Meta-Analysis of Same-Day Pegfilgrastim Administration Stratified by Myelotoxic Febrile Neutropenia Risk and Tumor Type

NEDA ALRAWASHDH,[1,2] PhD, PharmD, ALI McBRIDE,[3] PharmD, MS, BCPS, MOK OH,[1] PhD, PharmD, NIMER ALKHATIB,[1] PhD, PharmD, CHRISTOPHER LEE,[4] PhD, RN, FAHA, FAAN, FHFSA, JENNIFER MARTIN,[5] MA, KAREN MacDONALD,[6] PhD, RN, and IVO ABRAHAM,[1,3,6] PhD, RN

From [1]Center for Health Outcomes and PharmacoEconomic Research, University of Arizona, Tucson, Arizona; [2]Department of Clinical Translational Sciences, College of Medicine, University of Arizona, Tucson, Arizona; [3]Department of Pharmacy Practice and Science, College of Pharmacy, University of Arizona, Tucson, Arizona; [4]Connell School of Nursing, Boston College, Boston, Massachusetts; [5]Arizona Health Sciences Library, University of Arizona, Tucson, Arizona; [6]Matrix45, Tucson, Arizona

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Ivo Abraham, PhD, RN, Center for Health Outcomes and PharmacoEconomic Research, University of Arizona, 1295 N Martin Avenue, Tucson, AZ 85721. E-mail: abraham@pharmacy.arizona.edu.

https://doi.org/10.6004/jadpro.2022.13.8.6

Abstract

Background: Pegfilgrastim is recommended to be administered at least 24 hours following the completion of chemotherapy, yet some clinicians use a same-day administration protocol. In this meta-analysis, we compared the incidence of chemotherapy-induced (febrile) neutropenia (CIN/FN) as well as CIN/FN-related chemotherapy disruptions in cancer patients provided with pegfilgrastim same-day vs. next-day. **Methods:** Six databases were searched for comparative studies of same-day vs. next-day pegfilgrastim administration. Fixed or random-effects meta-analyses were conducted to estimate pooled odds ratios (ORs) and 95% confidence intervals (CIs). **Results:** Thirteen studies were included in this meta-analysis. The FN OR for same-day vs. next-day administration was 1.48 (95% CI = 1.06–2.08) across all cycles, attributable mainly to studies of high FN risk (OR = 2.46, 95% CI = 1.04–5.83) vs. intermediate FN risk regimens (OR = 1.41, 95% CI = 0.95–2.10), and breast cancer (OR = 3.15, 95% CI = 1.24–8.01) vs. non-Hodgkin lymphoma (NHL; OR = 1.48, 95% CI = 0.98–2.23) and gynecologic cancers (OR = 0.64, 95% CI = 0.11–3.85). Where available, ORs for first cycle of chemotherapy, grades 3 and/or 4 CIN, and chemotherapy dose delays or reductions were in line with these findings. **Conclusion:** In this independent study, same-day pegfilgrastim administration may or may not increase the likelihood of FN, grades 3 and/or 4 CIN, and chemotherapy dose reductions or delays; and this may be a function of the myelotoxicity of the regimens (elevated in high-risk but not intermediate-risk regimens) and tumor type (elevated in breast but not in NHL or gynecologic cancers). With due caution, same-day pegfilgrastim administration may be safe and beneficial in intermediate-risk regimens and selected tumor types.

J Adv Pract Oncol 2022;13(8):796–811

Severe chemotherapy-induced neutropenia (CIN) is a major dose-limiting toxicity associated with myelosuppressive regimens. Chemotherapy-induced neutropenia is classified as grade 4 when the absolute neutrophil count (ANC) is < 500/µl and grade 3 for ANCs < 1,000/µl but > 500/µl. Febrile neutropenia (FN) involves both neutropenia and fever and is diagnosed in patients who present with a single oral temperature ≥ 38.3C° or an oral temperature of ≥ 38.0C° sustained for > 1 hour with an ANC < 500/µl or ANC < 1,000/µl that is anticipated to decline to < 500/µl within the following 48 hours. Febrile neutropenia may be associated with infection, often requires hospitalization and/or antibiotic therapy, and may result in chemotherapy dose changes, treatment delays, and treatment cancellations (Aapro et al., 2011; Gascon et al., 2011; Griffiths et al., 2022). The average cost for treating an inpatient case of cancer-related neutropenia in the United States was $25,120 in 2012 (Centers for Disease Control and Prevention, 2017) and $32,206 in 2021 (U.S. Bureau of Labor Statistics, 2021).

Used extensively to prevent neutropenia, pegfilgrastim (Neulasta; Amgen Inc., 2021) and its biosimilars are chemically derivatized forms of recombinant human granulocyte colony-stimulating factor, a protein that promotes neutrophil production. Administration of this drug reduces the incidence, severity, and duration of both CIN and FN (Crawford et al., 2017; Holmes et al., 2002; Lane et al., 2006). Pegfilgrastim is typically provided as a single dose administered no less than 24 hours after completion of chemotherapy but not less than 14 days before the next scheduled chemotherapy administration (Griffiths et al., 2022; Amgen Inc., 2021). Theoretically, administering pegfilgrastim within 24 hours after chemotherapy increases the toxicity of the chemotherapy to the myeloid progenitor cells (Mehta et al., 2015). The 2022 National Comprehensive Cancer Network (NCCN) Guidelines for administration of hematopoietic growth factors state that "...some institutions have administered pegfilgrastim on the same day as chemotherapy for logistical reasons and to minimize travel burdens on long-distance patients" (Griffiths et al., 2022). A survey of 386 US oncologists revealed that about one third (31.6%) of their patients received pegfilgrastim on the same day as chemotherapy (Marion et al., 2016).

Observational (Athar et al., 2007; Bartels et al., 2021; Bilen et al., 2017; Billingsley et al., 2015; Cheng et al., 2014; Eckstrom et al., 2019; Gupta et al., 2007; Hoffmann, 2005; Ibrahim et al., 2011; Karol et al., 2013; Kumar et al., 2009; Lokich, 2005; Lokich, 2006; Matera et al., 2017; McBride et al., 2021; Micha et al., 2013; Schuman et al., 2009; Skarlos et al., 2009; Vance & Carpenter, 2006; Weycker et al., 2017; Whitworth et al., 2009; Woods et al., 2010) and randomized studies (Burris et al., 2010; Siefker-Radtke et al., 2016) have evaluated the extent of prophylaxis provided by a single dose of pegfilgrastim administered within the first 24 hours after completion of chemotherapy. Here, we present a meta-analysis of studies comparing the efficacy of same-day pegfilgrastim to the standard protocol of administration > 24 hours following completion of chemotherapy (next-day). Outcome parameters evaluated included FN, CIN grade 3/4, CIN grade 4, chemotherapy dose delays, and chemotherapy dose reductions.

METHODS

This meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist (Figure 1; Moher et al., 2009; PRISMA, 2021).

Search Strategy and Study Selection

We searched the following databases to identify retrospective and prospective studies that compared the timing of pegfilgrastim administration, including abstracts, published studies, conference papers, and reports: PubMed/MEDLINE (National Library of Medicine), Embase (Elsevier), Cochrane Library (Wiley), ScienceDirect (Elsevier), Web of Science (Clarivate Analytics), and Google Scholar. We also searched the conference and publication websites of the NCCN, the American Society of Clinical Oncology, the American Society of Hematology, and the National Cancer Institute. The search strategy included relevant Medical Subject Headings (MeSH) terms and the keyword terms pegfilgrastim, timing of administration, and chemotherapy.

Studies were selected according to PICOS (Population, Intervention, Comparison, Outcomes, and Study design) criteria (Huang et al., 2006):

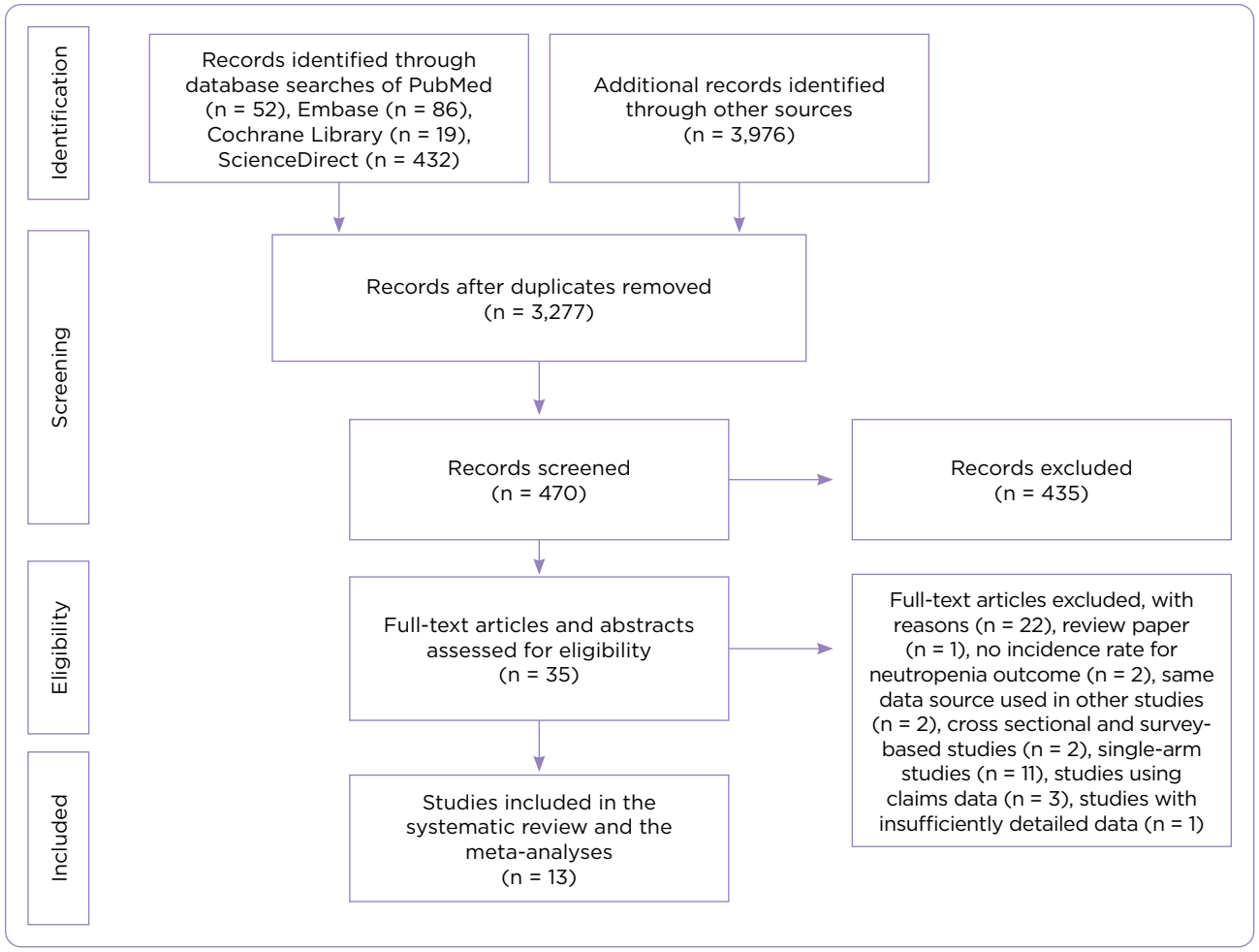


Figure 1. PRISMA flow diagram. Adapted from Moher et al. (2009).

- Participants: adult patients with solid tumors or lymphoma who were treated with originator pegfilgrastim or its biosimilars for prophylaxis of CIN/FN
- Interventions: pegfilgrastim provided as a 6 mg subcutaneous (SQ) injection either on the same day as chemotherapy or according to the standard protocol in which pegfilgrastim is administered within 24 to 72 hours of completion of chemotherapy
- Outcomes: incidence of FN in the first cycle and across all cycles of chemotherapy, grade 3/4 CIN, grade 4 CIN, as well as chemotherapy delays and/or dose reductions due to neutropenia or any serious adverse event associated with same-day administration of pegfilgrastim
- Study designs: retrospective and prospective cohort studies, randomized clinical trials, and case-control studies

Excluded were studies involving pediatric patients; reports lacking information on the number of chemotherapy cycles or the number of reportable events; reports on overlapping data sources; studies using sources other than clinical trial records or medical records (e.g., claims database studies); studies published in languages other than English; single-arm studies; and studies on the incidence of myelodysplastic syndromes in cancer patients treated with pegfilgrastim.

Data Synthesis and Quality Assessment

Abstracts were extracted by one reviewer and full articles were checked by two additional investigators to confirm eligibility. Any disagreements between reviewers were resolved by a senior investigator. The following data were retrieved from each article: publication date, study design, type and stage of cancer, age and sex of study partici-

pants, the timing of pegfilgrastim administration, chemotherapy regimens, number of chemotherapy cycles, risk estimates, number of participants in each study arm (same-day vs. next-day), and number of target events recorded, including FN in the first cycle and across all cycles of chemotherapy, grade 3/4 CIN, grade 4 CIN, and delays or dose reductions in chemotherapy due to neutropenia. The quality of the cohort and the case-control studies was assessed with the Newcastle-Ottawa Scale (NOS) and was based on selection of study groups, comparability of groups, and ascertainment of exposure and outcomes. The studies were rated using a star system and categorized from fair to good quality (Wells et al., 2018).

Statistical Analysis

Due to the paucity of studies that reported adjusted odds ratios (ORs), unadjusted (crude) ORs were calculated as a risk estimate for each outcome from a 2 × 2 contingency table created for each study. Analyses were performed using the meta, metasens, and metareg packages in R software (R Foundation for Statistical Computing, Vienna, Austria). The Mantel-Haenszel method was used to estimate the fixed-effect model and the Paule-Mandel method to estimate the random-effect model. Model selection was based on the level of between-studies variance. Heterogeneity was considered significant and favoring the random-effect model was assessed using the Cochrane *Q* test and I-squared (I^2) test. For the Cochrane *Q* test, a *p* value < .10 rather than < .05 was considered significant because of the small number of studies included (< 20; Aromataris & Munn, 2017). An I^2 > 50% was considered indicative of heterogeneity (Higgins & Thompson, 2002). Publication bias was assessed using the funnel plot of standard error by log ORs and Egger's regression test for asymmetry with *p* set at < .10 (Appendix A).

Meta-Analyses

Three levels of meta-analyses were conducted. We first performed non-stratified meta-analyses of same-day vs. next-day pegfilgrastim across all cycles and after the first cycle on the incidence of FN, grade 3/4 CIN, grade 4 CIN, as well as chemotherapy delays or dose reductions due to neutropenia over the course of chemotherapy. Next, we classified studies on the basis of the relative myelotoxicity of the chemotherapy regimens as high risk (> 20%) and intermediate risk (10%–20%) and performed meta-analyses stratified by FN risk level (Griffiths et al., 2022). Lastly, we performed meta-analyses stratified by tumor type (non-Hodgkin lymphoma [NHL], breast cancer, gynecologic cancers).

RESULTS

Systematic Review

We identified 13 publications (including one that reported results of 4 clinical trials (Burris et al., 2010) that met the inclusion criteria (Figure 1). Table 1 summarizes the reported outcomes by study design and tumor type of all included studies. Tumor types included non-Hodgkin lymphoma (NHL; 7 studies), gynecologic cancers (3 studies), breast cancer (2 studies), non–small cell lung cancer (NSCLC; 1 study), and urothelial cancer (1 study). Two studies included a mix of cancer types. Table 2 summarizes the studies in terms of tumor types, patients' age, chemotherapy regimens, and the regimens' FN risk classification. The Newcastle-Ottowa Scale scores for retrospective cohort or case-control studies were between 6 and 9 (Appendix B).

Non-Stratified Analyses

In these overall analyses, same-day administration was associated with an increased likelihood of developing FN across all cycles (OR = 1.48, 95% CI = 1.06–2.08; *k* = 14 studies; Figure 2A; Table 3) and after the first cycle of chemotherapy (OR = 2.23, 95% CI = 1.10–4.54; *k* = 7). On the other hand, in these unstratified analyses, same-day pegfilgrastim administration was not associated with an increased likelihood of grade 3 or 4 (OR = 1.17, 95% CI = 0.82–1.66; *k* = 5) or grade 4 neutropenia (OR = 0.96, 95% CI = 0.45–2.08; *k* = 5) across all chemotherapy cycles. However, there was an association with developing grade 4 neutropenia after the first cycle (OR = 2.57, 95% CI = 1.29–5.10; *k* = 6).

Analyses Stratified by Myelotoxic Febrile Neutropenia Risk

In studies involving high-risk (FN risk > 20%) chemotherapy regimens, same-day pegfilgrastim administration was associated with an increased likelihood of FN across all cycles (OR = 2.46, 95% CI = 1.04–5.83; *k* = 3; Figure 2B, Table

Table 1. Outcomes of Studies by Study Design and Cancer Type

Study	Number of patients who received PFG on the same day of chemotherapy	Number of patients who received PFG within 24–72 hours of chemotherapy	Results reported as: same-day vs. next-day administration
Retrospective cohort studies in breast cancer			
Kumar et al., 2009	43 patients	13 patients	• Overall FN incidence: 16% vs. 7% with OR = 2.1 (95% CI = 0.28–15.6)
Retrospective cohort studies in gynecologic cancer			
Billingsley et al., 2015	129 patients administered 506 PFG injections	353 patients administered 1,565 PFG injections	• Grade 3 or 4 neutropenia: 2.6% vs. 1.8%, aRR 1.6 (90% CI = 0.82–3.23 • Overall FN incidence: 0.2% vs. 0.1% • Dose modification due to neutropenia: 0.6% vs. 0.5 %, aRR 1.27 (90% CI = 0.39–4.11) • Treatment delay due to neutropenia: 0.8% vs. 1.7%, aRR 0.57 (90% CI = 0.25–1.31) • Bone pain: 7.7% vs. 5.6%, aRR 1.28 (90% CI = 0.85–1.93)
Whitworth et al., 2009	44 patients administered 490 PFG injections	143 patients administered 736 PFG injections	• Grade 3, 4 neutropenia: 4.9% vs. 5.7%, p = .63 • Dose modifications: 2.8% vs. 5.3%, p = .06 • Chemotherapy delay: 5.9% vs. 7.5%, p = 0.35 • Overall FN incidence: 0% vs. 0.4%, p = .41 • Bone pain: 14.9% vs. 12.4%, p = .23 • ANC nadir: 4,810/mm^3 vs. 4,212/m^3, p = .004
Retrospective cohort studies in NHL			
Cheng et al., 2014	57 patients (total number of PFG injections that were received = 320); 36 patients observed from their first cycle of chemotherapy	63 patients who received 335 total PFG injections; 54 patients observed from their first cycle	• Overall FN: 9.4% vs. 5.1%, p = .03 • FN in cycle 1: 19.4% vs. 11.1%, p = 0.27 • Mean duration of grade 4 neutropenia: 3.00 (SD 2.17) vs. 2.41 days (SD 1.28), p = .31 • Duration of hospital stays: 5.27 (SD 2.46) vs. 7.59 days (SD 4.90), p = 0.04 • Dose reduction of chemotherapy: 51.7% vs. 40%, p = 0.46
Ibrahim et al., 2011	60 chemotherapy cycles	57 chemotherapy cycles	• Total neutropenia: 26.67% vs. 10.53%. • FN incidence: 13.33% vs. 3.51% • Infection rate: 6.6% vs. 1.75%
Karol et al., 2013	31 patients	82 patients	• Overall FN: 25.81% vs. 25.61% cases, p = 0.91
Woods et al., 2010	162 chemotherapy cycles	31 chemotherapy cycles	• Overall FN: 6.17% vs. 9.68%, p = 0.4 • Grade 4 neutropenia: 32.10% vs. 45.16%, p = 0.4
Bartels et al., 2021	14 patients received 95 cycles	4 patients received 5 cycles	• Overall FN 5.3% vs. 0% • Overall grade 3/4 neutropenia: 10.5% vs. 0.0 • Overall grade 4 neutropenia: 6.32% vs. 0% • Grade 4 neutropenia after the first cycle: 14.29% vs. 0% • Hospitalization: 10.5% vs. 20.0%, p = .45 • Antibiotics administration: 6.3% vs. 40.0%, p = .05 • Chemotherapy dose delays or reductions: 16.8% vs. 0.0%
McBride et al., 2021	103 patients received 660 chemotherapy cycles	13 patients received 19 cycles	• First cycle FN: 6% vs. 8%, p > .05 • Overall FN: 4% vs. 5%, p > .05 • Overall grade 3/4 neutropenia: 11% vs. 16%, p > .05 • Overall grade 4 neutropenia: 8.18% vs. 0%, p > .05 • Grade 4 neutropenia after the first hospitalization: 8% vs. 11%, p > .05 • Dose delays/reductions incidences 11% vs. 5%, p > .05

Note. ANC = absolute neutrophil count; aRR = adjusted relative risk; DLBCL = diffuse large B-cell lymphoma; FN = febrile neutropenia; G-CSF = granulocyte colony stimulating factor; BC = breast cancer; NHL = non-Hodgkin lymphoma; NSCLC = non–small cell lung cancer; OC = ovarian cancer; OR = odds ratio; PFG = pegfilgrastim; SCLC = small cell lung cancer.

Table 1. Outcomes of Studies by Study Design and Cancer Type (cont.)

Study	Number of patients who received PFG on the same day of chemotherapy	Number of patients who received PFG within 24–72 hours of chemotherapy	Results reported as: same-day vs. next-day administration
Retrospective cohort studies that included patients with different types of cancer (NHL, NSCLC, ovarian cancer, breast cancer)			
Athar et al., 2007	112 chemotherapy cycles	100 chemotherapy cycles	• Overall FN: 0.04% vs. 0.05%
Hoffman et al., 2005	70 patients	89 patients	• Overall FN: 0.01% vs. 0.02% cases, $p > .05$
Prospective studies and randomized controlled trials			
Burris et al., 2010 (breast cancer)	45 patients received 229 PFG injections	45 patients received 246 PFG injections	• Grade 4 neutropenia in cycle 1: 93% vs. 78% • FN in cycle 1: 22% vs. 7% • FN in overall cycles: 33% vs. 11% • Mean duration of grade 4 neutropenia in cycle 1: 2.6 vs. 1.4 days
Burris et al., 2010 (NHL)	36 patients administered 174	39 patients administered 209	• Grade 4 neutropenia in cycle 1: 86% vs. 64% • FN in cycle 1: 11% vs. 3% • FN in overall cycles was 17% vs. 15% • Mean duration of grade 4 neutropenia in cycle 1: 2.1 vs. 1.2 days
Burris et al., 2010 (NSCLC)	44 patients	44 patients	• Grade 4 neutropenia in cycle 1: 5% vs. 5% • FN in cycle 1: 0% vs. 0%, same result for overall FN • Mean duration of grade 4 neutropenia in cycle 1: 0.05 vs. 0.05 days
Burris et al., 2010 (ovarian cancer)	8 patients	11 patients	• Grade 4 neutropenia in cycle 1: 75% vs. 55% • FN in cycle 1: 13% vs. 18%, same result for the overall FN • Mean duration of grade 4 neutropenia in cycle 1: 1.9 vs. 2.4 days
Siefker-Radtke et al., 2016 (metastatic or unresectable urothelial carcinoma)	32 patients received 164 PFG across all cycles	7 patients administered 15 PFG injections	• Overall FN: 1.83% vs. 6.76% • 33.3% of the patients experienced grade 3 or 4 neutropenia

Note. ANC = absolute neutrophil count; aRR = adjusted relative risk; DLBCL = diffuse large B-cell lymphoma; FN = febrile neutropenia; G-CSF = granulocyte colony stimulating factor; BC = breast cancer; NHL = non-Hodgkin lymphoma; NSCLC = non–small cell lung cancer; OC = ovarian cancer; OR = odds ratio; PFG = pegfilgrastim; SCLC = small cell lung cancer.

3). Analyses for cycle 1 only revealed no association between day of administration and the likelihood of patients treated with highly myelotoxic chemotherapy developing FN (OR = 2.70, 95% CI = 0.86–8.44; k = 2). However, high-risk patients administered pegfilgrastim on the same day were more likely to experience grade 4 neutropenia (OR = 3.20, 95% CI = 1.19–8.66; k = 2) after the first cycle.

In contrast, for the studies that focused on intermediate-risk (FN risk 10%–20%) chemotherapy regimens, there was no difference in FN likelihood between same-day and next-day patients across all cycles (OR = 1.41, 95% CI = 0.95–2.10; k = 9; Figure 2C, Table 3). Similarly, there was no difference in FN (OR = 1.98, 95% CI = 0.80–4.90; k = 5) or grade 4 CIN (OR = 2.12, 95% CI = 0.83–5.43; k = 4) likelihood between intermediate-risk patients prophylacted the same day vs. next day after the first cycle of chemotherapy.

Analyses Stratified by Tumor Type

Although limited to two studies, same-day administration was associated with a higher likelihood

Table 2. Febrile Neutropenia Risk Stratification Outcomes Based on the Received Chemotherapy and Cancer Type

Study	Cancer type	Median or mean of patients' age[a] (yr)	Chemotherapy regimens	FN risk stratification
Athar et al., 2007	NHL (42%) SCLC (18%) NSCLC (14%)	70 (whole cohort)	NA	NA
Bartels et al., 2021	NHL	66 (whole cohort)	Mini R-CHOP	Intermediate
Billingsley et al., 2015	Gynecologic cancer	59.4 (whole cohort)	Carboplatin/paclitaxel (42%) Carboplatin/docetaxel (11%)	Intermediate
Burris et al., 2010	Breast cancer	26/31	Docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2	High
Burris et al., 2010	NHL	28/26	Rituximab 375 mg/m^2; cyclophosphamide 750 mg/m^2; doxorubicin 50 mg/m^2; vincristine 1.4 mg/m^2; prednisone 100 mg (days 1–5)	Intermediate
Burris et al., 2010	NSCLC	36/40	Carboplatin/docetaxel	Intermediate
Burris et al., 2010	Ovarian cancer	38/36	Topotecan 1.5 mg/m^2 administered days 1–5 of each cycle	High
Cheng et al., 2014	NHL	58/63	CHOP or R-CHOP q3w	Intermediate
Hoffman et al., 2005	15 tumor types	NA	NA	NA
Ibrahim et al., 2011	NHL	Age range 40–80 for whole cohort	R-CHOP or CHOP q3w	Intermediate
Karol et al., 2013	NHL	NA	R-CHOP	Intermediate
Kumar et al., 2009	Breast cancer	52.9 for whole cohort	Docetaxel, doxorubicin hydrochloride, and cyclophosphamide	High
McBride et al., 2021	NHL/CLL	68/72.5	CHOP or R-CHOP or bendamustine plus rituximab	Intermediate
Siefker-Radtke et al., 2016	Urothelial carcinoma	72 for whole cohort	Gemcitabine 900 mg/m^2, paclitaxel 135 mg/m^2, doxorubicin 40 mg/m^2	High
Whitworth et al., 2009	Gynecologic: ovarian (70%), endometrial (19.2%), cervical (1.7%), fallopian tube (2.6%)	64 for whole cohort	Docetaxel/carboplatin (53%) Paclitaxel/carboplatin (19%)	Intermediate
Woods et al., 2010	Lymphoma	NA	CHOP	Intermediate

Note. FN = febrile neutropenia; PFG = pegfilgrastim; BC = breast cancer; NHL = non-Hodgkin lymphoma; NSCLC = non–small cell lung cancer; OC = ovarian cancer; SCLC = small cell lung cancer; R-CHOP = rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone; NA = not available.
[a]In patients who were administered PFG on the same day of chemotherapy or patients who were administered PFG within 24–72 hours of chemotherapy.

Table 3. Results of All Meta-Analyses

Across all cycles of chemotherapy	Included studies	Model	Heterogeneity, I^2% (95% CI), *p*-value	Results of meta-analysis, OR (95% CI), *p* value	Publication bias *p*-value of Egger's test[a]
Incidence of FN	Hoffman, Athar, Whitworth, Kumar, Burris (BC, NHL), Woods, Ibrahim, Karol, Cheng, Billingsley, Siefker-Radtke, Bartels, McBride	Fixed	2.5 (0–56.2), 0.422	1.48 (1.06–2.08), 0.023	0.111
Incidence of FN in high risk	Kumar, Burris (BC), Siefker-Radtke	Fixed	48.6 (0–85.0), 0.143	2.46 (1.04–5.83), 0.041	
Incidence of FN in intermediate risk	Whitworth, Burris (NHL), Woods, Ibrahim, Karol, Cheng, Billingsley, Bartels, McBride	Fixed	0 (0–62.1), 0.492	1.41 (0.95–2.10), 0.088	
Incidence of grade 3/4 neutropenia[b]	Whitworth, Ibrahim, Billingsley, Bartels, McBride	Fixed	34.2 (0–75.2), 0.193	1.17 (0.82–1.66), 0.398	0.652
Incidence of grade 4 neutropenia[b]	Whitworth, Woods, Billingsley, Bartels, McBride	Random	50.2 (0–81.7), 0.090	0.96 (0.45–2.08), 0.924	0.589
After first cycle of chemotherapy					
Incidence of FN after first cycle of chemotherapy	Burris (BC, NHL, NSCLC, OC), Cheng, Bartels, McBride	Fixed	0.0 (0.0–58.3), 0.693	2.23 (1.10–4.54), 0.027	0.458
Incidence of FN in high risk	Burris (BC, OC)	Fixed	33.0, *p* = .222	2.70 (0.86–8.44), 0.088	
Incidence of FN in intermediate risk	Burris (NHL, NSCLC), Cheng, Bartels, McBride	Fixed	0.0 (0–65.8), 0.719	1.98 (0.80–4.90), 0.140	
Incidence of grade 4 neutropenia	Burris (BC, NHL, NSCLC, OC), Bartels, McBride	Fixed	0.0 (0–49.3), 0.776	2.57 (1.29–5.10), 0.007	0.109
Grade 4 in high risk	Burris (BC, OC)	Fixed	0.0, *p* = .779	3.20 (1.19–8.66), 0.022	
Grade 4 in intermediate risk	Burris (NHL, NSCLC), Bartels, McBride	Fixed	0.0 (0–77.1), 0.572	2.12 (0.83–5.43), 0.119	
Breast cancer[c]					
FN across all cycles	Kumar, Burris (BC)	Fixed	0, *p* = 0.765	3.15 (1.24–8.01), 0.016	
Non-Hodgkin lymphoma[b]					
FN across all cycles	Burris (NHL), Woods, Ibrahim, Karol, Cheng, Bartels, McBride[d]	Fixed	0.0 (0–68.5), 0.475	1.48 (0.98–2.23), 0.062	0.361
FN after the first cycle	Burris (NHL), Cheng, Bartels, McBride	Fixed	0.0 (0–65.8), 0.719	1.98 (0.80–4.90), 0.140	0.971

Note. FN = febrile neutropenia; CIN = chemotherapy induced neutropenia; BC = breast cancer; NHL = non-Hodgkin lymphoma; NSCLC = non–small cell lung cancer; OC = ovarian cancer; OR = odds ratio; CI = confidence interval.
[a]Egger's test may lack the statistical power to detect bias when the number of studies is small. Funnel plots are available in supplementary.
[b]All studies in this meta-analysis included intermediate-risk chemotherapy regimens.
[c]All studies in this meta-analysis included high-risk chemotherapy regimens.
[d]This study included mixed patients (60% NHL and 40% CLL).

☞ *Continued on following page*

Table 3. Results of All Meta-Analyses (cont.)

Across all cycles of chemotherapy	Included studies	Model	Heterogeneity I^2% (95% CI), *p* value	Results of meta-analysis OR (95% CI), *p* value	Publication bias p-value of Egger's test[a]
Non-Hodgkin lymphoma[b] (cont.)					
Grade 3/4 neutropenia across all cycles	Ibrahim, Bartels, McBride	Fixed	41.5 (0–82.2), 0.181	1.76 (0.81–3.84), 0.153	0.800
Grade 4 neutropenia across all cycles	Woods, Bartels, McBride	Fixed	0.0 (0–86.0), 0.476	0.73 (0.37–1.47), 0.379	0.420
Grade 4 neutropenia after first cycle	Burris (NHL), Bartels, McBride	Fixed	0.0 (0.0–85.0), 0.500	2.58 (0.86–7.73), 0.090	0.687
Chemotherapy dose reductions or delays across all cycles	Bartels, McBride	Fixed	0, *p* = 0.99	2.25 (0.42–11.97), 0.341	
Gynecologic cancers[b]					
FN across all cycles	Whitworth, Billingsley	Fixed	40.0, *p* = 0.197	0.64 (0.11–3.85), 0.628	
Grade 3/4 neutropenia across all cycles	Whitworth, Billingsley	Fixed	34.6, *p* = 0.216	1.03 (0.68–1.54), 0.899	
Grade 4 neutropenia across all cycles	Whitworth, Billingsley	Random	81.4 (21.2–95.6), 0.020	1.16 (0.22–6.19), 0.859	
Chemotherapy dose delays across all cycles	Whitworth, Billingsley	Fixed	0, *p* = 0.623	0.51 (0.21–1.25), 0.140	
Chemotherapy dose reductions across all cycles	Whitworth, Billingsley	Fixed	0, *p* = 0.756	1.04 (0.32–3.35), 0.946	

Note. FN = febrile neutropenia; CIN = chemotherapy induced neutropenia; BC = breast cancer; NHL = non-Hodgkin lymphoma; NSCLC = non–small cell lung cancer; OC = ovarian cancer; OR = odds ratio; CI = confidence interval.
[a]Egger's test may lack the statistical power to detect bias when the number of studies is small. Funnel plots are available in supplementary.
[b]All studies in this meta-analysis included intermediate-risk chemotherapy regimens.
[c]All studies in this meta-analysis included high-risk chemotherapy regimens.
[d]This study included mixed patients (60% NHL and 40% CLL).

of FN across all cycles in breast cancer patients (OR = 3.15, 95% CI = 1.24–8.01; k = 2). No other data were available for this tumor type.

In contrast, in NHL patients there was no association between timing of administration and the likelihood of FN across all cycles (OR = 1.48, 95% CI = 0.98–2.23; k = 7), FN after cycle 1 (OR = 1.98, 95% CI = 0.80–4.90; k = 4), grade 3/4 CIN (OR = 1.76, 95% CI = 0.81–3.84; k = 3), grade 4 CIN across all cycles (OR = 0.73, 95% CI = 0.37–1.47; k = 3) and after cycle 1 (OR = 2.58, 95% CI = 0.86–7.37; k = 3), or the likelihood of chemotherapy dose reductions or delays (OR = 2.25, 95% CI = 0.42–11.97; k = 2). Likewise, in patients with gynecologic cancers, timing of administration was not associated with the likelihood of FN across all cycles (OR = 0.64, 95% CI = 0.11–3.85; k = 2) or grade 3/4 CIN (OR = 1.03, 95% CI = 0.68–1.54; k = 2) and grade 4 CIN across all cycles (OR = 1.16, 95% CI = 0.22–6.19; k = 2), nor with the likelihood of dose reductions (OR = 1.04, 95% CI = 0.32–3.35; k = 2) or chemotherapy delays (OR = 0.51, 95% CI = 0.21–1.25; k = 2).

Publication Bias

With the caveat that Egger's test may lack the statistical power to detect bias when the number of studies is small and data permitting, testing for publication bias on the outcomes of interest yielded statistically nonsignificant results (Table 3). This was also confirmed by the contoured forest plots (Figure 2).

DISCUSSION

While our findings suggest that same-day pegfilgrastim administration may be associated with an increased likelihood of developing FN and possibly grade 4 CIN, stratified analyses by myelotoxicity (intermediate-risk vs. high-risk regimens) and tumor type indicate that this elevated risk may not be generalizable to all chemotherapy regimens and across all tumor types. Support for this postulate of differentiation by myelotoxicity and tumor type is evident at several levels.

First, the 1.48-fold increase in the likelihood of an FN episode across all cycles of chemotherapy is attributable mainly to the case of breast cancer, treatment with highly myelotoxic chemotherapy regimens, and the interaction of both. No increased risk on any of the outcomes of interest was observed in the analyses for NHL and gynecologic cancers. Second, the 2.23-fold increase in the likelihood of developing FN following the first-cycle chemotherapy treatment seems paradoxical, as it was not observed in studies of either high-risk or intermediate-risk regimens. While no data were available for the two breast cancer studies, the cycle 1 data for NHL and gynecologic cancer were negative as FN and grades 3 and/or 4 CIN were negative. This merits further investigation in randomized clinical trials (RCTs), as only the four Burris and colleagues studies were RCTs, and data from retrospective studies may be subject to various biases. Third, the 2.57-fold higher likelihood of grade 4 CIN noted in the first cycle of chemotherapy may be attributable mainly to being treated with a highly myelotoxic regimen. No statistically significant risk was noted for intermediate-risk regimens. Fourth, the two breast cancer studies yielded statistically significant results, but this was not the case for the gynecologic cancers and NHL studies. This further points at the relevance of differentiating by tumor type.

In sum, the differential risk of FN, grades 3 and/or 4 CIN, and chemotherapy dose reductions or delays between same-day and next-day administration is likely to be a function of the myelotoxicity of the regimens (elevated in high-risk but not in intermediate-risk regimens) and tumor type (elevated in breast but not in NHL or gynecologic cancers). Thus, and with due caution, same-day pegfilgrastim administration may be safe and beneficial in intermediate-risk regimens and selected tumor types.

Although the breast cancer meta-analysis was based on only two studies, the findings are cause for concern in terms of timing of pegfilgrastim administration. The major first-line regimen for breast cancer consists of docetaxel, doxorubicin, and cyclophosphamide, which is a highly myelotoxic regimen. Conversely, in NHL, intermediate-risk CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) without or (more commonly) with rituximab (R-CHOP) administered in 3-week cycles are the most common regimens. The meta-analysis findings for NHL suggest that same-day administration is safe in this setting. Moreover, the meta-analysis on gynecologic tumors treated by paclitaxel or docetaxel and carboplatin suggests no difference between same-day and next-day administration.

The decision to administer pegfilgrastim on the same day should include other factors as well. For instance, relatively healthy NHL patients may be treated with R-CHOP in 2-week cycles, which is a high-risk regimen. Patient risk factors should be considered, such as age, gender, general health, performance status, nutritional status, and comorbidities, because these factors could impair a patient's response to myelosuppression.

The general finding of an elevated risk of FN in the first cycle of chemotherapy is certainly of clinical concern and underscores the importance of assessing FN risk at the start of a line of treatment, as is the elevated risk across all cycles of chemotherapy. Guidelines (NCCN, European Organization for Research and Treatment of Cancer [EORTC]) recommend that the risk of FN should be assessed at the beginning of each cycle, not just at the initiation of the line of treatment.

While FN is the primary and most clinically relevant outcome in the same-day vs. standard pegfilgrastim administration debate, our findings on secondary CIN outcomes are important as they provide a more comprehensive clinical perspective on same-day vs. next-day granulocyte colony-stimulating factor (G-CSF) support. As to CIN grade 4 (without fever), the meta-analyses did not yield a signal of concern relative to same-day administration; and neither did the analyses when broadening the outcome to CIN grades 3 or

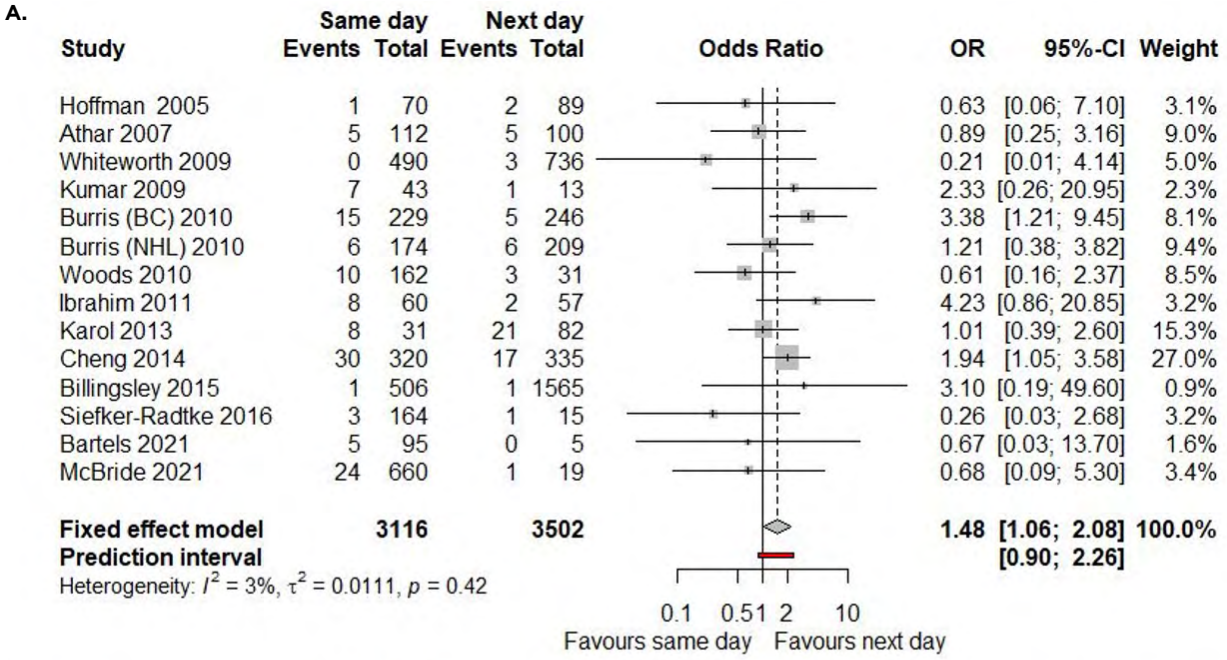


Figure 2. Forest plots of association between febrile neutropenia incidence across all cycles of chemotherapy and timing of pegfilgrastim administration (same-day vs. next-day) using (A) all studies reporting odds ratios; (B) studies with cohorts at high risk of developing FN; and (C) studies with cohorts at intermediate risk of developing FN.

4. However, it should be noted that the studies in these meta-analyses evaluated intermediate-risk regimens in NHL and gynecologic cancers.

As CIN/FN episodes may lead clinicians to consider delaying the next round of chemotherapy or reducing the dose of chemotherapy—both of which may impair tumor control—the corresponding meta-analyses in our study showed no statistically significant risk associated with same-day over next-day administration in patients with NHL on R±CHOP every 3 weeks or with gynecologic cancers and on a paclitaxel or docetaxel and carboplatin regimen. However, this might not be the case in patients with ovarian cancer and on topotecan (a regimen classified as high risk for FN).

Our study was focused on randomized and observational clinical studies; however, a claims database analysis of 53,814 cancer patients with solid tumors and NHL by Weycker and colleagues (2017) is of note. This analysis of claims in the period 2010 to 2016 evaluated pegfilgrastim prophylaxis administered the (last) day of chemotherapy (similar to our definition of "same-day") compared to days 1 to 3 and days 4 to 5. The authors reported odds of FN in cycle 1 of 1.4 (95% CI = 1.2–1.7) for patients prophylacted on the same day and 1.9 (95% CI = 1.2–3.0) for those administered pegfilgrastim on days 4 to 5. Our meta-analysis revealed a two-fold increase of FN in cycle 1, although our 95% CI (1.10–4.54) overlapped partially with the precision estimates reported by Weycker and colleagues (2017), whose precision should be attributed to the large sample size. This suggests the need for continued clinical research.

Our study builds on a previous systematic review by Lyman and colleagues (2017) that evaluated the efficacy and safety of same-day vs. next-day administration of pegfilgrastim. Although we included several of the same studies, Lyman and colleagues did not report a meta-analysis. They concluded that the administration of pegfilgrastim within 24 to 72 hours of chemotherapy resulted in improved health outcomes by reducing the incidence of FN and CIN based on subjective comparisons.

The evidence presented in our study stands in support of the relative efficacy and safety of same-day pegfilgrastim administration under consideration of tumor type and chemotherapy regimen (as NHL and R±CHOP every 3 weeks). Our findings lend comprehensive support for the current NCCN Guidelines to offer same-day pegfilgrastim in response to patient-related challenges (for instance, overnight stay, additional travel, additional direct and indirect costs, physical and psychological burden) and clinic-related factors (staffing and other resourcing) associated with an additional office visit. Furthermore, in the current COVID-19 pandemic and the additional risk of being exposed to infection, especially considering chemotherapy-related immunosuppression, same-day administration prevents an additional clinical visit and all the associated clinic-related and unrelated exposure risks. This is also aligned with Al-Shamsi and colleagues (2020) in their discussion of general approaches to minimizing the outbreak of COVID-19 in cancer patients, specifically that "Consideration of the risk and benefit for active intervention in the cancer population must be individualized and minimizing outpatient visits can help to mitigate exposure and possible further transmission." However, we should clarify here that the clinician's vigilance is needed to administer pegfilgrastim on the same day of chemotherapy to their patients.

Lastly, in the US, an on-body injector of pegfilgrastim (Amgen Inc., 2021) is available for originator pegfilgrastim—but not yet its biosimilars—which is applied the day of chemotherapy but is programmed to deliver prophylaxis about 27 to 28 hours later. However, failure and malfunction rates between 1.7% and 6.9% have been reported, putting patients at risk for not receiving G-CSF support (Joshi et al., 2017; Mahler et al., 2017; McBride et al., 2020; Stuessy et al., 2017). This increases the likelihood of FN at significant clinical and financial costs. Accordingly, same-day administration of pegfilgrastim may offer patients and caregivers convenience and assurance of prophylaxis by eliminating patient noncompliance to return the next day or failure of the delivery device.

Our study has limitations, many of which are related to the limited information that could be retrieved from studies. It is important to consider the mix of studies in our meta-analyses as some designs may be more subject to bias than others. The intermediate-risk findings came mainly from

retrospective cohort studies. Selection biases, other biases, and dilution of the true ORs cannot be excluded. The studies in the meta-analysis did not address the precise timing of next-day administration of pegfilgrastim, which could have been administered at timepoints earlier than 24 hours after the final dose of chemotherapy. Due to data limitations, we could not stratify analyses by patient characteristics. Studies did not detail the use of antibiotic prophylaxis to prevent fever due to infection (Cullen & Baijal, 2009; Pascoe & Steven, 2009), which could contribute to the incidence of CIN/FN. Studies were inconsistent in whether and how they reported the duration of CIN/FN, which made it unclear whether the duration of CIN/FN breakthrough events differed between both administration timings. Most studies did not adjust their risk estimates for patient demographics such as age, comorbidities, or other potentially relevant covariates; therefore, we could not run meta-analyses on the adjusted ORs.

CONCLUSION

This independent study found that same-day pegfilgrastim administration may or may not increase the likelihood of FN, grades 3 and/or 4 CIN, and chemotherapy dose reductions or delays. This may be a function of the myelotoxicity of the regimens (elevated in high-risk but not intermediate-risk regimens) and tumor type (elevated in breast but not in NHL or gynecologic cancers). While further research is needed, with due caution, same-day pegfilgrastim administration may be safe and beneficial in intermediate-risk regimens and selected tumor types.

Disclosure

Matrix45, LLC, which is co-owned by Dr. MacDonald and Dr. Abraham, received research support for an investigator-initiated study from Coherus Biosciences. The remaining authors have no conflicts of interest to disclose.

References

Aapro, M. S., Bohlius, J., Cameron, D. A., Dal Lago, L., Donnelly, J. P., Kearney, N.,...Zielinski, C. (2011). 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. *European Journal of Cancer*, *47*(1), 8–32. https://doi.org/10.1016/j.ejca.2010.10.013

Al-Shamsi, H. O., Alhazzani, W., Alhuraiji, A., Coomes, E. A., Chemaly, R. F., Almuhanna, M.,...Xie, C. (2020). A practical approach to the management of cancer patients during the novel coronavirus disease 2019 (COVID-19) pandemic: An International Collaborative Group. *Oncologist*, *25*(6), e936–e945. https://doi.org/10.1634/theoncologist.2020-0213

Amgen Inc. (2021). Neulasta (pegfilgrastim) package insert. https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/neulasta/neulasta_pi_hcp_english.pdf

Aromataris, E., & Munn, Z. (2017). *Joanna Briggs Institute Reviewer's Manual*. The Joanna Briggs Institute. https://reviewersmanual.joannabriggs.org/

Athar, U., Rajan, A., Gajra, A., & Lynch, T. P. (2007). Incidence of febrile neutropenia (FN) is not altered by the day of administration of pegfilgrastim (PEG). *Journal of Clinical Oncology*, *25*(18_suppl), 19636–19636. https://doi.org/10.1200/jco.2007.25.18_suppl.19636

Bartels, T., McBride, A., Alrawashdh, N., Moore, L., Persky, D. O., & Abraham, I. (2021). Same-day pegfilgrastim or pegfilgrastim-cbqv prophylaxis in miniCHOP chemotherapy based regimens for non-Hodgkin lymphoma. *Journal of Clinical Oncology*, *39*(15_suppl), e19542–e19542. https://doi.org/10.1200/JCO.2021.39.15_suppl.e19542

Bilen, M. A., Cauley, D. H., Atkinson, B. J., Chen, H. C., Kaya, D. H., Wang, X.,...Kim, J. (2017). Safety of same-day pegfilgrastim administration in metastatic castration-resistant prostate cancer treated with cabazitaxel with or without carboplatin. *Clinical Genitourinary Cancer*, *15*(3), e429–e435. https://doi.org/10.1016/j.clgc.2016.12.003

Billingsley, C. C., Jacobson, S. N., Crafton, S. M., Crim, A. K., Li, Q., Hade, E. M.,...O'Malley, D. M. (2015). Evaluation of the hematologic safety of same day versus standard administration (24- to 72-hour delay) of pegfilgrastim in gynecology oncology patients undergoing cytotoxic chemotherapy. *International Journal of Gynecological Cancer*, *25*(7), 1331–1336. https://doi.org/10.1097/IGC.0000000000000487

Burris, H. A., Belani, C. P., Kaufman, P. A., Gordon, A. N., Schwartzberg, L. S., Paroly, W. S.,...Saven, A. (2010). Pegfilgrastim on the same day versus next day of chemotherapy in patients with breast cancer, non-small-cell lung cancer, ovarian cancer, and non-Hodgkin's lymphoma: Results of four multicenter, double-blind, randomized phase II studies. *JCO Oncology Practice*, *6*(3), 133–140. https://doi.org/10.1200/jop.091094

Centers for Disease Control and Prevention. (2017). Cost of cancer-related neutropenia or fever hospitalizations. https://www.cdc.gov/cancer/dcpc/research/articles/neutropenia.htm

Cheng, C., Gallagher, E. M., Yeh, J. Y., & Earl, M. A. (2014). Rates of febrile neutropenia with pegfilgrastim on same day versus next day of CHOP with or without rituximab. *Anticancer Drugs*, *25*(8), 964–969. https://doi.org/10.1097/CAD.0000000000000115

Crawford, J., Becker, P. S., Armitage, J. O., Blayney, D. W., Chavez, J., Curtin, P.,...Pluchino, L. (2017). Myeloid Growth Factors, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*, *15*(12), 1520–1541. https://doi.

org/10.6004/jnccn.2017.0175
Cullen, M., & Baijal, S. (2009). Prevention of febrile neutropenia: Use of prophylactic antibiotics. *British Journal of Cancer*, *101*(Suppl 1), S11–S14. https://doi.org/10.1038/sj.bjc.6605270
Eckstrom, J., Bartels, T., Abraham, I., Patel, H., Elquza, E., Scott, A. J.,...McBride, A. (2019). A single-arm, retrospective analysis of the incidence of febrile neutropenia using same-day versus next-day pegfilgrastim in patients with gastrointestinal cancers treated with FOLFOX or FOLFIRI. *Supportive Care in Cancer*, *27*(3), 873–878. https://doi.org/10.1007/s00520-018-4373-0
Gascon, P., Aapro, M., Ludwig, H., Rosencher, N., Turner, M., Song, M.,...Abraham, I. (2011). Background and methodology of MONITOR-GCSF, a pharmaco-epidemiological study of the multi-level determinants, predictors, and clinical outcomes of febrile neutropenia prophylaxis with biosimilar granulocyte-colony stimulating factor filgrastim. *Critical Reviews in Oncology/Hematology*, *77*(3), 184–197. https://doi.org/10.1016/j.critrevonc.2010.01.014
Griffiths, E. A., Roy, V., Alwan, L. M., Bachiashvili, K., Baird, J., Cool, R.,...Petel, S. (2022). NCCN Guidelines Insights: Hematopoietic Growth Factors, Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf
Gupta, N. K., Thorpe, S., Vanderhoff, P., Gomez, S., Stiltner, M., Alvares, D.,...Bohnen, R. (2007). Pegfilgrastim can be effectively administered the same day as chemotherapy to prevent neutropenia-related complications. *Journal of Clinical Oncology*, *25*(18_suppl), 19571–19571. https://doi.org/10.1200/jco.2007.25.18_suppl.19571
Higgins, J. P., & Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine*, *21*(11), 1539–1558. https://doi.org/10.1002/sim.1186
Hoffmann, P. S. (2005). Administration of pegfilgrastim on the same day or next day of chemotherapy. *Journal of Clinical Oncology*, *23*(16_suppl), 8137–8137. https://doi.org/10.1200/jco.2005.23.16_suppl.8137
Holmes, F. A., Jones, S. E., O'Shaughnessy, J., Vukelja, S., George, T., Savin, M.,...Liang, B. C. (2002). Comparable efficacy and safety profiles of once-per-cycle pegfilgrastim and daily injection filgrastim inchemotherapy-induced neutropenia: a multicenterdose-finding study in women with breast cancer. *Annals of Oncology*, *13*(6), 903–909. https://doi.org/10.1093/annonc/mdf130
Huang, X., Lin, J., & Demner-Fushman, D. (2006). Evaluation of PICO as a knowledge representation for clinical questions. AMIA: *Annual Symposium Proceedings, 2006*, 359–363. https://www.ncbi.nlm.nih.gov/pubmed/17238363
Ibrahim, Z., Hughes, J., McQuillan, A., Baker, R., Powell, A., Peter, D.,...Parsons, R. (2011). The effect of pegylated granulocyte-colony stimulating factor administration timing after CHOP or CHOP-R regimen administration in non-Hodgkin's Lymphoma patients on the development of neutropenia. *Asia-Pacific Journal of Clinical Oncology*, *7*, 135–136. https://r.search.yahoo.com/_ylt=Awr9Dug_4zxcMwoAoxpXNyoA;_ylu=X3oDMTEybW5pYXNpBGNvbG8DZ3ExBHBvcwMxBHZ0aWQDQjI5NDRfMQRzZWMDc3I-/RV=2/RE=1547523007/RO=10/RU=https%3a%2f%2faccp.confex.com%2faccp%2f2012vp%2frecordingredirect.cgi%2fid%2f66/RK=2/RS=OTnuXp6YrmOhFuiDlcV5jwU_E0A-
Joshi, R. S., Egbuna, O. I., Cairns, A. S., Friedman, M. J., Abosaleem, B., Reiner, M. T., & Morrow, P. K. (2017). Performance of the pegfilgrastim on-body injector as studied with placebo buffer in healthy volunteers. *Current Medical Research and Opinion*, *33*(2), 379–384. https://doi.org/10.1080/03007995.2016.1257980
Karol, J., Rybicki, L., Sweetenham, J., Smith, M. R., Hill, B. T., Pohlman, B.,...Dean, R. M. (2013). Similar incidence of febrile neutropenia with same-day versus subsequent day G-CSF administration in non-Hodgkin lymphoma patients receiving R-CHOP chemotherapy. *Blood*, *122*(21), 4357. https://doi.org/10.1182/blood.V122.21.4357.4357
Kumar, P., Ingle, A. M., Miller, S., Woods, M., & Thomas, S. P. (2009). Incidence of febrile neutropenia (FN) with pegfilgrastim (PF) on day of chemotherapy (D1) versus 24–72 hrs later (D2). *Journal of Clinical Oncology*, *27*(15S), e20664–e20664. https://doi.org/10.1200/jco.2009.27.15_suppl.e20664
Lane, S. W., Crawford, J., Kenealy, M., Cull, G., Seymour, J. F., Prince, H. M.,...Mollee, P. N. (2006). Safety and efficacy of pegfilgrastim compared to granulocyte colony stimulating factor (G-CSF) supporting a dose-intensive, rapidly cycling anti-metabolite containing chemotherapy regimen (Hyper-CVAD) for lymphoid malignancy. *Leukemia & Lymphoma*, *47*(9), 1813–1817. https://doi.org/10.1080/10428190600632832
Lokich, J. (2005). Same-day pegfilgrastim and chemotherapy. *Cancer Investigation*, *23*(7), 573–576. https://doi.org/10.1080/07357900500276899
Lokich, J. J. (2006). Same day pegfilgrastim and CHOP chemotherapy for non-Hodgkin lymphoma. *American Journal of Clinical Oncology*, *29*(4), 361–363. https://doi.org/10.1097/01.coc.0000217816.16236.22
Lyman, G. H., Allcott, K., Garcia, J., Stryker, S., Li, Y., Reiner, M. T., & Weycker, D. (2017). The effectiveness and safety of same-day versus next-day administration of long-acting granulocyte colony-stimulating factors for the prophylaxis of chemotherapy-induced neutropenia: A systematic review. *Supportive Care in Cancer*, *25*(8), 2619–2629. https://doi.org/10.1007/s00520-017-3703-y
Mahler, L., DiBlasi, R., Perez, A., Gaspard, J., & McCauley, D. (2017). On-body injector: An administration device for pegfilgrastim. *Clinical Journal of Oncology Nursing*, *21*(1), 121–122. https://doi.org/10.1188/17.CJON.121-122
Marion, S., Tzivelekis, S., Darden, C., Price, M. A., Sherif, B., Garcia, J.,...Chandler, D. (2016). "Same-Day" administration of pegfilgrastim following myelosuppressive chemotherapy: Clinical practice and provider rationale. *Supportive Care in Cancer*, *24*(9), 3889–3896. https://doi.org/10.1007/s00520-016-3193-3
Matera, R. M., Relias, V., & Saif, W. M. (2017). Safety and efficacy of same-day administration of pegfilgrastim in patients (pts) receiving chemotherapy for gastrointestinal (GI) malignancies. *Journal of Clinical Oncology*, *35*(15_suppl), 10112–10112. https://doi.org/10.1200/JCO.2017.35.15_suppl.10112
McBride, A., Alrawashdh, N., Bartels, T., Moore, L., Persky, D. O., & Abraham, I. (2021). Evaluation of same day pegfilgrastim (PFG) or PFG-cbqv prophylaxis of chemotherapy induced (Febrile) neutropenia (CIN/FN) in bendamustine plus rituximab (BR) and CHOP+/-R regimens in patients with lymphoma and chronic lymphocytic leukemia (CLL): Real-world, single-center experience. *Jour-*

nal of Clinical Oncology, *39*(15_suppl), e19541–e19541. https://doi.org/10.1200/JCO.2021.39.15_suppl.e19541

McBride, A., Krendyukov, A., Mathieson, N., Campbell, K., Balu, S., Natek, M.,...Abraham, I. (2020). Febrile neutropenia hospitalization due to pegfilgrastim on-body injector failure compared to single-injection pegfilgrastim and daily injections with reference and biosimilar filgrastim: US cost simulation for lung cancer and non-Hodgkin lymphoma. *Journal of Medical Economics*, *23*(1), 28–36. https://doi.org/10.1080/13696998.2019.1658591

Mehta, H. M., Malandra, M., & Corey, S. J. (2015). G-CSF and GM-CSF in Neutropenia. *Journal of Immunology*, *195*(4), 1341–1349. https://doi.org/10.4049/jimmunol.1500861

Micha, J. P., Brown, J. V., 3rd, Rettenmaier, M. A., Abaid, L. N., Mendivil, A. A., Lopez, K. L., & Goldstein, B. H. (2013). Pegfilgrastim safely administered on the same day as dose-dense chemotherapy for patients with advanced-stage ovarian carcinoma. *Clinical Oncology*, *25*(6), 390. https://doi.org/10.1016/j.clon.2013.02.003

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Annals of Internal Medicine*, *151*(4), 264–269. https://doi.org/10.7326/0003-4819-151-4-200908180-00135

Pascoe, J., & Steven, N. (2009). Antibiotics for the prevention of febrile neutropenia. *Current Opinion in Hematology*, *16*(1), 48–52. https://journals.lww.com/co-hematology/Fulltext/2009/01000/Antibiotics_for_the_prevention_of_febrile.10.aspx

Preferred Reporting Items for Systematic Reviews and Meta-Analyses. (2021). PRISMA statement. http://www.prisma-statement.org/PRISMAStatement/PRISMAStatement.aspx

Schuman, S. I., Lambrou, N., Robson, K., Gluck, S., Myriounis, N., Pearson, J. M., & Lucci, J. A., 3rd. (2009). Pegfilgrastim dosing on same day as myelosuppressive chemotherapy for ovarian or primary peritoneal cancer. *Journal of Supportive Oncology*, *7*(6), 225–228. https://pubmed.ncbi.nlm.nih.gov/20380330/

Siefker-Radtke, A. O., Campbell, M. T., Munsell, M. F., Harris, D. R., Carolla, R. L., & Pagliaro, L. C. (2016). Front-line treatment with gemcitabine, paclitaxel, and doxorubicin for patients with unresectable or metastatic urothelial cancer and poor renal function: Final results from a phase II study. *Urology*, *89*, 83–89. https://doi.org/10.1016/j.urology.2015.12.007

Skarlos, D. V., Timotheadou, E., Galani, E., Samantas, E., Grimani, I., Lianos, E.,...Fountzilas, G. (2009). Pegfilgrastim administered on the same day with dose-dense adjuvant chemotherapy for breast cancer is associated with a higher incidence of febrile neutropenia as compared to conventional growth factor support: matched case-control study of the Hellenic Cooperative Oncology Group. *Oncology*, *77*(2), 107–112. https://doi.org/10.1159/000229504

Stuessy, P., Sanchez, F. A., & Schober, M. (2017). Retrospective review of pegfilgrastim on-body injector delivery rates in a large health system. *Journal of Clinical Oncology*, *35*(15_suppl), e18273–e18273. https://doi.org/10.1200/JCO.2017.35.15_suppl.e18273

U.S. Bureau of Labor Statistics. (2021). Consumer Price Index for All Urban Consumers: Medical Care in US City Average [CPIMEDSL], retrieved from FRED, Federal Reserve Bank of St. Louis. https://fred.stlouisfed.org/series/CPIMEDSL

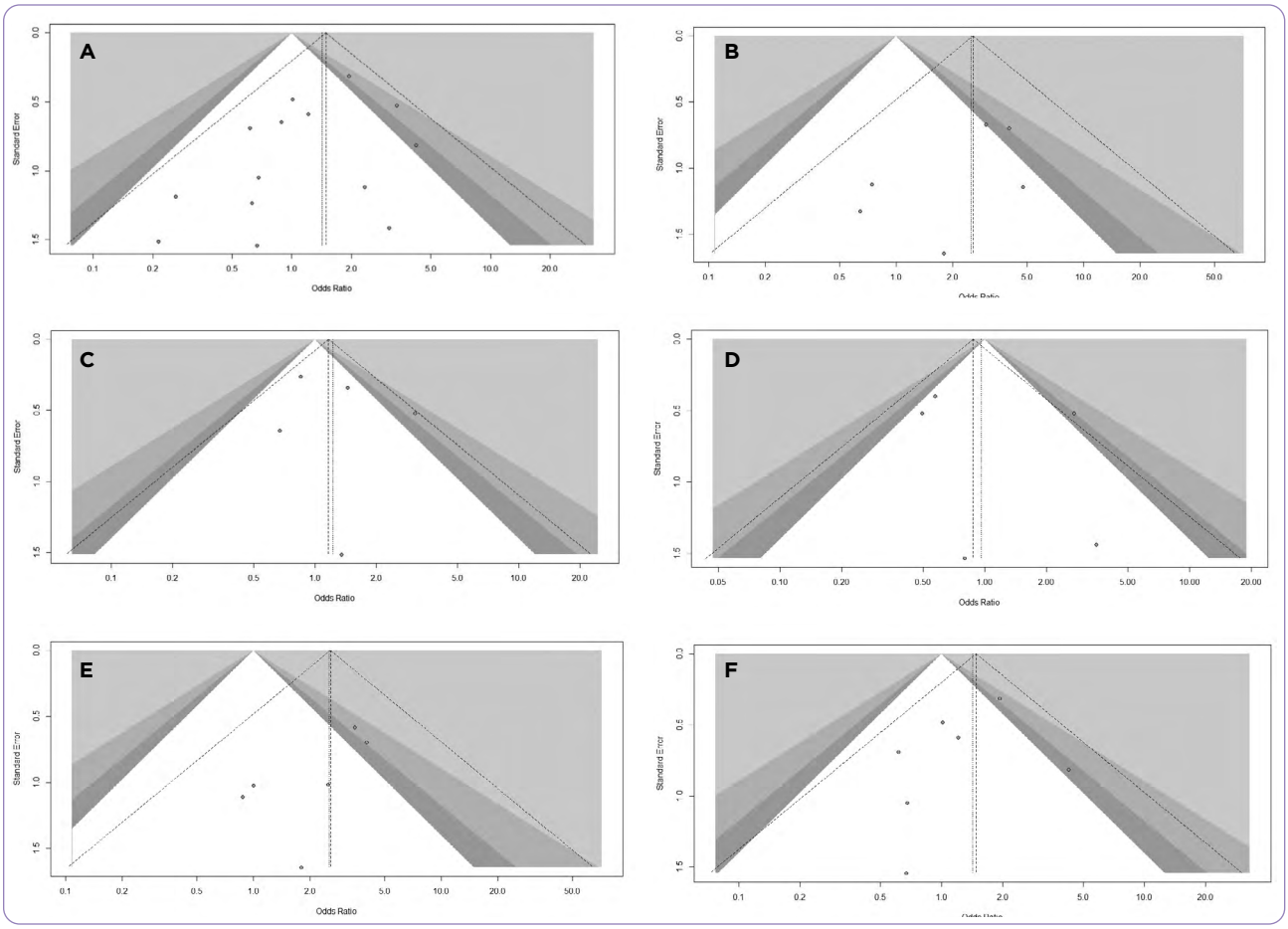
Vance, K. T., & Carpenter, J. (2006). Same day administration of pegfilgrastim with dose dense doxorubicin in early breast cancer patients. *Journal of Clinical Oncology*, *24*(18_suppl), 671–671. https://doi.org/10.1200/jco.2006.24.18_suppl.671

Wells, G. A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2018). The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

Weycker, D., Bensink, M., Lonshteyn, A., Doroff, R., & Chandler, D. (2017). Risk of chemotherapy-induced febrile neutropenia by day of pegfilgrastim prophylaxis in US clinical practice from 2010 to 2015. *Current Medical Research and Opinion*, *33*(12), 2107–2113. https://doi.org/10.1080/03007995.2017.1386858

Whitworth, J. M., Matthews, K. S., Shipman, K. A., Numnum, T. M., Kendrick, J. E., Kilgore, L. C., & Straughn, J. M., Jr. (2009). The safety and efficacy of day 1 versus day 2 administration of pegfilgrastim in patients receiving myelosuppressive chemotherapy for gynecologic malignancies. *Gynecologic Oncology*, *112*(3), 601–604. https://doi.org/10.1016/j.ygyno.2008.10.025

Woods, M. A., Lopez, T., Thomas, S. P., Harwood, H., & Kettler, S. M. (2010). Incidence of febrile neutropenia in lymphoma patients receiving CHOP with Day 1 or 2 pegfilgrastim. *Journal of Clinical Oncology*, *28*(15_suppl), e18562–e18562. https://doi.org/10.1200/jco.2010.28.15_suppl.e18562



Appendix A. Funnel plots of standard error by effect estimate for meta-analyses of (A) FN across all cycles; (B) FN after the first cycle; (C) grade 3/4 neutropenia across all cycles; (D) grade 4 neutropenia across all cycles; (E) grade 4 neutropenia after the first cycle; (F) FN across all cycles in NHL.

Appendix B. Newcastle-Ottawa Scale Scores of Cohorts Studies

Study	Study design	Selection	Comparability	Outcome/Exposure	Quality score	Quality
Athar et al., 2007	Retrospective cohort	***0	*0	***	7	Good
Bartels et al., 2021	Retrospective cohort	****	**	0**	8	Good
Billingsley et al., 2015	Retrospective cohort	****	**	***	9	Good
Cheng et al., 2014	Retrospective cohort	****	0*	***	8	Good
Hoffman et al., 2005	Retrospective cohort	***0	0*	*0*	6	Good
Ibrahim et al., 2011	Retrospective cohort	****	**	***	9	Good
Karol et al., 2013	Retrospective cohort	**0*	0*	***	7	Good
Kumar et al., 2009	Retrospective cohort	****	**	**0	8	Good
McBride et al., 2021	Retrospective cohort	****	**	0**	8	Good
Whiteworth et al., 2009	Retrospective cohort	****	**	***	9	Good
Woods et al., 2010	Retrospective cohort	****	0*	***	7	Good

Note. Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain. Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain. Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.