Comparing the efficacy and safety of long and short acting drugs targeting Granulocyte Colony-stimulating Factor in cancer patients after chemotherapy: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Granulocyte Colony-Stimulating Factor (G-CSF) is widely targeted for the treatment of cancer patients after chemotherapy. However, the safety and efficacy comparisons of long (L-G-CSF) and short-acting (S-G-CSF) drugs targeting G-CSF are still lacking. Thus, herein, we attempted to address this issue by undertaking meta-analyses of existing studies using different drugs targeting G-CSF.

Methods: The relevant studies were identified by searching Pubmed, EMBASE, Cochrane Library, and China National Knowledge Infrastructure (CNKI) databases. Febrile neutropenia (FN) was considered as the direct primary efficacy endpoint, while severe neutropenia (SN) and the duration of severe neutropenia (DSN) served as secondary efficacy endpoints. Bone pain (BP) was used as an indicator for safety analysis. All identified trials were assessed using the Cochrane Collaboration Tool and meta-analysis was performed using Review Manager 5.3 and STATA 15.0 software.

Results: Our meta-analyses based on 20 randomized controlled trials (RCTs) revealed that L-G-CSF drugs including empegfilgrastim, L-G-CSF biosimilars, and pegfilgrastim were overall better in reducing FN incidence compared to S-G-CSF drugs like filgrastim and lenograstim (odds ratio [OR]=0.70, 95% confidence interval [CI]=0.54~0.92, p=0.01). Specifically, filgrastim resulted in higher FN risk than pegfilgrastim (OR=0.66, 95% CI=0.50~0.87, p=0.004). However, L-G-CSF and S-G-CSF drugs revealed no differences in terms of SN, DSN, and BP endpoints (SN: OR=0.92, 95% CI=0.78~1.09, p=0.33; DSN: RR=-0.04, 95% CI=0.17~0.09, p=0.53; BP: OR=0.87, 95% CI=0.67~1.14, p=0.31).

Conclusion: Based on our analyses, L-G-CSF drugs in comparison to S-G-CSF drugs resulted in significantly lower FN incidence, but no difference in terms of the SN, DSN, and BP endpoints.

Introduction

Neutropenia is the most common dose-limiting toxicity observed during chemotherapy in cancer patients [1]. It usually increases the risk of infection, and often leads to severe neutropenia (SN), characterized as an absolute neutrophil count (ANC) of < 0.5 × 10^9/L, and febrile neutropenia (FN), defined as severe reduction in neutrophils accompanied by fever of > 38.3 °C measured orally &
lasting for 1 hr with absolute neutrophil count (ANC) of < 500 neutrophils [2, 3]. Both FN and SN not only result in delaying the chemotherapy cycles or reducing the chemotherapy dose in subsequent cycles [2, 4], but also seem to be associated with serious infections and increased morbidity and mortality risk in cancer patients [2]. Additionally, FN has been shown to be associated with lengthy hospitalization, higher treatment costs, and reduced qualify of life [5]. Therefore, the occurrence of FN and SN is a serious issue for cancer patients treated with myelosuppressive chemotherapy.

Granulocyte colony-stimulating factors (G-CSFs), which typically stimulate the proliferation, differentiation, and activation of hematopoietic cells [6], have also been shown to be involved in reducing the incidence of FN and SN upon being targeted as prophylaxis treatment following chemotherapy [5, 7]. In this context, the guidelines of the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), and European Society for Medical Oncology (ESMO) suggest that G-CSF be used as primary prophylaxis in cancer patients receiving chemotherapy and displaying > 20% risk of FN [8–10]. Daily injections of G-CSF targeting drug filgrastim are widely used to increase the neutrophil count in clinical therapy. However, over a period of time and with the development of additional G-CSF drugs, long-acting (L-G-CSF) drugs like empegfilgrastim, L-G-CSF biosimilars, pegteograstim, and pegfilgrastim were also approved for clinical use. However, there have been some reports about the varying effects of S-G-CSF and L-G-CSF drugs in reducing FN and SN incidence rate after chemotherapy [11–14]. Multiple studies have indicated that pegfilgrastim is more effective than filgrastim based on ANC evaluation in patients receiving myelosuppressive chemotherapy [11, 12, 15–28]. Thus, there are differing accounts about the benefits of S-G-CSF and L-G-CSF drugs and the subject requires further clarification.

Despite the efficacy of some G-CSF drugs in clinical practice with regard to FN and SN complications, a few cancer patients also display adverse events [29–31]. Bone pain (BP) is the most common adverse event reported in clinical trials, but the exact mechanism of G-CSF drug-mediated BP induction is not fully known [29]. Some studies have indicated that administrating different G-CSF drugs can lead to varying degrees of BP, and oncologists have observed that pegfilgrastim can induce more frequent and severe BP than filgrastim [32]. However, very few studies in the literature have
directly compared the degree of BP induction by L-G-CSF and S-G-CSF drugs. Overall, multiple studies have established the significant efficacy of G-CSF drugs [5, 7], but there is still a dispute about the efficacy of L-G-CSF and S-G-CSF drugs. In some clinical trials, L-G-CSF drugs, especially pegfilgrastim, have been demonstrated to be better than S-G-CSF drugs [15, 19, 21, 26], but other studies reported no such differences [11, 33]. Therefore, herein, we have undertaken a systematic review and meta-analysis based on available RCTs on the use of different G-CSF-targeting drugs after chemotherapy for reducing the incidence of FN, SN, DSN, and BP.

Methods

Search strategy

All relevant studies between January 1, 2000 and May 1, 2019 were systematically identified using Pubmed, EMBASE, Cochrane Library, and China National Knowledge Infrastructure (CNKI) databases. The following search terms were used: “cancer” or “tumor” or “neoplasm” or “carcinoma” and “L-G-CSF biosimilar” or “Empegfilgrastim” or “Balugrastim” or “Pegteograstim” or “pegfilgrastim” or “Mecapegfilgrastim” or “Lipegfilgrastim” or “PEG-rhG-CSF” or “PEG SD-01” and “Filgrastim” and “S-G-CSF biosimilar” or “Leridistim” or “Lenograstim”. Next, additional studies were further manually searched using reference lists from the relevant retrieved articles and reviews.

Eligibility criteria for inclusion and exclusion

The following criteria was used to select studies for our meta-analyses: (1) Randomized controlled trials (RCTs) comparing the use of L-G-CSF and S-G-CSF drugs in cancer patients after chemotherapy; (2) Publications with human subjects only; (3) Studies in English and Chinese languages only; (4) RCTs using FN, SN, DSN, or BP as important indicators; and (5) patients with any kind of cancer. However, the studies were excluded if they were: (1) Non-RCTs (case reports, cohort studies, review articles, meta-analyses, animal experiments, etc.); (2) studies in a language than English or Chinese; (3) studies without sufficient data to calculate the odds ratios (ORs) or risk ratios (RRs) and their 95% confidence intervals (CIs); (4) studies reporting no outcome measures; and (5) those with duplicate publications.
Data extraction

The data was independently reviewed, extracted, and assessed by two independent authors (X. W. Zhang and Y. Wang) on the basis of the above selection criteria. All disagreements were resolved by discussion and consensus with the third author (Y. Li). Important information such as the first name, year of publication, country, and source of the sample were recorded. The following information about clinicopathological parameters was extracted from the selected studies: patient age and gender, histological type of cancer, cancer stage, and ANC baseline. All information was subsequently organized in a tabular format for further analyses.

Outcome measure

To assess the efficacy of G-CSF drugs post chemotherapy, FN was chosen as the primary outcome, while SN and DSN served as the secondary outcomes. In addition, BP assessment was used as the primary endpoint for safety analysis of the G-CSF drugs. More specifically, FN was defined as ANC of <0.5 or 1.0×10⁹/L and oral temperature of ≥38.0°C, while SN was defined as ANC of <0.5 or 1.0×10⁹/L. When trials showed data indicative of both grades 3 and 4 bone marrow suppression (ANC <0.5 and 1.0×10⁹/L), data for the ANC <0.5×10⁹/L were adopted for analysis because grade 3 has less clinical significance and was not always reported in the included studies.

Quality assessment

The quality of all included RCTs was independently assessed by two investigators using the Cochrane Collaboration tool [34]. Each RCT was assessed based on the following three criteria: selection, comparability, and clinical outcomes, and was scored between 0 and 9, where a score of ≥7 indicated good quality.

Statistical analysis
All meta-analyses were conducted using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) and STATA 15.0 (Stata Corporation, TX, USA) statistical software. Heterogeneity among different RCTs was estimated using Cochran’s Q test ($p<0.05$ indicated significant heterogeneity) and the $I^2$ statistic. An $I^2$ value of 0~25% represented low heterogeneity, while a value of 25~50% showed moderate heterogeneity. An $I^2$ value of 50~75% indicated high heterogeneity and a value of 75~100% revealed extremely high heterogeneity. According to Cochrane’s handbook guidelines, meta-analyses were conducted using the random effects model when the $I^2$ value was $\geq 50\%$. Otherwise, the fixed effects model was used [35, 36]. In addition, studies were stratified based on the use of different L-G-CSF and S-G-CSF drugs. Sensitivity analysis was performed upon observing a statistically significant heterogeneity between different RCTs. The publication bias was estimated using funnel plots [37, 38] and Begg's test [39], where a $p$ value of $<0.05$ indicated significant publication bias.

Results

**Study selection and patient characteristics.**

Our literature search effort initially identified 703 potentially relevant studies. Based on the inclusion criteria, only 20 RCTs were eligible to be included for quantitative data synthesis [11-28, 30, 40]. The complete study selection process has been summarized in Figure 1. All trials were conducted between the years 2000 and 2019 in 10 different countries, namely China, United States of America, Japan, Spain, Australia, South Korea, Germany, Italy, India, and Russia. The studies included a total of 3635 cancer patients with various tumor types including Breast cancer (BC), Non-small-cell lung carcinoma (NSCLC), Lymphoma, Non-Hodgkin lymphoma (NHL), Head and neck cancer (HNC), Acute myeloid leukemia (AML), Sarcomas, and Diffuse large B-cell lymphoma (DLBCL). All the RCTs were of high quality according to the Cochrane Collaboration Tool. The basic characteristics of all the included studies have been summarized in Table 1.

**Analysis of primary and secondary efficacy endpoints**
Among the 20 RCTs involving 3635 patients that were included in our meta-analysis, 1970 patients received L-G-CSF treatment (empegfilgrastim, L-G-CSF biosimilars, pegfilgrastim), while 1665 patients had S-G-CSF treatment (filgrastim, lenograstim). Our meta-analyses indicated that L-G-CSF drugs were better at reducing the FN incidence rate in comparison to S-G-CSF drugs (OR=0.70, 95% CI=0.54~0.92, \( p=0.01 \)). Further, stratification of patients in the L-G-CSF group based on different drug treatments revealed that pegfilgrastim clearly had significant benefits in comparison to other drugs (OR=0.66, 95% CI=0.50~0.87, \( p=0.004 \)), while empegfilgrastim and L-G-CSF biosimilars had no significant differences [(OR=0.65, 95% CI=0.31~1.34, \( p=0.24 \)) and (OR=1.61, 95% CI=0.21~12.57, \( p=0.65 \)], respectively.

In addition, upon comparing the impact of L-G-CSF and S-G-CSF drugs on the secondary endpoints SN and DSN, our analyses depicted no significant differences. The observed OR for SN was 0.92, 95% CI=0.78~1.09, \( p=0.33 \), and the RR for DSN was -0.04, 95% CI=0.17~0.09, \( p=0.53 \), as shown in Supplementary Figures 1 and 2, respectively.

### Comparing the impact on safety endpoint

BP was the most common safety endpoint reported after pegfilgrastim and L-G-CSF biosimilar treatments. Thus, we used this parameter as the safety endpoint to compare the effects of L-G-CSF and S-G-CSF drugs on safety. Our data showed very small but non-significant pooled mean differences for BP between the L-G-CSF and S-G-CSF drug treatment groups (OR=0.87, 95% CI=0.67~1.14, \( p=0.31 \)), as shown in Supplementary Figure 3.

### Sensitivity analyses

For FN and SN endpoint meta-analyses, the fixed-effect model was used, as no heterogeneity was observed among different RCTs (\( I^2=3\% \), \( p=0.42 \) and \( I^2=0\% \), \( p=0.99 \), respectively). However, DSN and BP parameters showed moderate heterogeneity with \( I^2=53\% \), \( p=0.03 \) and \( I^2=44\% \), \( p=0.05 \), respectively, among different RCTs. To assess the stability of our results, we analyzed the changes in
overall OR/RR for FN, SN, DSN, and BP by omitting one study at a time. Our data, as shown in Figures 3A-D, indicated no changes in the pooled OR/RR for any of the endpoints, thereby establishing the stability of our analysis.

**Publication bias analyses**

The publication bias was assessed using funnel plots and Begg's test. As seen in Figures 4A-D, the funnel plots suggested no publication bias between studies comparing L-G-CSF and S-G-CSF drugs in reference to the FN (Figure 4A, SN (Figure 4B), DSN (Figure 4C), and BP (Figure 4D) endpoints. Similarly, based on Begg's test, we again observed no significant publication bias for these different endpoints, as seen in Figures 4E-H.

**Discussion**

The role of G-CSF drugs has been critical to address the incidence of chemotherapy-induced neutropenia. Specifically, the S-G-CSF drug filgrastim is widely used in the clinic at a dose of 5 µg/kg once every day. Currently, a few L-G-CSF drugs including empegfilgrastim, L-G-CSF biosimilars, and pegfilgrastim have been approved. In our study, we attempted to compare the efficacy and safety of L-G-CSF and S-G-CSF drugs for treating neutropenia in patients with different tumor types who underwent chemotherapy. This meta-analysis was performed with the intent of gaining more insight into beneficial clinical treatments. Our meta-analyses results clearly established that L-G-CSF drugs have a significant effect on reducing the incidence of FN but did not show any significant differences in terms of SN, DSN, and BP endpoints.

We used FN incidence as the primary endpoint in our study to assess the impact of G-CSF drugs because many previous studies clearly indicated that G-CSF drugs are associated with improved FN incidence after chemotherapy. More specifically, in our study, pegfilgrastim was the most effective at reducing FN incidence among different L-G-CSF drugs. Consistent with our observation, multiple studies have also indicated the effectiveness of pegfilgrastim (L-G-CSF drug) over filgrastim (S-G-CSF...
drug) at reducing FN incidence [21, 26, 41]. On the contrary, one meta-analysis showed no difference between pegfilgrastim and filgrastim in reducing the risk of FN [33]. However, further stratification of L-G-CSF drugs indicated no differences between the efficacy of empegfilgrastim and L-G-CSF biosimilars for FN incidence, and this can be attributed to the low number of patients in these groups. Importantly, one of the immediate implications of our results is that having a single injection of L-G-CSF drugs can help patients comply easily in comparison to a situation where they have to take multiple shots of S-G-CSF drugs. There is some documentation about patients’ poor compliance when they have to take treatments/injections very frequently [42].

To achieve better understanding about the differences in the efficacy of L-G-CSF and S-G-CSF drugs in cancer patients after chemotherapy, we also analyzed secondary endpoints like SN and DSN. However, we did not observe any differences between L-G-CSF and S-G-CSF drugs. In this regard, some earlier patient trials have indicated that lenograstim drug was more effective than filgrastim in terms of the SN and SDN incidence [11, 13, 16], but differences between L-G-CSF and S-G-CSF drugs were not statistically significant. Some of the tentative reasons for the lack of a difference could be because of few patient data points and other factors like the chemotherapy regimen and cancer type differentially impacting the incidence rate of SN and DSN.

The safety profiles for these two groups of drugs were compared using BP as an endpoint, because it is a common adverse event that occurs in clinics when patients are injected with various G-CSF drugs post chemotherapy [29]. Our data showed that both types (S-G-CSF and L-G-CSF) of drugs had no significant differences with respect to BP induction. In contrast, two other studies indicated that pegfilgrastim was obviously better than filgrastim in terms of BP outcome [15, 19]. One other meta-analysis study comparing the efficacy and safety of pegfilgrastim or filgrastim with those of lipegfilgrastim using FN, SN, DSN, and BP as endpoints showed that in pooled analysis, pegfilgrastim clearly displayed a lower risk for FN (RR = 1.54, 95% CI = 1.03 ~ 2.29, p = 0.04), but no significant difference for DSN and BP [43]. Thus, due to conflicting observations, we suspect that BP alone as a safety endpoint may not be sufficient to conclusively compare the safety profiles of these two types of drugs, and hence, other adverse events like back pain should also be considered for overall
It is important to highlight that to the best of our knowledge, this is the first meta-analysis directly comparing the efficacy and safety of different L-G-CSF and S-G-SCF drugs in varied tumor types. All the included RCTs in our meta-analysis were of high quality based on the Cochrane Collaboration Tool. Moreover, we adopted more extensive indicators and methods in our meta-analysis to evaluate the efficacy and safety of these drugs in comparison to other previously published relevant meta-analysis studies [43, 44]. Nevertheless, there are still some limitations in our meta-analysis: 1) relatively small number of RCTs for the overall analysis, 2) we should have included other indicators in addition to BP for safety analysis, like back pain or myalgia events, 3) the presence of some potential bias due to different cancer types, stages, and chemotherapy regimens.

Finally, our study demonstrated that L-G-CSF drugs were clearly better in reducing FN incidence than S-G-CSF drugs, but had no advantages with regard to SN, DSN, and BP endpoints. In addition, we did not observe any publication bias in our meta-analysis. Based on our and previously published data [44], it is evident that pegfilgrastim is superior to other S-G-CSF drugs like filgrastim though it is quite expensive [41, 46, 47]. However, the benefits of L-G-CSF drugs cannot triumph over the high price, and if there is no restriction based on economic factors, it is worth recommending pegfilgrastim for neutropenia treatment in cancer patients after chemotherapy. There is also the possibility of trying cheaper biosimilars. Finally, additional large-scale studies will be helpful to effectively and conclusively address the issue of efficacy and safety for these two groups of G-CSF drugs in patients with different cancer types.

Declarations

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Authors’ contributions

1. W. Zhang and Y. Wang conceived and designed the study. All authors collected scientific literature; critically appraised individual articles for inclusion, analyzed and
interpreted the findings. X. W. Zhang and Y. Wang drafted the manuscript, Y. Li reviewed it. X. W. Zhang prepared the final version for publication. All authors read and approved the final version.

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**Availability of data and materials**

All the data is contained within the manuscript and additional files.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interest.

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Table 1: Baseline characteristics of eligible studies

| No. | Study                          | Country | type           | Stages      | Chemotherapy     | Treatment           |
|-----|--------------------------------|---------|----------------|-------------|------------------|---------------------|
| 1   | Kubo et al. 2016              | Japan   | Lymphoma       | I/ II/ III/ IV | CHASE(R)        | Pegfilgrastim       |
| 2   | Zhang et al. 2015             | China   | BC             | NA          | TAC              | Pegfilgrastim       |
| 3   | Shi et al. 2013               | China   | BC/NSCLC/NHL/HNC | I/ II/ III/ IV | PC/AC/PA/ CHOP  | Pegfilgrastim       |
| 4   | Fox et al. 2009               | USA     | Sarcomas       | III/ IV     | VDC/IE           | Pegfilgrastim       |
| 5   | Sierra et al. 2008            | Spain   | AML            | NA          | IA               | Pegfilgrastim       |
| 6   | Grigg et al. 2003             | USA     | NHL            | I/ II/ III/ IV | CHOP           | Pegfilgrastim       |
| 7   | Vose et al. 2003              | USA     | Lymphoma       | I/ II/ III/ IV | CHOP           | Pegfilgrastim       |
| 8   | Green et al. 2003             | Australia | BC     | II/ III/ IV  | DA               | Pegfilgrastim       |
| 9   | Holmes et al. 2002 study1     | USA     | BC             | II/ III/ IV | DA               | Pegfilgrastim       |
| 10  | Holmes et al. 2002 study2     | USA     | BC             | II/ III/ IV | DA               | Pegfilgrastim       |
| 11  | Xu et al. 2016                | China   | BC/NSCLC       | NA          | AC/TAC          | Pegfilgrastim       |
| 12  | Xie et al. 2018               | China   | BC             | NA          | EC/ET/TC        | Pegfilgrastim       |
| 13  | Park et al. 2017              | SK      | BC             | I/ II/ III/ IV | TAC           | L-G-CSF Bio         |
| 14  | Park et al. 2013              | SK      | BC             | II/ III     | TAC              | L-G-CSF Bio         |
| 15  | Johnston et al. 2000          | USA     | NSCLC          | NA          | DC               | Pegfilgrastim       |
| 16  | von Minckwitz et al. 2008     | Germany | BC             | I/ II/ III/ IV | TAC           | Pegfilgrastim       |
| 17  | Bozzioli et al. 2015          | Italy   | DLBCL          | I/ II/ III/ IV | CHOP+rituximab | Pegfilgrastim       |
| 18  | Filon et al. 2015             | Russia  | BC             | II/ III/ IV | DA               | Empegfilgrastim     |
| 19  | Satheesh et al. 2009          | India   | BC             | NA          | DA               | Pegfilgrastim       |
| 20  | Salafet et al. 2013           | Russia  | BC             | NA          | DA               | Empegfilgrastim     |

Note: NA: not available. M: male. F: female. SD: standard deviation. ANC: absolute neutrophil count.
USA: United States of America. SK: South Korea. BC: Breast cancer. NSCLC: Non-small-cell lung carcinoma. NHL: Non-Hodgkin lymphoma. HNC: Head and neck cancer. AML: Acute myeloid leukemia. DLBCL: Diffuse large B-cell lymphoma. CHASE(R): cyclophosphamide, cytarabine, etoposide, dexamethasone rituximab. TAC: docetaxel, doxorubicin, cyclophosphamide. PC: paclitaxel, carboplatin or cisplatin AC: doxorubicin or pirarubicin or epirubicin, cyclophosphamide. PA: paclitaxel, doxorubicin or pirarubicin or epirubicin. CHOP: cyclophosphamide, doxorubicin, or pirarubicin or epirubicin, vincristine, prednisone. VDC: vincristine, doxorubicin, cyclophosphamide. IE: etoposide, ifosfamide. IA: idarubicin, cytarabine. DA: docetaxel, doxorubicin. TAC: docetaxel, doxorubicin, cyclophosphamide. EC: epirubicin, cyclophosphamide. ET: docetaxel, cyclophosphamide. TC: docetaxel, cyclophosphamide.

Figures
Figure 1

Flow chart depicting study selection process.
Figure 2

(A) Forest plots representing efficacy of different G-CSF targeting drugs and FN as the endpoint. (B) Efficacy analysis of different long-acting G-CSF targeting drugs after their stratification and FN as endpoint.

Figure 3

Sensitivity analysis of different G-CSF targeting drugs by omitting a single study at a time for the following endpoints, (A) FN; (B) SN; (C) DSN, and (D) BP.

Figure 4

Funnel plot analyses to assess the publication bias between different G-CSF targeting drugs and the following endpoints: (A) FN, (B) SN, (C) DSN, and (D) BP. Begg’s funnel plot analyses to assess the publication bias between different G-CSF drugs and the following endpoints; (E) FN, (F) SN, (G) DSN, and (H) BP.

Supplementary Files

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