Efficacy and tolerability of granulocyte colony-stimulating factors in cancer patients after chemotherapy: A systematic review and Bayesian network meta-analysis

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The optimum granulocyte colony-stimulating factor (G-CSF) treatment for cancer patients after being treated with cytotoxic chemotherapy remains unknown. Therefore, a systematic review and Bayesian network meta-analysis were performed to assess the efficacy and tolerability of 11 G-CSF drugs on patients after chemotherapy. A total of 73 randomized controlled trials (RCTs) containing 15,124 cancer patients were included for the final network meta-analysis. Compared with pegfilgrastim, there were a higher risk with filgrastim for incidence of febrile neutropenia (FN) (OR [95% CI]: 1.63 [1.07, 2.46]), and a higher risk with short-acting G-CSF (S-G-CSF) biosimilar and lenograstim for incidence of bone pain (BP) (OR [95% CI]: 6.45 [1.10, 65.73], 5.12 [1.14, 26.12], respectively). Mecapegfilgrastim, lipegfilgrastim and balugrastim were best G-CSF drugs in reducing FN (cumulative probabilities: 58%, 15%, 11%, respectively). S-G-CSF biosimilar, empegfilgrastim, and long-acting G-CSF (L-G-CSF) biosimilar were best G-CSF drugs in reducing severe neutropenia (SN) (cumulative probabilities: 21%, 20%, 15%, respectively). Mecapegfilgrastim, balugrastim, lipegfilgrastim and L-G-CSF biosimilar were best G-CSF drugs in reducing BP (cumulative probabilities: 20%, 14%, 8%, 8%, respectively). Mecapegfilgrastim, lipegfilgrastim and balugrastim might be the most appreciate G-CSF drugs with both good efficacy and tolerability when treating cancer patients after cytotoxic chemotherapy.

Febrile neutropenia (FN) and severe neutropenia (SN) are the most common and serious complications of cancer patients after treatment with cytotoxic chemotherapy⁷. These complications lead to chemotherapy delay, dose reduction, and increased risk of infection⁸. Patients with these complications need to be treated with antibiotics and hospitalization⁹, which indirectly increases the cost for care of these patients⁴. Furthermore, the condition could deteriorate and lead to death as a result of FN and/or SN after chemotherapy⁴,⁵.

Granulocyte colony-stimulating factors (G-CSFs) promote the growth of neutrophils, decrease the incidence of FN and SN, shorten the time of hospital stay, reduce the severity and duration of neutropenia, decrease the risk of infection, and improve the tolerance to cytotoxic chemotherapy⁶. The guidelines of National Comprehensive Cancer Network (NCCN) recommend primary prophylaxis with G-CSF when the risk of FN associated with chemotherapy regimen is greater than 20%⁷. Filgrastim was the first short acting G-CSF drug approved for

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treatment of neutropenia by the United States Food and Drug Administration (FDA) in 1991. Subsequently, a number of new G-CSF drugs have been invented for the treatment of neutropenia worldwide. Long-acting G-CSFs (L-G-CSFs) are PEGylated forms of short-acting G-CSFs (S-G-CSFs) with decreased elimination and increased half-life in serum after subcutaneous injection. Moreover, some of these new G-CSF biosimilar drugs are not as glycosylated as filgrastim. Since the structure and mechanism of drugs differ, the effect of different G-CSFs remains unclear.

Bone pain (BP) is the most frequent adverse event associated with G-CSF drugs. Patients might give up treatment due to severe adverse events. The incidence and degree of bone pain after the injection of different G-CSF drugs are diverse. Although some reviews on the difference of several G-CSF drugs have been reported, these reviews did not include sufficient studies and samples, trials that assessed new G-CSF drugs, or a complete list of G-CSF drugs. The effect of G-CSFs and the optimum choice remains unclear.

Since there is no evidence from head-to-head trials, pairwise meta-analysis for mixed treatment comparisons between multiple medical interventions appears to be impossible. The Bayesian network meta-analysis, which combined direct and indirect evidence to obtain an estimated effect value, has been considered to be a statistical method for mixed multiple trial data comparisons, when a head-to-head trial is not available. In the present study, a Bayesian network meta-analysis was performed to compare the major 11 G-CSF drugs (balugrastim, empegfilgrastim, filgrastim, S-G-CSF Biosimilar, L-G-CSF Biosimilar, lenograstim, leridistim, lipegfilgrastim, mecapegfilgrastim, pegfilgrastim, and pegteograstim) in terms of efficacy (FN and SN) and tolerability (BP) in the treatment of patients after cytotoxic chemotherapy. This aimed to summarize the direct evidence obtained from the results of randomized controlled trials (RCTs), in order to provide reliable information for guiding clinical treatment decisions.

**Results**

**Inclusion studies.** A total of 2,551 potentially relevant articles were identified based on the selection criteria (Fig. 1). After the titles and abstracts were examined, 2,451 literatures that did not meet the criteria were excluded. The full texts of 203 eligible articles were further assessed in detail, and 132 of these were further excluded (Fig. 1). Overall, 70 studies of the 73 RCTs from 1991 to 2018 were included for the final network meta-analysis (Table 1). The assessment of risk of bias indicated low risk of bias among the RCTs (Supplementary Figs S1 and S2). These trials were carried out in 19 countries, and almost half of these clinical trials were conducted in Europe. These trials contained a total of 15,124 cancer patients with 12 kinds of tumors. These 12 types of cancers were breast cancer (BC), lung cancer (LC), gastric cancer (GC), ovarian cancer (OC), head and neck cancer (HNC), colorectal cancer (CRC), germ cell malignancy (GCM), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), lymphoma, sarcoma, and neuroblastoma. These patients were randomly assigned to one of the 12 treatments (11 G-CSF drugs and one placebo group). BC (approximately 42%) was the main disease with the most patients among all kinds of tumors. The additional basic characteristics of all the included studies are presented in Table 1.

Eligible comparisons for the multiple-treatments network meta-analysis were shown in Fig. 2. A total of 66 trials containing 13,770 patients were included in the FN analysis, a total of 41 trials containing 9,298 patients were included in the SN analysis, and a total of 45 trials containing 10,021 patients were included in the BP analysis. Furthermore, 72 RCTs were two-arm trials, while only one RCT was a three-arm trial, which compared S-G-CSF biosimilar, filgrastim and placebo. Moreover, 46 trials respectively contained more than 100 participants, and most of the participants were between 45 and 65 years old.
| No. | Author Year | Study design | Country | Tumour type | Stages | Patients | Sex (M/F) | Treatment group | Intervention Dose |
|-----|-------------|--------------|---------|-------------|--------|----------|-----------|----------------|-----------------|
| 1   | Crawford et al. | Phase III, DB | USA | SCLC | Limited/Extensive | 231 | 149/82 | Pegfilgrastim vs. Placebo | 5 μg/kg/day vs. - |
| 2   | Fossà et al. | Phase III, NA | UK | GCM | IV | 259 | NA | Filgrastim vs. Placebo | 5 μg/kg/day vs. - |
| 3   | Dunlop et al. 1998 study1 | NA, NA | UK | HL | I/II/III/IV | 25 | 15/10 | Filgrastim vs. Placebo | 5 μg/kg/day vs. - |
| 4   | Dunlop et al. 1998 study2 | NA, NA | UK | HL | I/II/III/IV | 22 | 17/7 | Filgrastim vs. Placebo | 5 μg/kg/day vs. - |
| 5   | Geisser et al. | Phase III, NA | Australia | ALL | I/II/III/IV | 51 | 27/24 | Pegfilgrastim vs. Placebo | 5 μg/kg/day vs. - |
| 6   | Pinter et al. | Phase III, DB | USA | CRC | Advanced | 845 | 512/333 | Pegfilgrastim vs. Placebo | 6 mg/cycle vs. - |
| 7   | Kubo et al. | Phase III, DB | Japan | Lymphoma | I/II/III/IV | 107 | 66/41 | Pegfilgrastim vs. Filgrastim | 3.6 mg/cycle vs. 50 μg/m2/day |
| 8   | Zhang et al. | Phase II, OL | China | BC | NA | 86 | 0/86 | Pegfilgrastim vs. Filgrastim | 100 μg/kg/cycle vs. 5 μg/kg/day |
| 9   | Kosaka et al. | Phase III, DB | Japan | BC | I/II/III | 346 | 0/346 | Pegfilgrastim vs. Placebo | 6 mg/cycle vs. - |
| 10  | Shi et al. | Phase II, OL | China | BC/NSCLC/NHL/HNC | I/II/III/IV | 326 | 128/198 | Pegfilgrastim vs. Filgrastim | 100 μg/kg/cycle vs. 5 μg/kg/day |
| 11  | Hecht et al. | Phase II, DB | USA | CRC | II/III/IV | 241 | 162/79 | Pegfilgrastim vs. Placebo | 6 mg/cycle vs. - |
| 12  | Fox et al. | NA, NA | USA | Sarcomas | III/IV | 34 | 17/17 | Pegfilgrastim vs. Filgrastim | 100 μg/kg/cycle vs. 5 μg/kg/day |
| 13  | Sierra et al. | Phase II, DB | Spain | AML | NA | 83 | 39/44 | Pegfilgrastim vs. Filgrastim | 6 mg/cycle vs. 5 μg/kg/day |
| 14  | Vogel et al. | Phase III, DB | USA | BC | I/II/III/IV | 928 | 6/922 | Pegfilgrastim vs. Placebo | 6 mg/cycle vs. - |
| 15  | Grigg et al. | Phase II, OL | USA | NHL | I/II/III/IV | 27 | 14/13 | Pegfilgrastim vs. Filgrastim | 100 μg/kg/cycle vs. 5 μg/kg/day |
| 16  | Vose et al. | Phase II, OL | USA | Lymphoma | I/II/III/IV | 60 | 36/24 | Pegfilgrastim vs. Filgrastim | 100 μg/kg/cycle vs. 5 μg/kg/day |
| 17  | Green et al. | Phase III, DB | Australia | BC | I/II/III/IV | 152 | 1/151 | Pegfilgrastim vs. Filgrastim | 6 mg/cycle vs. 5 μg/kg/day |
| 18  | Holmes et al. study1 | Phase III, DB | USA | BC | I/II/III/IV | 296 | 3/293 | Pegfilgrastim vs. Filgrastim | 100 μg/kg/cycle vs. 5 μg/kg/day |
| 19  | Holmes et al. study2 | Phase II, DB | USA | BC | I/II/III/IV | 71 | 0/71 | Pegfilgrastim vs. Filgrastim | 100 μg/kg/cycle vs. 5 μg/kg/day |
| 20  | Zhou et al. | Phase III, DB | China | NSCLC | IIIIB/IV | 151 | 101/44 | Mecapegfilgrastim vs. Placebo | 6 mg or 100 μg/kg/cycle vs. - |
| 21  | Volovat et al. | Phase III, DB | Romania | NSCLC | IIIIB/IV | 365 | 325/50 | Lippegfilgrastim vs. Placebo | 6 mg/cycle vs. - |
| 22  | Buchner et al. | Phase II, DB | Germany | BC | I/II/III/IV | 104 | 1/103 | Lippegfilgrastim vs. Pegfilgrastim | 6 mg/cycle vs. 6 mg/cycle |
| 23  | Bondarenko et al. | Phase III, DB | Ukraine | BC | I/II/III/IV | 202 | 0/202 | Lippegfilgrastim vs. Pegfilgrastim | 6 mg/cycle vs. 6 mg/cycle |
| 24  | Gladkov et al. | Phase III, OL | Russian | BC | I/II/III/IV | 172 | 0/172 | Balugrastim vs. Pegfilgrastim | 40 mg/cycle vs. 6 mg/cycle |
| 25  | Volovat et al. | Phase III, DB | Romania | BC | NA | 381 | 0/381 | Balugrastim vs. Pegfilgrastim | 40 mg/cycle vs. 6 mg/cycle |
| 26  | Lee et al. | Phase III, DB | SK | BC | NA | 116 | 0/116 | Pegteograstim vs. Pegfilgrastim | 6 mg/cycle vs. 6 mg/cycle |
| 27  | Xu et al. | Phase III, NA | China | BC/NSCLC | NA | 500 | 61/439 | Pegfilgrastim vs. Filgrastim | 6 mg or 100 μg/kg/cycle vs. 5 μg/kg/day |
| 28  | Xie et al. | Phase III, OL | China | BC | NA | 569 | 5/564 | Pegfilgrastim vs. Filgrastim | 6 mg or 100 μg/kg/cycle vs. 5 μg/kg/day |
| 29  | Blackwell et al. | Phase III, DB | USA | BC | I/II/III | 214 | 0/214 | S-G-CSF Bio vs. Filgrastim | 5 μg/kg/day vs. 5 μg/kg/day |
| 30  | Park et al. | Phase III, OL | SK | BC | I/II/III/IV | 74 | 0/74 | L-G-CSF Bio vs. Filgrastim | 6 mg/cycle vs. 100 μg/m2/day |
| 31  | Park et al. | Phase II, OL | SK | BC | I/II/III | 41 | 0/41 | L-G-CSF Bio vs. Filgrastim | 6 mg/cycle vs. 100 μg/m2/day |
| 32  | Hegg et al. | Phase III, OL | Brazil | BC | I/II/III/IV | 217 | 0/217 | S-G-CSF Bio vs. Filgrastim | 5 mg/m2/day vs. 5 mg/m2/day |
| 33  | Blackwell et al. | Phase III, DB | USA | BC | I/II/III/IV | 308 | 0/308 | L-G-CSF Bio vs. Pegfilgrastim | 6 mg/cycle vs. 6 mg/cycle |
| 34  | Harbeck et al. | NA, DB | Germany | BC | I/II/III/IV | 316 | 0/316 | L-G-CSF Bio vs. Pegfilgrastim | 6 mg/cycle vs. 6 mg/cycle |

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| No. | Author. Year | Study design | Country | Tumour type | Stages | Patients | Sex (M/F) | Treatment group | Intervention Dose |
|-----|-------------|-------------|---------|-------------|--------|----------|-----------|-----------------|------------------|
| 35  | Waller et al. | Phase III, DB | Germany | BC | NA | 278 | 0/278 | S-G-CSF Bio vs. Filgrastim | 5 mg/kg/day vs. 5 µg/kg/day |
| 36  | Gatzemeier et al. | Phase III, DB | Brazil | LC | Limited/Extensive | 237 | 188/49 | S-G-CSF Bio vs. Filgrastim | 5 mg/kg/day vs. 5 µg/kg/day |
| 37  | A. Engert et al. | Phase III, DB | Germany | NHL | NA | 92 | 48/44 | S-G-CSF Bio vs. Filgrastim | 5 mg/kg/day vs. 5 µg/kg/day |
| 38  | Giglio et al. | Phase III, DB | Brazil | BC | II/III/IV | 348 | 2/346 | S-G-CSF Bio vs. Filgrastim vs. Placebo | 5 mg/kg/day vs. 5 µg/kg/day vs. - |
| 39  | Gisselbrecht et al. | Phase III, DB | France | NHL | II/III/IV | 162 | 93/69 | Lenograstim vs. Placebo | 5 µg/kg/day. - |
| 40  | Bui et al. | Phase II, DB | France | Sarcoma | Advanced | 48 | 26/22 | Lenograstim vs. Placebo | 5 µg/kg/day vs. - |
| 41  | Nabbolz et al. | Phase III, DB | USA | BC | II/III/IV | 274 | 0/274 | Lenograstim vs. Filgrastim | 5 µg/kg/day vs. 5 µg/kg/day |
| 42  | Welte et al. | Phase III, DB | Germany | ALL | NA | 34 | 27/7 | Filgrastim vs. Placebo | 5 µg/kg/day vs. - |
| 43  | Petrovskis | Russian | Phase III, OL | BC | I/II/III/IV | 20 | 0/20 | Filgrastim vs. Placebo | 5 µg/kg/day |
| 44  | Johnston et al. | NA, OL | UK | NHL | II/III/IV | 80 | 53/27 | Filgrastim vs. Placebo | 230 µg/m²/day vs. - |
| 45  | Timmer-Bonte et al. | Phase III, OL | Netherlands | NSCLC | NA | 13 | 8/5 | Pegfilgrastim vs. Filgrastim | 30/100/300 µg/kg/cycle vs. 5 µg/kg/day |
| 46  | Crawford et al. | Phase III, DB | USA | SCLC | I/II/III/IV | 175 | 113/62 | Filgrastim vs. Placebo | 300 µg/kg/cycle vs. - |
| 47  | Osby et al. | Phase III, DB | Sweden | Lymphoma | I/II/III/IV | 205 | 106/99 | Filgrastim vs. Placebo | 5 µg/kg/day vs. - |
| 48  | Osby et al. | Phase III, DB | Sweden | Lymphoma | I/II/III/IV | 250 | 134/116 | Filgrastim vs. Placebo | 5 µg/kg/day vs. - |
| 49  | Tillet-Lenoir et al. | Phase III, DB | France | SCLC | I/II/III/IV | 129 | 89/40 | Filgrastim vs. Placebo | 230 µg/m²/day vs. - |
| 50  | Zanini et al. | NA, NA | Italy | NHL | II/III/IV | 149 | 69/80 | Filgrastim vs. Placebo | 5 µg/kg/day vs. - |
| 51  | von Minckwitz et al. | NA, NA | Germany | BC | II/III/IV | 682 | 0/682 | Pegfilgrastim vs. Filgrastim | 6 mg/cycle vs. 5 µg/kg or 150 µg/m²/day |
| 52  | Balducci et al. | Phase IV, OL | USA | LC/BC/OC | NA | 686 | 235/451 | Pegfilgrastim vs. Placebo | 6 mg/cycle vs. - |
| 53  | Balducci et al. | Phase IV, OL | USA | NHL | NA | 146 | 69/77 | Pegfilgrastim vs. Placebo | 6 mg/cycle vs. - |
| 54  | Doorduijn et al. | Phase III, NA | Nederland | NHL | II/III/IV | 389 | 216/173 | Filgrastim vs. Placebo | 300 µg/day vs. - |
| 55  | Chevallier et al. | Phase III, DB | France | BC | NA | 120 | 0/120 | Lenograstim vs. Placebo | 5 µg/kg/day vs. - |
| 56  | Gebbia et al. | NA, NA | Italy | BC/SCLC/HNC/HC/GC | Advanced | 86 | 31/55 | Filgrastim vs. Placebo | 5 µg/kg/day vs. - |
| 57  | Romieu et al. | Phase II, OL | France | BC | II/III | 60 | 0/65 | Pegfilgrastim vs. Placebo | 6 mg/cycle vs. - |
| 58  | Bovelli et al. | Phase III, DB | Italy | DLBL | I/II/III/IV | 51 | 20/31 | Pegfilgrastim vs. Filgrastim | 6 mg/cycle vs. 300 µg/day |
| 59  | Filon et al. | Phase III, DB | Russia | BC | II/III/IV | 82 | 0/82 | Empegfilgrastim vs. Filgrastim | 6 mg/cycle vs. 5 µg/kg/day |
| 60  | Salafet et al. | Phase II, OL | Russia | BC | NA | 39 | 0/39 | Empegfilgrastim vs. Filgrastim | 6 mg/cycle vs. 5 µg/kg/day |
| 61  | Satheesh et al. | NA, NA | India | BC | NA | 71 | 0/71 | Pegfilgrastim vs. Filgrastim | 6 mg/cycle vs. 5 µg/kg/day |
| 62  | Glaspy et al. | Phase II, OL | USA | BC | II/III/IV | 232 | 0/232 | L-G-CSF Bio vs. Pegfilgrastim | 80/240/320 µg/kg/cycle vs. 6 mg/cycle |
| 63  | Usuki et al. | NA, NA | Japan | AML | NA | 245 | 158/87 | Filgrastim vs. Placebo | 200 µg/m²/day vs. - |
| 64  | Desai et al. | Phase III, DB | Canada | BC | II/III | 589 | 0/589 | L-G-CSF Bio vs. Pegfilgrastim | 6 mg/cycle vs. 300 µg/day |
| 65  | Ottmann et al. | Phase III, OL | Germany | ALL | NA | 76 | 51/25 | Filgrastim vs. Placebo | 5 µg/kg/day vs. - |
| 66  | Bondarenko et al. | Phase II, DB | Ukraine | BC | II/III/IV | 104 | 0/104 | Lippegfilgrastim vs. Pegfilgrastim | 6 mg/cycle vs. 6 mg/cycle |
| 67  | Godwin et al. | Phase III, DB | USA | AML | NA | 211 | 122/89 | Filgrastim vs. Placebo | 400 µg/m²/day vs. - |
| 68  | Gladkov et al. | Phase II, OL | Russia | BC | II/III/IV | 47 | 0/47 | Balugrastim vs. Pegfilgrastim | 40 mg/cycle vs. 6 mg/cycle |
| 69  | Michom et al. | Phase II, OL | France | Neuroblastoma | IV | 60 | 43/17 | Filgrastim vs. Placebo | 5 µg/kg/day vs. - |
| 70  | Maher et al. | Phase III, DB | Australia | SC/ALL/Lymphoma | NA | 216 | 103/113 | Filgrastim vs. Placebo | 12 µg/kg/day vs. - |

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Efficacy and tolerability of G-CSF drugs from pair-wise meta-analysis. A traditional direct pair-wise meta-analysis was performed, as shown in Table 2. The result revealed that filgrastim, pegfilgrastim, lenograstim and mecapegfilgrastim could reduce the incidence of FN (OR [95% CI]: 0.49 [0.38, 0.62]; 0.18 [0.06, 0.56]; 0.47 [0.29, 0.76]; 0.05 [0.00, 0.96]) and SN (OR [95% CI]: 0.29 [0.22, 0.38]; 0.16 [0.06, 0.47]; 0.37 [0.19, 0.72]; 0.30 [0.11, 0.81]) compared with placebo. Furthermore, the OR of mecapegfilgrastim compared with placebo was the lowest, but only one trial was included. The incidence of BP was greater in patients treated with filgrastim, pegfilgrastim, or lenograstim, when compared to placebo (OR [95% CI]: 2.07 [1.08, 3.97]; 1.91 [1.27, 2.87]; 8.31 [4.11, 16.80]). Filgrastim was better than leridistim in terms of reducing the incidence of FN (OR [95% CI]: 0.32 [0.11, 0.90]), but was worse than S-G-CSF biosimilar with regard to the incidence of BP (OR [95% CI]: 0.54 [0.30, 0.99]). Filgrastim was worse than pegfilgrastim in terms of reducing the incidence of FN (OR [95% CI]: 1.46 [1.07, 1.99]). The heterogeneity of these meta-analyses was mostly low or moderate. In the meta-analysis of RCTs that compared pegfilgrastim with placebo, a high heterogeneity was observed with FN ($I^2 = 89\%$), SN ($I^2 = 91\%$) and BP ($I^2 = 56\%$). This heterogeneity might have been introduced by the variation that resulted from the multiple types of tumors, since there were approximately five kinds of tumors in these seven trials. Since the sample size for every specific kind of tumor in these trials containing multiple types of tumors that was too small, it was difficult to implement an effective subgroup analysis. In the sensitivity analysis, no significant heterogeneity change was observed after removing studies from the analysis.

Efficacy and tolerability of G-CSF drugs from network meta-analysis. Figure 3 summarizes the results of the random-effects network meta-analysis for the efficacy of G-CSF drugs based on FN and SN and acceptability, in terms of BP. There was no direct comparison trial of pegteograstim (transverse line indicate no comparison in Fig. 3) on SN, or direct comparison trial of empegfilgrastim, leridistim, and pegteograstim on BP. Pegfilgrastim significantly reduced the incidence of FN, when compared with filgrastim (OR [95% CI]: 1.63 [1.07–2.46]). There was no difference among other drugs in reducing the incidence of FN and SN. Compared with placebo, filgrastim, S-G-CSF biosimilar, lippegfilgrastim and pegfilgrastim significantly ($P < 0.05$) reduced the incidence of FN and SN, while balugrastim and L-G-CSF biosimilar reduced the incidence of SN. Although
| Treatment                          | OR [95% CI] | I² (%) | P value |
|-----------------------------------|-------------|--------|---------|
| Pegfilgrastim vs. Placebo         | 1.16 [0.98, 1.36] | 0% | 0.31   |
| L-G-CSF Biosimilar vs. Placebo   | 1.06 [0.81, 1.39] | 0% | 0.68   |
| S-G-CSF Biosimilar vs. Placebo   | 1.00 [0.85, 1.17] | 0% | 1.00   |
| Empegfilgrastim vs. Placebo      | 0.81 [0.62, 1.05] | 0% | 0.17   |
| Leridistim vs. Placebo            | 0.99 [0.81, 1.20] | 0% | 0.89   |
| Placebo vs. Filgrastim            | 0.66 [0.52, 0.84] | 0% | 0.00   |
| Balugrastim vs. Placebo           | 0.94 [0.75, 1.20] | 0% | 0.54   |
| L-G-CSF Biosimilar vs. Placebo   | 1.01 [0.80, 1.28] | 0% | 1.00   |
| Lipegfilgrastim vs. Placebo      | 0.98 [0.78, 1.24] | 0% | 0.40   |
| Pegteograstim vs. Placebo         | 0.87 [0.70, 1.09] | 0% | 0.21   |
| Placebo vs. Lenograstim           | 0.99 [0.81, 1.20] | 0% | 0.89   |
| Placebo vs. Lipegfilgrastim       | 0.95 [0.78, 1.15] | 0% | 0.54   |
| Placebo vs. Mecapegfilgrastim     | 0.81 [0.63, 1.05] | 0% | 0.21   |

**Table 2.** Response for efficacy (FN and SN) and tolerability (BP) in the pair-wise meta-analysis. Note: FN, febrile neutropenia; SN, severe neutropenia; BP, bone pain; OR, odds ratios; CI, confidence interval; OR with statistical significance are in bold.

the difference was not statistically significant (95% CI contains 1), a reduction in the incidence of FN and SN was observed when empegfilgrastim, lenograstim, leridistim, mecapegfilgrastim, and pegteograstim were compared with placebo. The reason may be because the number of trials included was too small. In terms of the incidence of FN, and SN and BP, the difference was not statistically significant with regards to FN, SN and BP.

**Comparison of the possibility of efficacy and tolerability of G-CSF drugs.** Figure 4 shows the distribution of possibility rank of the 12 treatments in terms of FN, SN, and BP. The higher the probability rank of the 12 treatment, the lower the probability of FN, SN and BP. Mecapegfilgrastim, lipegfilgrastim and balugrastim may be among the three best effective G-CSF drugs that could prevent the incidence of FN in cumulative probabilities: 58%, 15%, and 11%, respectively. S-G-CSF biosimilar, empegfilgrastim, and L-G-CSF biosimilar are possibly among the three more favorable G-CSF drugs that could prevent the occurrence of SN in cumulative probabilities: 21%, 20%, and 15%, respectively. Mecapegfilgrastim, balugrastim, lipegfilgrastim and L-G-CSF biosimilar were ranked as the lowest G-CSF drugs on incidence of BP in cumulative probabilities: 20%, 14%, 8%, and 8%, respectively.
In the present network meta-analysis, the efficacy and tolerability of 11 different G-CSF drugs for cancer patients after chemotherapy in 73 RCTs containing 15,124 patients were evaluated using FN, SN and BP as indicators. It was found that pegfilgrastim was better than filgrastim in reducing FN, and more tolerable than S-G-CSF biosimilar and lenograstim in terms of the incidence of BP. In terms of both efficacy and tolerance, mecapegfilgrastim, lipegfilgrastim and balugrastim might be the most efficacious and tolerable among G-CSF drugs.

Since FN is the main and severe adverse event for many chemotherapy regimens, and is intimately associated with chemotherapy-related mortality, FN was chosen as the primary outcome of the G-CSF drug treatment and a crucial indicator to evaluate the efficacy of G-CSF drugs. In the present study, it was found that compared with placebo, most of the G-CSF drugs could reduce the risk of the incidence of FN, except for emepgfilgrastim.

**Figure 3.** The pooled odds ratios (ORs) for the efficacy (FN and SN) and tolerability (BP) of the 12 treatments. The ORs are the column treatments compared with the row treatments in efficacy (FN and SN), and the row treatments compared with the column treatments in tolerability (BP). The results of efficacy (FN and SN) are in blue and orange, and the results of tolerability (BP) are in green. The first line of efficacy (FN and SN) in blue is the OR of FN, while the second line in orange is the OR of SN. The numbers in bold indicate the significant results. 

**Figure 4.** The ranking of treatments for efficacy (FN and SN) and tolerability (BP).

**Discussion**

In the present network meta-analysis, the efficacy and tolerability of 11 different G-CSF drugs for cancer patients after chemotherapy in 73 RCTs containing 15,124 patients were evaluated using FN, SN and BP as indicators. It was found that pegfilgrastim was better than filgrastim in reducing FN, and more tolerable than S-G-CSF biosimilar and lenograstim in terms of the incidence of BP. In terms of both efficacy and tolerance, mecapegfilgrastim, lipegfilgrastim and balugrastim might be the most efficacious and tolerable among G-CSF drugs.

Since FN is the main and severe adverse event for many chemotherapy regimens, and is intimately associated with chemotherapy-related mortality, FN was chosen as the primary outcome of the G-CSF drug treatment and a crucial indicator to evaluate the efficacy of G-CSF drugs. In the present study, it was found that compared with placebo, most of the G-CSF drugs could reduce the risk of the incidence of FN, except for emepgfilgrastim.
leridistim, and pegteograstim. While leridistim might have an opposite effect, although the effect was not statistically significant. The network meta-analysis revealed that there was no difference or inferiority among the tested G-CSF drugs, except for filgrastim and pegfilgrastim in FN (filgrastim vs. pegfilgrastim OR [95% CI]: 1.63 [1.07 – 2.46]). Filgrastim, pegfilgrastim, lipegfilgrastim and lenograstim reduced the incidence of FN in cancer patients undergoing chemotherapy compared with placebo. Lipegfilgrastim appeared to lead to a greater reduction in the incidence of FN, when compared to pegfilgrastim and filgrastim, although the difference was not statistically significant. These findings were consistent with the previous observations. In accordance with previous reports, pegfilgrastim was more effective than filgrastim in reducing the incidence of FN and SN. SN is also another important evaluation indicator of G-CSF drug efficacy. Filgrastim, pegfilgrastim, lipegfilgrastim, S-G-CSF biosimilar, mecapegfilgrastim, and lenograstim reduced the incidence of SN in patients undergoing myelosuppressive chemotherapy based on direct and indirect evidence. All these results indicate that compared with placebo, most of the tested G-CSF drugs were effective to prevent the incidence of FN and SN.

BP is one of the most common adverse events associated with G-CSF drug treatment, and is an indicator of G-CSF drug tolerance. Filgrastim (OR [95% CI]: 3.93 [2.07, 8.90]), lenograstim (OR [95% CI]: 11.82 [3.14, 52.88]), pegfilgrastim (OR [95% CI]: 2.32 [1.16, 4.91]) and S-G-CSF biosimilar (OR [95% CI]: 14.84 [2.62, 156.59]) led to a higher incidence of BP, when compared with placebo. Lenograstim (OR [95% CI]: 5.12 [1.14, 26.12]) and S-G-CSF biosimilar (OR [95% CI]: 6.45 [1.10, 65.73]) led to a much higher incidence of BP than pegfilgrastim. However, the level of incidence of BP widely varied among the RCTs of G-CSF drugs, which might have resulted from the differences in race of patients, stage and type of tumors, chemotherapy regimens, and definition of BP. These results suggest that patients might have different tolerances to different G-CSF drugs.

Even though there was no difference in efficacy among the tested G-CSF drugs and tolerability among patients to these G-CSF drugs in the pair-wise meta-analysis, the comparison of these 12 G-CSF drug treatments suggest that mecapegfilgrastim, lipegfilgrastim and balugrastim might be more effective than leridistim, filgrastim and S-G-CSF biosimilar in preventing the incidence of FN, and S-G-CSF biosimilar, empegfilgrastim and L-G-CSF biosimilar might be more effective than filgrastim and pegfilgrastim in preventing the incidence of SN. In terms of BP, mecapegfilgrastim, balugrastim, lipegfilgrastim and L-G-CSF biosimilar might be more tolerable for patients, when compared to other G-CSF drugs. Those results indicate that mecapegfilgrastim, lipegfilgrastim and balugrastim might be the most efficacious and tolerable G-CSF drugs, and might provide a guideline for the selection of G-CSF drugs for patients after chemotherapy.

Caution should be taken in interpreting the results, since there might be inconsistencies between the direct and indirect comparisons. These inconsistencies might have resulted from the different characteristics of trials, such as the study design, definition of indicators, inclusion criteria of subjects, and method of implementation, as well as the differences in identifying the external effect on the mean effect of the specific comparison between the network meta-analysis and pair-wise meta-analysis methods. Although no inconsistency was found in FN, SN and BP through the node-split method in the main network analysis, the direct and indirect meta-analyses revealed contradictory results in terms of the comparisons between filgrastim vs. S-G-CSF biosimilar and filgrastim vs. L-G-CSF biosimilar. This mutually exclusive result could be explained as follows: (1) if the direct evidence of the pair-wise meta-analysis was true, the comparison between other G-CSF drugs in indirect evidence of the network meta-analysis might overstate or understate the efficacy and tolerance; (2) if the indirect evidence was true, significant intrinsic heterogeneity might exist in the comparison among filgrastim, S-G-CSF biosimilar and L-G-CSF biosimilar. A low or moderate heterogeneity was observed in the pair-wise meta-analysis, indicating that the direct pair-wise meta-analysis was true.

Although the present study is the first network meta-analysis to comprehensively assess clinically and commonly used G-CSF drugs, it should be acknowledged that there were some limitations with the present analysis. First, many factors correlated with neutropenia after chemotherapy were not analyzed, such as the duration of neutropenia, duration of SN, depth of the absolute neutrophil count (ANC) nadir, time to recovery of ANC, FN-related hospitalization, and other toxic or side effects of G-CSF drugs. Second, in most of the included trials, the report for FN, SN and BP was incomplete, which caused some of the G-CSF drugs to be ruled out for comparison in terms of SN and BP. Third, trials on some G-CSF drugs were too few to be assessed. For example, merely one trial on mecapegfilgrastim has been reported to date. Fourth, the definition of BP and other indicators varied among these studies. Furthermore, the dose of G-CSF drugs also varied across the studies. These might be the source of heterogeneity and inconsistency. Fifth, the outcomes might only apply to developed countries, since some G-CSF drugs are not available on the market in many developing countries.

In summary, based on the present network meta-analysis, evidence suggests that compared with placebo, most of the tested G-CSF drugs are not different in terms of efficacy and tolerability, except for pegfilgrastim, which is more effective than filgrastim in reducing FN. Furthermore, pegfilgrastim is more tolerable for patients, when compared to S-G-CSF biosimilar and lenograstim, in terms of BP. Mecapegfilgrastim, lipegfilgrastim and balugrastim might be the most appreciate G-CSF drugs, which have both better efficacy and tolerance. It is noteworthy that more large-scale RCTs would be required to further confirm the efficacy and tolerance of the G-CSF drugs observed in the present study. The benefit-risk ratio of these G-CSF drugs still deserves to be further explored.

Methods
Search strategies and selection criteria. A network meta-analysis was performed following the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines and PRISMA network meta-analysis extension statement. RCTs on 11 G-CSF drugs (balugrastim, empegfilgrastim, filgrastim, S-G-CSF Biosimilar, L-G-CSF Biosimilar, lenograstim, leridistim, lipegfilgrastim, mecapegfilgrastim, pegfilgrastim, and pegteograstim) for cancer patients after cytotoxic chemotherapy were searched in PubMed, Embase, Cochrane Library, Cochrane Collaboration Central Register of Controlled Clinical Trials, American Society of Clinical Oncology, and ClinicalTrials.gov up to the 8th of October 2018, without language restrictions. The terms
Ibe accepted when this was designated as extremely high heterogeneity. According to the Cochrane handbook, heterogeneity can be categorized as moderate heterogeneity, if I² ≤ 50% and 1.0 × 10⁹/L. If both data of both grade 3 and 4 bone marrow suppression (ANC < 0.5 and 1.0 × 10⁹/L) were reported in a study, the data of the ANC < 0.5 × 10⁹/L was used with priority for analysis, because grade 3 had lesser clinical significance, and was not always reported in the included studies.

Outcome measurements. The incidence of FN after cytotoxic chemotherapy within two weeks was taken as the primary indicator of efficacy of G-CSF drugs, the incidence of SN was taken as the secondary indicator of efficacy of G-CSF drugs, and BP was taken as the primary indicator for the tolerability of G-CSF drugs. FN was defined as an absolute neutrophil count (ANC) < 0.5 × 10⁹/L. SN was defined as ANC = 0.5 to 1.0 × 10⁹/L. If both data of both grade 3 and 4 bone marrow suppression (ANC < 0.5 and 1.0 × 10⁹/L) were reported in a study, the data of the ANC < 0.5 × 10⁹/L was used with priority for analysis, because grade 3 had lesser clinical significance, and was not always reported in the included studies.

Statistical analyses. Pair-wise meta-analysis was carried out for FN, SN and BP to compare the corresponding interventions. The random effects model for pair-wise meta-analysis was used to account for the heterogeneity. The heterogeneity among different trials was estimated by Cochran’s Q-test (P < 0.05 indicated significant heterogeneity) and I² statistic. If I² = 0–25%, it is designated as low heterogeneity, if I² = 25–50%, this was designated as moderate heterogeneity, if I² = 50–75%, this was designated as high heterogeneity, and if I² = 75–100%, this was designated as extremely high heterogeneity. According to the Cochrane handbook, heterogeneity can be accepted when I² ≤ 50%. Pair-wise meta-analysis was performed using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) and STATA 12.0 (Stata Corporation, TX, USA) statistical software.

Random-effects models were applied for the network meta-analysis. Bayesian network meta-analysis was used to combine the collected data. The Bayesian network meta-analysis was performed with WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK). Random effects models were used to incorporate the effects from different studies, while heterogeneity within the comparison was evaluated in a relatively conservative and appropriate manner. The models were performed using the Markov Chain Monte Carlo simulation. The initial values were set for three different chains, 150,000 interactions with 5,000 burn-in samples were produced to obtain the model parameters from the posterior distributions, and 50 thinning rates were adopted for each chain. The odds ratios (ORs) were collected or calculated from combining the direct evidence, and the significance was assessed by P < 0.05, or the 95% confidence interval (CI) did not contain 1. The best efficacious and tolerant regimen was confirmed by ranking the included G-CSF drugs according to the OR for each G-CSF drug compared with placebo, and assessing the probability. Inconsistencies in the present study were assessed by comparing the direct evidence with indirect evidence from the network meta-analysis using the node-split method.

A sensitivity analysis was performed by determining whether there was statistically significant heterogeneity in the meta-analysis after studies were randomly removed from the others.

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