4 neutropenia, incidence of febrile neutropenia, duration of grade 4 neutropenia, and recovery of absolute neutrophil count and bone pain in the treatment of CIN.

Keywords: Filgrastim, Pegfilgrastim, Chemotherapy-induced Neutropenia, Neutropenia, Meta-analysis

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Introduction

Neutropenia is a major common complication in patients, who are treated with myelosuppressive chemotherapy. Febrile neutropenia is defined as severe neutropenia with fever, a potentially life-threatening side effect which increases the risk of infection, requiring unplanned hospitalization and treatment with broad-spectrum antibiotics. Specifically, this causes unplanned hospitalizations and delay in the process of chemotherapy in a large proportion of the patients. The most important complication of febrile neutropenia in chemotherapy is reduction of doses or delays in chemotherapy in the majority of patients. It has been shown that the risk of mortality in the patients hospitalized due to febrile neutropenia grows by 9.5%. Prophylaxis with granulocyte colony-stimulating factors (G-CSFs) such as filgrastim, which was approved in the US in 1991, has been shown to reduce the incidence, duration, and severity of chemotherapy-induced neutropenia (CIN) and related complications. They improve chemotherapy-related quality of life among patients with solid tumors or non-myeloid malignancies. The use of colony-stimulating factors is recommended when the risk of febrile neutropenia associated with chemotherapy is ≥ 20% based on age, medical history, disease characteristics, and myelotoxicity of the chemotherapy regimen. This
treatment is used as both primary and secondary prophylaxis\textsuperscript{17}. Filgrastim is normally administered 24 hours after the last dose of chemotherapy as a daily injection for an average of 11 days in a chemotherapy cycle\textsuperscript{6,15}.

Pegfilgrastim is a PEGylated form of filgrastim which requires one injection per chemotherapy cycle after 24 hours off the last dose of chemotherapy\textsuperscript{16}. Mild to moderate bone pain is a commonly reported side effect of pegfilgrastim with an incidence of approximately 25–40\%\textsuperscript{17,18}. The current clinical guidelines in both Europe and the US assume that filgrastim and pegfilgrastim are clinically equivalent\textsuperscript{19}. Two pivotal non-inferiority trials, upon which licensing depended, concluded that filgrastim and pegfilgrastim are comparable in efficacy, safety, and tolerance\textsuperscript{20,21}. Although some studies claim the superiority of pegfilgrastim in terms of the safety and efficacy, the evidence for any superiority of PEGylated filgrastim is equivocal\textsuperscript{22}. This review aims to gather and evaluate updated evidence on the efficacy of single subcutaneous injection of pegfilgrastim as compared with daily injection of filgrastim against chemotherapy-induced febrile neutropenia in patients with solid tumors and lymphoma.

**Materials and methods**

This systematic review and meta-analysis were performed following PRISMA statement and also registered in PROSPERO (CRD42018108130).

**Search strategy**

A systematic search was undertaken in bibliographic databases including PubMed/MEDLINE, Cochrane Library, Scopus, Embase, and Web of science. The databases were searched through a combination of relevant keywords such as Neoplasm, Neoplasms, Cancer, Tumor, Lymphoma, Neutropenia, Chemotherapy-Induced Neutropenia, Filgrastim, Neupogen, Granulocyte Colony-Stimulating Factor, G-CSF Recombinant Human Methionyl, Recombinant-Methionyl Human, r-metHuG-CSF, Amgen brand of Filgrastim, XM02, daily G-CSF, Pegfilgrastim, PEG SD-01, PEG-rmetHuG-CSF, SD-01, SD-01-filgrastim, Neulasta, PEGylated Filgrastim, PEGylated G-CSF. There were no restrictions in terms of language and time. The reference lists of included studies were reviewed for additional citations. The search strategy for PubMed database is presented in supplement 1.

**Inclusion and exclusion criteria**

Studies were eligible for inclusion if they were randomized controlled trials and compared the efficacy or safety of filgrastim versus pegfilgrastim. Studies that reported neutropenia due to other causes such as congenital neutropenia, bone marrow or peripheral blood stem cell transplantation, other types of tumors (other than solid tumor and lymphoma) were excluded. The studies where filgrastim and pegfilgrastim were compared in combination with other drugs were not included. Animals’ studies were also excluded.

**Study selection**

Following the search, all identified citations were collated and uploaded into Endnote X7, with duplicates removed. After this removal, two reviewers (MM&MA) screened the records based on the title, abstract, and full text to identify included studies based on the eligibility criteria. Any disagreements that arose between the reviewers were resolved through discussion.

**Data extraction**

The data were extracted by two reviewers (MM&MA) independently and checked by a third reviewer (A.A), when discrepancies existed, and using the Cochrane data extraction checklist\textsuperscript{23}. The extracted data included specific details about the interventions, populations, study methods, and outcomes of significance to the review question and specific objectives. Other extracted data included the author’s name, year of publication, country, the doses, type of cancer, chemotherapy regimen used in patients, and patients’ study period. In addition to data on incidence of FN, as the main outcome, data of incidence of G4 neutropenia, duration of G4 neutropenia, time to ANC (absolute neutrophil count) recovery and incidence of bone pain were also extracted.

**Quality appraisal**

Selected studies were critically appraised at the study level using the Cochrane risk of bias tool to assess potential sources of bias. Then, several important risk of bias which may have affected the results of clinical trials was examined. These biases included selection bias, performance bias, detection bias, attrition bias, and reporting bias. Quality appraisal was performed by two independent reviewers. All disagreements were resolved by discussion.
Summary measures
For the binary outcome, risk ratio (RR) and 95% confidence interval was used as the summary of the measure. The binary outcomes included incidence of FN, the main outcome, as well as incidence of G4 neutropenia and bone pain. For continuous outcomes, duration of G4 neutropenia, and time to ANC recovery (day), the mean difference and its 95% confidence interval was used as the summary measure. Other measures of effect and their confidence intervals were transformed to these summary measures in RevMan (review manager) transformation table.

Synthesis of results
RevMan software was used for meta-analysis. For binary outcomes the Mantel-Haenszel method, while for continuous outcomes, the Inverse Variance method was employed. The heterogeneity was assessed using I^2 test. The I^2<50% indicated low heterogeneity and was considered as the justification for pooling the results. Random Effect was used for pooled CIs estimation.

Results
Number and characteristics of studies
A total of 971 studies were retrieved from the databases search. After removing duplicates as well as checking titles, abstracts and full texts, studies were included for the final analysis (Fig. 1).

These primary studies were conducted in patients with breast cancer, non-Hodgkin's lymphoma, lymphoma, and various solid tumors. Three of the studies had been performed in UK, two in US, two in Korea, two in China, one in Japan, and one in Russia. All of the included studies were RCTs. Of the 1,578 participating patients in the included studies, 779 patients were assigned to Filgrastim arm and 799 patients in the Pegfilgrastim arm. The publication years of studies were between 2002 and 2016. The summary characteristics of the included studies are presented in Table 1.

Quality appraisal
Of 11 RCT studies, three had Good quality, five Moderate qualities, and three Weak qualities. Randomization was performed in all studies, and blinding was performed in three studies. Risk of bias graph and risk of bias summary are presented in Supplement 2 and 3, respectively. Publication bias was not likely to have much effect on our results, as studies have been evenly distributed symmetrically on both sides of RR for febrile neutropenia (Supplement 4).

Febrile Neutropenia (FN)
Ten of the included studies reported febrile neutropenia. The risk for FN across the chemotherapy cycles was smaller for pegfilgrastim than for filgrastim, though
Table 1  Summary characteristics of included studies

| Author, Year, Country, Cancer type | Study Design | Chemotherapy regimen | N | Number of cycles | Intervention (N) | Comparator (N) |
|-----------------------------------|-------------|----------------------|---|-----------------|-----------------|---------------|
| Holmes et al, 2002(21) US, Breast | DB, RCT, Phase 3 | Docetaxel 75 mg/m² And Doxorubicine 60 mg/m² | 296 | 4 | Pegfilgrastim 100 μg/kg (N = 149) | Filgrastim 5 μg/kg/day (N = 147) |
| Holmes et al, 2002(17) US, Breast | DF, RCT, Phase 2 | Docetaxel 75 mg/m² And Doxorubicine 60 mg/m² | 71 | 4 | Pegfilgrastim 100 μg/kg (N = 46) | Filgrastim 5 μg/kg/day (N = 25) |
| Green et al, 2003(20) UK, Breast | DB, RCT, Phase 3 | Docetaxel 75 mg/m² And Doxorubicine 60 mg/m² | 152 | 4 | Pegfilgrastim 6 mg (N = 77) | Filgrastim 5 μg/kg (N = 75) |
| Vose et al, 2003(31) UK, Lymphoma | OL, RCT, phase 2 | ESHAP | 66 | 4 | Pegfilgrastim 100 μg/kg (N = 33) | Filgrastim 5 μg/kg (N = 33) |
| Grigg et al, 2003(29) UK, NHL | OL, DF, RCT, Phase2 | CHOP | 27 | 6 | Pegfilgrastim 100 μg/kg (N = 14) | Filgrastim 5 μg/kg/day (N = 13) |
| Park et al, 2013(30) Korea, Breast | Randomized, multi-center, OL, Phase 2 | TAC | 41 | 6 | PEGylatingFilgrastim 6 mg (N = 20) | Filgrastim 100 μg/m²/day (N = 21) |
| Yuan et al, 2013(28) China, Solid tumors | Multicenter, randomized, crossover, Phase 3 | PC, AC, CHOP | 313 | 2 | PEGylatingFilgrastim 100 μg/kg (N = 313) | Filgrastim 5 μg/kg/day (N = 313) |
| Zhang et al, 2015(27) China, Breast | OL, Randomized, multicenter, DF, Phase 2 | TAC | 86 | 1 | Pegfilgrastim 100 μg/kg (N = 43) | Filgrastim 5 μg/kg/day (N = 43) |
| Safafet et al, 2013(32) Russia, Breast | OL, randomized, active comparator, Non inferiority | Docetaxel 75 mg/m² And Doxorubicine 60 mg/m² | 39 | 1 | Pegylationfilgrastim 6 mg (N = 20) | Pegfilgrastim 5 μg/kg (N = 19) |
| Park et al, 2016(33) Korea, Breast | randomized, multi-center, open-label, Phase II | doxorubicin 50 mg/m², cyclophosphamide 500 mg/m², docetaxel 75 mg/m² | 74 | 6 | PEGylatingFilgrastim 6 mg (N = 36) | Filgrastim 100 μg/m²/day (N = 38) |
| Kubo et al, 2016(26) Japan, malignant lymphoma | phase III, multi-center (47 sites), double-blind, randomized trial | cyclophosphamide, etoposide, dexamethasone arituximab (CHAS) | 107 | 1 | Pegfilgrastim 3.6 mg (N = 53) | Pegfilgrastim 50 μg/m² (N = 54) |

it was not statistically significant (RR = 0.76; 95% CI: 0.51–1.13). Further, the heterogeneity was low (I² = 4%). The results of FN are demonstrated for cycle 1, cycles 1 and 2, and overall separately (Fig. 2).

Grade IV neutropenia

Seven of eleven included studies reported the rate of grade 4 neutropenia, but some of them did not report it for all cycles. All seven studies reported it for the first cycle, four studies in cycle 2, and two studies reported this outcome in cycles 3 and 4. According to RR and 95% CI, the difference between pegfilgrastim and filgrastim was not significant in any of the cycles. The value of I² showed that heterogeneity was low in cycles 1, 2, and 4 and high in cycle 3 (Fig. 3).

The duration of neutropenia

Ten studies reported the duration of neutropenia in the first cycle. There were 457 patients in Pegfilgrastim and 445 patients in Filgrastim groups. The pooled MD (mean difference) for the duration of neutropenia in the first cycle was not statistically significant. In other words, there was no difference between two groups in cycle 1 (MD = 0.00; 95% CI: -0.18, 0.15, P = 0.86). Also, MD was low in favor of Pegfilgrastim, but according to mean difference and confidence interval, this difference was not statistically significant in cycles 2, 3, and 4 (Fig. 4).

Time to ANC recovery

Data from nine studies were pooled for this outcome. Six studies in the first cycle and three studies in overall reported this outcome. Pooled MD for the time to ANC recovery revealed that the MD between filgrastim and pegfilgrastim arms was not statistically significant (MD = -0.34; 95% CI: -0.75, 0.08). The pooled MD for time to ANC recovery in cycle 1 was lower in filgrastim compared to pegfilgrastim. This difference was not statistically significant in cycle 1 between two arms (cycle 1, MD = -0.03; 95% CI: -0.34, 0.29). The value of I² indicated that the heterogeneity between the studies was high, and the result should be interpreted carefully (Fig. 5).

Bone pain

Bone pain was the only common safety outcome between the primary studies. In studying this outcome, bone pain or skeletal pain were considered together. Nine studies reported this outcome. The pooled RR of 0.96
(95% CI: 0.79, 1.17) was not statistically significant and incidence of bone pain was similar for pegfilgrastim and filgrastim, although the risk of incidence for pegfilgrastim was lower than filgrastim. Heterogeneity was low according to $I^2 = 12\%$ (Supplement 5).

**Discussion**

This study revealed no superiority of the effect for prevention of febrile neutropenia in filgrastim as compared to pegfilgrastim. No significant difference was observed
Fig. 2 Forest plot for incidence of febrile neutropenia comparing Pegfilgrastim and Filgrastim sub-grouped by chemotherapy cycles

Fig. 3 Forest plot for incidence of grade IV neutropenia comparing Pegfilgrastim and Filgrastim sub-grouped by chemotherapy cycles
### Pegfilgrastim and Neutropenia

#### Results of Clinical Trials

| Study or Subgroup | Pegfilgrastim | Filgrastim | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|--------------|------------|-----------------------------------|-----------------------------------|
| **1.4.1 Cycle 1** |              |            |                                   |                                   |
| Green 2003        | 1.0          | 1.4        | 77 1.0 1.1 75 17.7%              | 0.20 0.40 0.69                  |
| Grigg 2003        | 0.6 0.9 5   | 0.5 0.3 7 | 11.9%                             | 0.10 0.10 0.20                  |
| Holmest 2002      | 1.3 1.1 4.6 | 1.1 1.3 25 7.4%                   | -0.30 -0.60 0.30                |
| Holmest 2002a     | 1.7 1.5 149 | 1.8 1.4 147 25.6%                | -0.10 -0.40 0.20                |
| Kang 2005         | 6.2 1.3 53 | 5.1 1.3 54 11.6%                 | 0.10 0.20 0.30                  |
| Park 2013         | 2.0 0.5 10 | 2.4 0.9 13 8.9%                   | -0.40 -0.70 0.01                |
| Park 2016         | 0.2 1.1 4  | 0.0 1.1 4 10.1%                   | 0.01 0.10 0.20                  |

**Fig. 4** Forest plot of duration of grade IV Neutropenia comparing Pegfilgrastim and Filgrastim sub-grouped by chemotherapy cycles

| Study or Subgroup | Pegfilgrastim | Filgrastim | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|--------------|------------|-----------------------------------|-----------------------------------|
| **1.4.2 Cycle 2** |              |            |                                   |                                   |
| Green 2003        | 1.1 1.2 76  | 0.9 1.1 74 34.6%              | 0.20 0.40 0.65                  |
| Holmest 2002      | 0.7 0.9 140 | 1.1 1.1 105 40.3%              | -0.40 -0.60 0.17                |
| Vora 2013         | 0.4 0.9 22  | 0.6 1.1 20 25.1%               | -0.20 -0.40 0.05                |
| Subtotal (95%)    | 238          | 216 100.0%                     | -0.01 -0.06 0.01                |

**Fig. 5** Forest plot for time to ANC recovery comparing Pegfilgrastim and Filgrastim sub-grouped by chemotherapy cycles

| Study or Subgroup | Pegfilgrastim | Filgrastim | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|--------------|------------|-----------------------------------|-----------------------------------|
| **1.4.3 Cycle 3** |              |            |                                   |                                   |
| Green 2003        | 1.1 1.2 76  | 0.9 1.1 73 43.7%                | 0.20 0.40 0.67                  |
| Holmest 2002      | 0.6 0.9 138 | 1.2 1.4 143 51.1%               | -0.50 -0.60 0.33                |
| Subtotal (95%)    | 213          | 206 100.0%                     | -0.01 -0.06 0.01                |

**Fig. 6** Forest plot for bone pain comparing Pegfilgrastim and Filgrastim sub-grouped by chemotherapy cycles

| Study or Subgroup | Pegfilgrastim | Filgrastim | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|--------------|------------|-----------------------------------|-----------------------------------|
| **1.4.4 Cycle 4** |              |            |                                   |                                   |
| Green 2003        | 1.1 1.2 74  | 1.1 1.3 70 45.6%                | 0.20 0.40 0.67                  |
| Holmest 2002      | 0.8 1.2 130 | 1.3 1.5 132 54.4%               | -0.40 -0.50 0.08                |
| Subtotal (95%)    | 212          | 206 100.0%                     | -0.01 -0.06 0.01                |

**Fig. 7** Forest plot for bone pain comparing Pegfilgrastim and Filgrastim sub-grouped by chemotherapy cycles

| Study or Subgroup | Pegfilgrastim | Filgrastim | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|--------------|------------|-----------------------------------|-----------------------------------|
| **1.5.1 All cycles** |              |            |                                   |                                   |
| Green 2003        | 1.0 0.986    | 0.9 0.996 | 14 1.0 9.8 13 17.4%              | 0.00 0.05 0.10                  |
| Holmest 2002      | 0.5 0.806    | 0.4 0.868 | 46 8.4 10.0%                     | 0.25 0.50 0.75                  |
| Park 2013         | 9.9 1.6 20  | 9.8 0.8 20 16.2%                | 0.10 0.20 0.30                  |
| Vora 2013         | 9.0 1.58     | 9.0 1.00 | 36 10.0%                         | 0.75 1.50 2.00                  |
| Yuen 2013         | 16.1 5.511   | 16 5.0 5.51 21 8.5%             | 0.01 0.10 0.20                  |
| Wei Zhang 2015    | 1.16 1.91    | 1.43 1.16 | 31 2.1 31 7.6%                   | 0.01 0.10 0.20                  |
| Subtotal (95%)    | 212          | 206 100.0%                     | -0.01 -0.06 0.01                |

**Fig. 8** Forest plot for time to ANC recovery comparing Pegfilgrastim and Filgrastim sub-grouped by chemotherapy cycles

| Study or Subgroup | Pegfilgrastim | Filgrastim | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|--------------|------------|-----------------------------------|-----------------------------------|
| **1.5.2 All cycles** |              |            |                                   |                                   |
| Green 2003        | 9.1 1.003    | 7.9 1.003 | 76 37.2%                          | 0.00 0.05 0.10                  |
| Holmest 2002      | 9.1 1.244    | 8.7 1.244 | 159 29.0%                         | -0.40 -0.50 0.05                |
| Yuen 2013         | 0.9 0.97     | 0.9 0.84 | 20 1.5%                          | 0.00 0.01 0.02                  |
| Subtotal (95%)    | 543          | 539 100.0%                     | -0.02 -0.06 0.01                |

**Fig. 9** Forest plot for bone pain comparing Pegfilgrastim and Filgrastim sub-grouped by chemotherapy cycles

| Study or Subgroup | Pegfilgrastim | Filgrastim | Mean Difference IV, Random, 95% CI | Mean Difference IV, Random, 95% CI |
|-------------------|--------------|------------|-----------------------------------|-----------------------------------|
| **Supplement 5**  |              |            |                                   |                                   |

Test for subgroups: $\chi^2 = 1.30$, df = 2, $p = 0.56$.

Test for overall effect: $Z = 1.19$, $p = 0.16$.

Test for subgroups: $\chi^2 = 1.00$, df = 6, $p = 0.96$.

Test for overall effect: $Z = 1.16$, $p = 0.10$.

Test for subgroups: $\chi^2 = 1.48$, df = 5, $p = 0.79$.

Test for overall effect: $Z = 1.48$, $p = 0.07$.

Test for subgroups: $\chi^2 = 0.95$, df = 3, $p = 0.95$.

Test for overall effect: $Z = 1.59$, $p = 0.09$.

Test for subgroups: $\chi^2 = 0.43$, df = 2, $p = 0.13$.

Test for overall effect: $Z = 1.27$, $p = 0.05$.
between pegfilgrastim and filgrastim in other outcomes such as incidence of G4 neutropenia, duration of neutropenia, time of ANC recovery, and incidence of bone pain over cycles. However, the review showed some tendency in safety and efficacy toward pegfilgrastim in later cycles of chemotherapy. This result should be confirmed by new trials as the number of trials in later cycles was too low to make a reliable judgment about cycle-specific results.

This review examined eleven trials which included four additional trials as compared to the last review. The included studies were conducted in patients with breast cancer, non-Hodgkin’s lymphoma, lymphoma, and various solid tumors. Tree of the studies had been performed in UK, two of them in US, two in China, one in Russia, two in Korea, and one in Japan. The last former similar systematic review suggested that pegfilgrastim is effective in reduction the incidence of FN compared to filgrastim with RR = 1.54 (95% CI: 1.03–2.29). The other outcomes in the study did not unveil any significant differences between pegfilgrastim and filgrastim. Also, there was another systematic review conducted in 2007 including 5 RCTs on pegfilgrastim vs. filgrastim, which indicated a protective effect of pegfilgrastim with RR = 0.64 (95% CI: 0.43–0.97), where there was no significant effect for the other outcomes. Our study results are in favor of two previous systematic reviews in terms of incidence of grade 4 neutropenia, duration of neutropenia, time to ANC recovery, and incidence of bone pain. However, it revealed different results for incidence of FN suggesting that newer studies have advocated the non-superiority.

There is a tendency to replacing filgrastim with PEGylated either among patients or physicians. It has resulted from easier administration which alleviates treatment burden for patients through lowering the number of treatment sessions. Considering the advantages of PEGylated form of filgrastim, non-inferiority in efficacy and comparability in incidence of SAR (serious adverse reaction) would be enough for using pegfilgrastim instead of filgrastim in eligible patients. Although this review supported comparability of pegfilgrastim and filgrastim for eligible patients, it should be kept in mind that pharmacovigilance and observational studies could reveal whether these two treatments are comparable in terms of expected and unexpected SAE/R (serious adverse event/reaction). This review did not show any significant difference for bone pain. On the other hand, newer RCTs have indicated some protective effects for Peg on incidence of bone pain. Overall, the results revealed comparability of bone pain across the treatments. This comparability was more supported by larger studies.

Overall, the risk of bias was moderate in the included studies. The sample sizes ranged from 27 to 313. The allocation process in all studies was based on the randomization that had been followed through the studies. There was a low probability of bias arising from randomization process and bias due to deviation from the intended interventions. In recent studies, there were less blinded participants and personnel, yet no study reported missing data analysis or the effect of missing data. According the appraisal of results, risk of bias in the measurement of outcome due to un-blinded outcome assessors was prevalent in included studies. However, the type of studies’ outcomes was almost independent of the assessors or reporter judgment. There was an exception for the safety outcome (bone pain) since it was based on the patients’ reports and assessor subjectivity. Studies with a high risk of bias due to outcome assessor reported less bone pain for pegfilgrastim group, while studies with an unclear risk of bias reported no difference between the study groups.

Considering other biases, there was a high risk in terms of effect of conflict of interest.

The depicted funnel graph for the main outcome did not provide conclusive evidence to reject the risk of publication bias. Although all studies have reported FN as the main outcome, there was discrepancy between the number of cycles and approach of reporting on different cycles. One study, out of seven studies that had reported incidence of FN over all cycles, showed a significant protective effect of pegfilgrastim. This study had been conducted in the US with an overall low risk of bias. Its sample size included 297 breast cancer patients undergoing naïve or adjuvant chemotherapy.

There was some heterogeneity across the study results, especially regarding the number of reported cycles. All studies had relatively agreed upon no difference between pegfilgrastim and filgrastim in terms of different outcomes in cycle 1. However, the results were inconclusive for other cycles. There were some studies reporting protective effect of pegfilgrastim for later cycles. Further primary studies can focus on the effect of long-term use of pegfilgrastim as compared to filgrastim. Finally, note that the patients and chemotherapy regimens were different.

In conclusion, this review with 11 included studies did not show any superior protective effect of single dose of pegfilgrastim as compared to 10–14 days of filgrastim in the treatment of chemotherapy induced FN.

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Conflict of interest:
The authors declare that they have no conflict of interest.
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