BBCIC Research Network Analysis of First-Cycle Prophylactic G-CSF Use in Patients Treated With High–Neutropenia Risk Chemotherapy

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ABSTRACT

Background: Chemotherapy-induced febrile neutropenia (FN) is prevented or minimized with granulocyte colony-stimulating factors (G-CSFs). Several G-CSF biosimilars are approved in the United States. The Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) is a nonprofit initiative whose objective is to provide scientific evidence on real-world use and comparative safety and effectiveness of biologics and biosimilars using the BBCIC distributed research network (DRN). **Patients and Methods:** We describe real-world G-CSF use in patients with breast or lung cancer receiving first-cycle chemotherapy associated with high FN risk. We assessed hospitalizations for FN, availability of absolute neutrophil counts, and G-CSF–induced adverse events to inform future observational comparative effectiveness studies of G-CSF reference products and their biosimilars. A descriptive analysis of 5 participating national health insurance plans was conducted within the BBCIC DRN. **Results:** A total of 57,725 patients who received at least one G-CSF dose were included. Most (92.5%) patients received pegfilgrastim. FN hospitalization rates were evaluated by narrow (<0.5%), intermediate (1.91%), and broad (2.99%) definitions. Anaphylaxis and hyperleukocytosis were identified in 1.15% and 2.28% of patients, respectively. This analysis provides real-world evidence extracted from a large, readily available database of diverse patients, characterizing G-CSF reference product use to inform the feasibility of future observational comparative safety and effectiveness analyses of G-CSF biosimilars. We showed that the rates of FN and adverse events in our research network are consistent with those reported by previous small studies. **Conclusions:** Readily available BBCIC DRN data can be used to assess G-CSF use with the incidence of FN hospitalizations. Insufficient laboratory result data were available to report absolute neutrophil counts; however, other safety data are available for assessment that provide valuable baseline data regarding the effectiveness and safety of G-CSFs in preparation for comparative effectiveness studies of reference G-CSFs and their biosimilars.

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Background

Prophylaxis with the recombinant human granulocyte colony-stimulating factors (G-CSFs) filgrastim and pegfilgrastim prevents chemotherapy-induced neutropenia; reduces febrile neutropenia (FN) risk and infection-related and early mortality; and allows higher relative chemotherapy dose intensity.[1–5] Primary prophylaxis is recommended for all patients receiving chemotherapy associated with high (>20%) FN risk and considered for use with chemotherapy associated with intermediate (10%–20%) FN risk.[6–8] Overall reported FN rates are 17% in patients with early-stage breast cancer[9] and 13.1% in patients with newly diagnosed breast, colorectal, lung, lymphoid, or ovarian cancer.[10] However, with G-CSF primary prophylaxis, the FN rate is <5%.[9]

Despite the high costs associated with G-CSF administration, use of G-CSFs is cost saving, and G-CSFs are a critical part of cancer therapy.[11] Thus, biosimilar availability in the United States was anxiously awaited. In 2010, the United States enacted the Biologics Price Competition and Innovation Act of 2009 to establish an abbreviated regulatory approval pathway for biosimilars.[12] The basic tenet of biosimilars is that they have no clinically meaningful differences from their reference products.[13] However, critical issues associated with biosimilar use in oncology were identified.[14] In addition to comparability to reference biologics, assurance of patient safety, and improved patient access, effective pharmacovigilance vital to ensuring ongoing biosimilar safety and effectiveness was noted.[15,16] Healthcare providers and patients expressed concerns regarding safety.[17–22] An NCCN survey identified challenges associated with biosimilar introduction into the clinic, and studies assessing safety and efficacy of biosimilars were deemed most important.[18] Subsequently, ASCO and ESMO each issued guidance

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regarding biosimilar filgrastim use and highlighted the need for pharmacovigilance with real-world evidence.[23,24]

As of May 2020, two filgrastim and three pegfilgrastim biosimilar products are available in the United States.[13] Randomized controlled trials confirm their efficacy, tolerability, and safety compared with the reference products.[25–28] A subsequent meta-analysis of clinical trials demonstrated no significant differences in the mean duration of severe neutropenia, absolute neutrophil count (ANC) nadir depth or time to ANC recovery, FN incidence, or safety.[29] Data regarding G-CSF biosimilar use in real-world settings are maturing, and critical pharmacovigilance of these products depends on the understanding of their use and clinical impact.[30,31] Similar clinical and safety outcomes of the G-CSF biosimilars compared with their reference products are reported.[32–34] These studies are consistent with initial, small, retrospective, observational analyses demonstrating equivalence or noninferiority with the reference product regarding FN incidence.[30,31]

The Biologics and Biosimilars Collective Intelligence Consortium (BBCIC), a nonprofit public service initiative, is dedicated to providing scientific, real-world evidence on the use and comparative safety and effectiveness of biologics and biosimilars.[35] The objective of this descriptive analysis was to evaluate real-world G-CSF reference product use by evaluating administrative data extracted from a large, diverse network to characterize real-world G-CSF reference product use in patients receiving first-cycle chemotherapy associated with high FN risk for breast or lung cancer in preparation for future comparative effectiveness studies with G-CSF biosimilars. This work will inform future observational comparative safety and effectiveness analyses of G-CSF biosimilars.

Patients and Methods

Study Design, Data Source, and Participating Sites

This retrospective, incident user cohort study assessed our ability to identify and describe G-CSF administration, describe hospitalizations for FN events, and determine the availability of potential confounders. The BBCIC leverages FDA Sentinel Initiative infrastructure, including a distributed research network (DRN) with access to curated data formatted in the Sentinel Common Data Model (SCDM), and publicly available Sentinel analytic tools.[36] The BBCIC DRN includes insurance claims data from 5 health plans: Aetna (via Healthagen), Harvard Pilgrim Health Care (HPHC), Anthem (via HealthCore), HealthPartners, and Kaiser Permanente Washington. The Institutional Review Boards at HPHC for the BBCIC DRN and each health plan determined that the analysis did not meet the definition of human subjects research.

Study Population

Adults aged ≥18 years with newly diagnosed breast or lung cancer who received at least one G-CSF dose between January 1, 2008, and September 30, 2015, were included in the analysis. Because the first G-CSF biosimilar was not approved in the United States until September 2015, biosimilar G-CSF use was not included. A minimum of 1 inpatient or 2 outpatient claims at least 30 days apart for breast or lung cancer with ICD-9 codes 174.x–175.x or 162.x–165.x, respectively, before the index G-CSF dispensing (index date) were required for study inclusion. Histology codes were not assessed; therefore, we refer to patients as having lung cancer, but treatment with topotecan implies that included patients had small cell lung cancer. This is based on clinical guidelines indicating that topotecan is appropriate for small cell lung cancer and not non–small cell lung cancer.[37,38] Patients were required to be continuously enrolled in a participating health plan with both medical and drug coverage for at least 183 days before the index date, allowing coverage gaps up to 45 days (Figure 1).

Patients were excluded if they had any claim within 183 days before the index date for care in a skilled nursing facility or hospice care, a second cancer diagnosis identified by ICD-9 codes 140.x–195.x or 200.x–209.x, excluding the aforementioned breast cancer and lung cancer codes for study inclusion. Other exclusion criteria were claims for conditions associated with neutropenia, such as bone marrow or stem cell transplant (CPT codes 38230, 38231, 38240, 38241, 38242), a diagnosis of HIV/AIDS (ICD-9-CM codes 042–044, 795.1, V08), or other non–oncology-related neutropenia (ICD-9-CM code 288.0).

Exposures

Chemotherapy regimens were limited to those associated with high FN risk and defined by the combinations of drug claims and/or dates of service for medication administration observed in each cycle (Table 1). The index date was defined as the first identified claim for G-CSF during the study period (Figure 1). Patients were required to have at least one outpatient claim for G-CSF on or before 2 days after the end of chemotherapy administration during the first cycle of treatment. The analysis was limited to G-CSF administered within the first 2 days after receipt of chemotherapy. Claims observed 3 to 14 days after chemotherapy administration were categorized as G-CSF treatment of neutropenia. Breast cancer treatment regimens were 1 day in length, and the lung cancer regimen was 5 days in length. Thus, chemotherapy was administered on day 1 for breast cancer and on day 1 and once daily for the following 4 days for lung cancer.

G-CSF exposures were classified as filgrastim, pegfilgrastim, and tbo-filgrastim. Pegfilgrastim administration was defined as a single injection. Filgrastim and
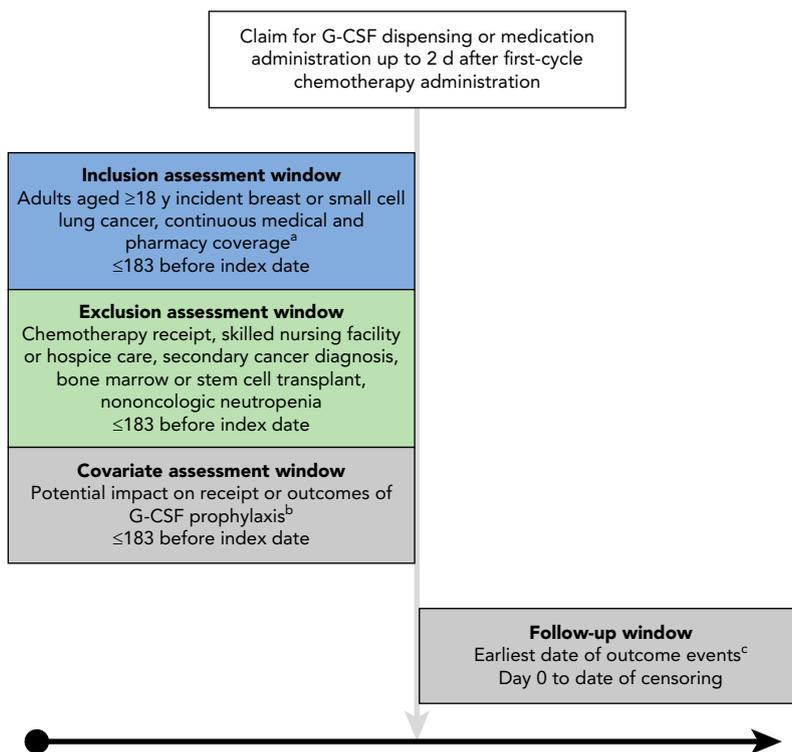
Claim for G-CSF dispensing or medication administration up to 2 d after first-cycle chemotherapy administration

Inclusion assessment window
Adults aged ≥18 y incident breast or small cell lung cancer, continuous medical and pharmacy coverage[a]
≤183 before index date

Exclusion assessment window
Chemotherapy receipt, skilled nursing facility or hospice care, secondary cancer diagnosis, bone marrow or stem cell transplant, nononcologic neutropenia
≤183 before index date

Covariate assessment window
Potential impact on receipt or outcomes of G-CSF prophylaxis[b]
≤183 before index date

Follow-up window
Earliest date of outcome events[c]
Day 0 to date of censoring

Figure 1. Exposure-based cohort entry after application of exclusion criteria.
Abbreviation: G-CSF, granulocyte colony-stimulating factor.
[a]As many as 45-day gaps in medical or pharmacy enrollment were allowed.
[b]See supplemental eAppendix 3.
[c]Death, end of enrollment, outcome adverse event (inpatient diagnosis febrile neutropenia, severe neutropenia, or combined safety outcome), treatment with next chemotherapy cycle, or new chemotherapy regimen.

tbo-filgrastim exposures were stratified into 2 groups: <6 injections and ≥6 injections. National Drug Codes and HCPCS procedure codes were used to identify G-CSF exposures for analysis and are available in supplemental eAppendix 1 (available with this article at JNCCN.org).

Follow-up began the day the first G-CSF exposure of interest was administered or dispensed and continued until the first occurrence of (1) health plan disenrollment, (2) the study end date, (3) the end of the 21-day exposure episode, or (4) a study outcome. For each eligible patient,

only the first incident exposure episode during the study period was considered.

Outcomes
In order to characterize the outcome and identify the most appropriate definition of FN for future studies, the primary outcome was identification of inpatient FN diagnoses during the first treatment cycle using ICD-9-CM codes in any position based on the following definitions: (1) narrow: a diagnosis of neutropenia (288.0x) and fever (780.6) on the

Table 1. High-FN-Risk Chemotherapy Regimens for Breast and Small Cell Lung Cancers

Cancer Therapy	Regimen
Breast: docetaxel + trastuzumab (metastatic or relapsed)	Docetaxel, 80–100 mg/m^2 IV day 1, cycled every 21 d or 35 mg/m^2 IV days 1, 8, and 15 (weekly) Trastuzumab, 8 mg/kg IV day 1, followed by 6 mg/kg IV every 21 d or 4 mg/kg IV day 1, followed by 2 mg/kg IV weekly
Breast: dose-dense AC followed by T (adjuvant)	Doxorubicin, 60 mg/m^2 IV day 1, cycled every 14 d for 4 cycles Cyclophosphamide, 600 mg/m^2 IV day 1, cycled every 14 d for 4 cycles Followed by paclitaxel, 175 mg/m^2 by 3-h IV infusion day 1, cycled every 14 d for 4 cycles
Breast: TAC (adjuvant)	Docetaxel, 75 mg/m^2 IV day 1, cycled every 21 d for 6 cycles Doxorubicin, 50 mg/m^2 IV day 1, cycled every 21 d for 6 cycles Cyclophosphamide, 500 mg/m^2 IV day 1, cycled every 21 d for 6 cycles
Small cell lung cancer	Oral topotecan, 2.3 mg/m^2/d or IV topotecan, 1.5 mg/m^2/d on days 1–5 every 3 wk

Chemotherapy regimens are based on NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer, Version 1.2015, and NCCN Guidelines for Small Cell Lung Cancer, Version 2.2014; to view the most recent versions, visit NCCN.org.
Abbreviations: A, doxorubicin; C, cyclophosphamide; FN, febrile neutropenia; IV, intravenous; T, taxane.

same day; (2) intermediate: neutropenia (288.0x) only; and (3) broad: neutropenia (288.0x) or fever (780.6) or infection (001.x–139.x).[30,31,39,40]

Secondary outcomes included the incidence of severe neutropenia (ANC $<0.5/mm^3$) and a safety event (anaphylaxis, glomerulonephritis, capillary leak syndrome, hyperleukocytosis, and splenic rupture incidence). All adverse events were defined using ICD-9-CM codes, CPT codes, and Logical Observation Identifiers Names and Codes (supplemental eAppendix 2). Outcome events were assessed through the earliest of death, end of health plan enrollment, a safety outcome event, treatment with the next chemotherapy cycle, or a switch to another chemotherapy treatment regimen.

Covariates

We identified baseline covariates in the 183 days before the index date potentially associated with G-CSF receipt or study outcomes (supplemental eAppendix 3). Standard demographic covariates include age (grouped as 18–49, 50–64, 65–79, and ≥80 years), sex, and calendar year. A combined comorbidity score derived from the Charlson and Elixhauser measures was calculated for each study subject.[41]

Analyses

A distributed data approach utilizing the SCDM Cohort Identification and Descriptive Analysis tool (version 5.0.3) was used for this analysis.[42,43] Only aggregate data were shared outside of each data partner site for analysis and reporting. To calculate the mean of specific data (eg, age of study subjects), ad hoc programs were distributed to evaluate individual-level data, with final aggregated results provided. The frequencies of new G-CSF users in the breast and lung cancer cohorts were assessed. The distribution and mean number of days of G-CSF use and the frequency of ANC data were estimated. The prevalence of each exposure category and incidence of each outcome (FN hospitalizations, severe neutropenia [ANC $<0.5/mm^3$], and anaphylaxis) were stratified by age group, sex, and year and reported separately for breast and lung cancers. G-CSF exposures ≥3 days after the end of chemotherapy administration were reported separately for each diagnosis. Covariate frequencies and percentages (or means and standard deviations) were estimated in each cohort.

Frequencies of FN events were reported according to the primary and varying definitions (Table 2), crude incidences, and associated 95% confidence intervals. Frequencies of adverse events in G-CSF users in each cancer cohort were also reported. Incidences were defined as the ratio of first adverse events divided by the total chemotherapy cycles during the study period and estimated as overall and stratified by the predefined age groups, year

Table 2. Frequency of FN Hospitalizations and AEs in Patients Who Received G-CSF Prophylaxis for First-Line Therapy of Breast or Lung Cancer[a]

	Frequency	(95% CI)
FN events		
Broad definition	2.99%	(2.5–3.57)
Intermediate definition	1.91%	(1.53–2.38)
Narrow definition	<0.5%	NC
Anaphylaxis	1.15%	(0.86–1.54)
Hyperleukocytosis	2.28%	(1.86–2.79)
Combined outcome of rare AEs: glomerulonephritis, capillary leak syndrome, splenic rupture	<0.5%	NC

Abbreviations: AE, adverse event; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; NC, not calculated.
[a]Breast or lung cancer diagnosis occurred before index G-CSF exposure.

of G-CSF initiation, and sex. Per the Sentinel System's standard operating procedures, all data elements in the SCDM undergo a rigorous quality assurance and curation process.[44,45]

Results

Baseline Characteristics

We identified 38,721 unique patients with breast cancer and 19,004 unique patients with lung cancer who received at least one dose of G-CSF (Table 3). The average ages of subjects with breast and lung cancer were 55.1 and 63.7 years, respectively. Most (83.1%) patients with breast cancer were aged <65 years, and nearly all (98.9%) were women, whereas 44.2% with lung cancer were aged 50 to 64 years, and approximately half (51%) were women. The average combined comorbidity score was lower in the breast cancer cohort (mean [SD], 4.2 [2.9]). Baseline covariates potentially affecting G-CSF receipt or outcomes associated with G-CSF therapy are available in supplemental eAppendix 3. Nearly half of all patients had a history of metastatic disease (Table 3). Of those, 9.3% with breast cancer and 22.4% with lung cancer had metastases that spread to the bone. Both groups had previous receipt of a bone-modifying agent such as zoledronic acid, which could indicate confounding if bone pain was included as a secondary outcome.

Of those who received G-CSF, 4,896 met our criteria for analysis (4,745 with breast cancer and 151 with lung cancer) (Table 4). Most (99%) patients with breast cancer and more than half (57%) with lung cancer were women, and nearly all (92%) exposures were due to pegfilgrastim. Filgrastim administration was low across users, and, because of small sample sizes, administration stratified by <6 days and ≥6 days after chemotherapy administration is not presented. The primary outcome, rate of

Table 3. Characteristics of All Patients With Breast or Lung Cancer Who Received G-CSF Prophylaxis

Characteristic	Breast Cancer n (%)	Lung Cancer n (%)
Unique patients, n	38,721	19,004
Age, mean [SD], y	55.1 [10.9]	63.7 [10.9]
18–49	12,767 (33.0)	1,956 (10.3)
50–64	19,381 (50.1)	8,408 (44.2)
65–79	5,988 (15.5)	7,385 (38.9)
≥80	585 (1.5)	1,255 (6.6)
Female sex	38,307 (98.9)	9,690 (51)
Combined comorbidity score, mean [SD]	4.2 [2.9]	6.4 [3.0]
Baseline covariates (183 d before index exposure)		
Anaphylaxis	1,344 (3.5)	1,031 (5.4)
Anemia	6,945 (17.9)	7,234 (38.1)
Arthritis	1,294 (3.3)	873 (4.6)
Bone marrow/SCT[a]	<10 (<0.1)	<10 (<0.1)
Bone pain	6,141 (15.9)	3,659 (19.3)
Cancer-related radiation	3,065 (7.9)	6,699 (35.3)
Capillary leak syndrome	53 (0.1)	20 (0.1)
Congestive heart failure	1,057 (2.7)	1,742 (9.2)
COPD	5,096 (13.2)	10,149 (53.4)
Glomerulonephritis	23 (0.1)	24 (0.1)
HIV/AIDS[a]	40 (0.1)	65 (0.3)
Hyperleukocytosis	742 (1.9)	1,284 (6.8)
Kidney disorder	339 (0.9)	270 (1.4)
Latex allergy	188 (0.5)	44 (0.2)
Severe liver impairment	836 (2.2)	717 (3.8)
Lumpectomy/Mastectomy	22,561 (58.3)	368 (1.9)
Metastatic cancer	18,450 (47.6)	8,637 (45.4)
Other cancer diagnosis[a]	7,344 (19)	9,683 (51)
Neutropenia	4,949 (12.8)	3,217 (16.9)
Peptic ulcer disease	225 (0.6)	376 (2.0)
Poor nutritional status	3,307 (8.5)	2,286 (12.0)
Splenic rupture	11 (<0.1)	12 (0.1)
Recent surgery/wounds	25,131 (64.9)	4,506 (23.7)
Thyroid disorder	7,096 (18.3)	3,113 (16.4)
Antibiotics	21,231 (54.8)	11,647 (61.3)
Endocrine drug products	5,627 (14.5)	1,523 (8.0)
BMAs (eg, zoledronic acid, bisphosphonates)	1,342 (3.5)	666 (3.5)
Other chemotherapy (breast/lung)	1,279 (3.3)	8,040 (42.3)
Other chemotherapy (not breast/not lung)	1,486 (3.8)	1,678 (8.8)

Based on FDA Sentinel Initiative reporting tool functionality, any values <10 were rounded to 10, and totals are reported as approximate values.
Abbreviations: BMA, bone-modifying agent; COPD, chronic obstructive pulmonary disease; G-CSF, granulocyte colony-stimulating factor; SCT, stem cell transplant.
[a]Patients excluded from study analysis.

Table 4. Characteristics of Patients Who Received G-CSF Prophylaxis for First-Cycle Treatment of Breast or Lung Cancer

Characteristic	Breast Cancer	Lung Cancer	Combined
Demographics			
Unique patients, n	4,745	151	4,896
Mean age, n			
18–49 y	1,676	<10	NC
50–64 y	2,366	70	2,436
65–79 y	675	64	739
≥80 y	28	<10	NC
Female sex, %	99.32	56.95	98.02
G-CSF exposures (total)			
Filgrastim, %	7.17	27.15	7.78
Pegfilgrastim, %	92.52	72.19	91.89
Tbo-filgrastim, %	0.31	0.66	0.33

Breast or lung cancer diagnosis occurred before index G-CSF exposure.
Abbreviations: G-CSF, granulocyte colony-stimulating factor; NC, not calculated due to small cell counts.

hospitalization for a diagnosis of FN, varied greatly across the neutropenia definitions previously provided. Narrow (<0.5%), intermediate (1.91%), and broad (2.99%) definitions are described in Table 2. Secondary outcomes were anaphylaxis (1.15%); hyperleukocytosis (2.28%); and a combined rare event outcome of glomerulonephritis, capillary leak syndrome, and splenic rupture (<0.14%). Laboratory data are not entered into the databases of 2 of the 5 participating research partners. Therefore, ANC <500/mm^3 was identified in <10 patients, and ANC ≥500/mm^3 was identified in only 48 patients (data not shown). Bone pain was attributed to 1% of eligible patients. When FN events were assessed by age, there was wide variation between definitions, with too few events identified for the narrow definition or for those aged ≥80 years (data not shown).

Discussion

We characterize and describe real-world use of G-CSFs for FN prophylaxis in patients with breast or lung cancer in the BBCIC DRN, including availability of key data elements and identification of potential confounders. This analysis will inform future observational comparative safety and effectiveness analyses of G-CSF biosimilar use. We assessed the ability to measure the incidence of hospitalizations for FN, ANC <0.5/mm^3, depth of ANC nadir, time to ANC recovery, and changes from baseline ANC. Specifically, we analyzed G-CSF administration and availability of ANC measures across sites. The breast cancer cohort was expectedly younger and mostly women; those with lung cancer were older, and half of them were women. Incident FN counts using broad,

intermediate, or narrow definitions were consistent with those in previous reports.[30,31]

Schwartzberg et al[30] evaluated FN rates in 3,297 patients with solid tumors. Roughly one-third had previous G-CSF use. Reference G-CSF was compared with the biosimilar, filgrastim-sndz. FN defined as fever/neutropenia, neutropenia/infection, or neutropenia/infection/ fever occurred in 0.9%, 1.7%, and 0.3%, respectively. Administrative codes seemed to be similar despite our population being slightly younger (55.1 and 63.7 years for patients with breast and lung cancer, respectively vs 64.7 years) among those receiving reference filgrastim. Baseline comorbidity scores were similar at 5.8 versus 4.2 and 6.4 in breast and lung cancer, respectively, in our study, and safety outcomes were not evaluated.

Douglas et al[31] compared filgrastim with filgrastim-sndz in 88 patients with any G-CSF use and Medicare Advantage coverage from October 1, 2015, to September 30, 2016. FN incidence associated with the reference G-CSF was based on broad (neutropenia or infection, 3.4%) and narrow (neutropenia and infection, 1.1%) definitions. The population was older (mean age, 71.3 years) and 55.7% were women. Safety was measured using a combined composite score for splenic rupture, acute respiratory syndrome, serous allergic reaction, capillary leak syndrome, thrombocytopenia, leukocytosis, cutaneous vasculitis, and bone and muscle ache, which cannot be compared with our combined safety score due to included variables. Combined neutropenia and infection codes were similar between studies: 1.7% for Schwartzberg et al[30] and 1.1% for Douglas et al,[31] and fever and neutropenia occurred in 1% in our study and 0.9% in the study by Schwartzberg et al.[30]

The unavailability of ANC data is consistent with other analyses using administrative data.[30,31] This does not preclude our ability to identify and report FN events. However, ANC data could provide insight into the degree of severe neutropenia. Future studies may include new partners capturing ANC data. As expected, anaphylaxis, bone pain, hyperleukocytosis, and combined rare event rates were low and consistent with other findings.[32] We identified 1% of patients with bone pain; however, this is low based on clinical studies reporting rates of 19% and 24.7%.[32,46] Because a specific ICD-9 code is lacking, bone pain is likely underreported or attributed to other codes. Furthermore, patients using bone-modifying agents at baseline confound our ability to attribute bone pain to G-CSFs, and the inclusion of bone pain as a safety event is limited. Similarly, the low incidence of hyperleukocytosis associated with our findings is likely due to the limited laboratory data available in our database.

This study has a number of strengths, including readily available, standardized, curated data across several large health insurance plans and integrated health systems representing a large, diverse population. The retrospective study design limits our analysis to exposures, covariates, and outcomes captured in claims data when a patient uses medical and pharmacy benefits. The occurrence of FN events occurring outside of health systems contributing data could be unreported; however, the data are administrative claims filed, regardless of the site of care, and we expect the number of missing claims to be low.[39,47,48] It is possible that FN was not the diagnosis assigned to the hospitalization and was therefore not captured in the administrative data. Furthermore, this analysis was designed using NCCN Guidelines that are no longer the current guidelines available for clinical practice, and outcomes may vary with updated guidelines. Because administrative data do not include dose and administration details, we cannot guarantee that patients received the exact chemotherapy regimen listed in the guidelines; however, we are certain the patients received the drug(s) listed in each regimen.

This analysis was limited to chemotherapy regimens associated with high FN risk to eliminate the ambiguity of available administrative claims for the use of G-CSF prophylaxis related to chemotherapy associated with intermediate FN risk and therefore the result of clinical decision-making. The inclusion of intermediate FN risk is of great interest and concern but is beyond the scope of this initial analysis and will be a focus of future work involving biosimilars. The administration of intermediate-risk chemotherapy and G-CSF prophylaxis extends beyond chronologic age and the presence of comorbidities to include individual patient performance status.[49–52] The use of administrative data is limited by the lack of clinical information such as the degree of liver dysfunction or neutropenia or performance status. Because physiologic age rather than chronologic age better predicts clinical status, this is likely the reason for the importance of performance status when determining chemotherapy administration. Another key factor that potentially plays a role in the determination of performance status is frailty. Frailty is known to be predictive of patient toxicity during chemotherapy, regardless of chronologic age.[53] It is also not characterized or quantified by existing administrative codes. Studies to identify and validate measures of frailty and performance status using administrative data are evolving.[54–57] An association between claims-based frailty indices and clinical outcomes has been demonstrated .[58] This work using Medicare claims data has recently expanded into other healthcare databases; however, there remains a need for validation in administrative data from large insurers. Notably, the choice of claims-based measures can influence the identification of frailty.[59] Thus, critical evaluation of these measures in new data sources is warranted before it can be readily used for research studies. Use of these measures is of great interest, and we anticipate incorporating them in

future work in this area; however, the magnitude of efforts to assess and validate these measures in a new data source extends beyond the scope of the present work. As with all observational studies, the analysis was limited in its ability to control for all sources of potential bias. Exposures, inclusions, and covariates may have been misclassified due to imperfect algorithms used to identify them. However, based on the comparable event rates determined by this analysis, we believe that if misclassification occurred, it was at a very low rate.

Conclusions

This analysis represents one of the first large-scale assessments of G-CSF use across a diverse population of patients receiving chemotherapy for breast or lung cancer with high neutropenia risk, showing data utility and ability to identify outcomes consistent with previous smaller analyses. It also provides valuable information that will contribute to future observational comparative safety and effectiveness studies of G-CSFs and their biosimilars.

Acknowledgments

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BBCIC Research Network Analysis of First-Cycle Prophylactic G-CSF Use in Patients Treated With High–Neutropenia Risk Chemotherapy

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eAppendix 1. List of NDCs and HCPCS Codes Used for G-CSF Exposures in Patients With Breast or Lung Cancer		
Medication	**Code**	**Code Type**
Filgrastim	54569482400	NDC
Filgrastim	54868252200	NDC
Filgrastim	54868252201	NDC
Filgrastim	54868305000	NDC
Filgrastim	54868502000	NDC
Filgrastim	55513020901	NDC
Filgrastim	55513020910	NDC
Filgrastim	55513020991	NDC
Filgrastim	55513034701	NDC
Filgrastim	55513034710	NDC
Filgrastim	55513034801	NDC
Filgrastim	55513034810	NDC
Filgrastim	55513053001	NDC
Filgrastim	55513053010	NDC
Filgrastim	55513054601	NDC
Filgrastim	55513054610	NDC
Filgrastim	55513092401	NDC
Filgrastim	55513092410	NDC
Filgrastim	55513092491	NDC
Filgrastim	J1440	HCPCS
Filgrastim	J1441	HCPCS
Filgrastim	J1442	HCPCS
Filgrastim	Q5101	HCPCS
Pegfilgrastim	54868522900	NDC
Pegfilgrastim	55513019001	NDC
Pegfilgrastim	55513019201	NDC
Pegfilgrastim	J2505	HCPCS
Tbo-filgrastim	61314030401	NDC
Tbo-filgrastim	61314030410	NDC
Tbo-filgrastim	61314031201	NDC
Tbo-filgrastim	61314031210	NDC
Tbo-filgrastim	63459091011	NDC
Tbo-filgrastim	63459091015	NDC
Tbo-filgrastim	63459091017	NDC
Tbo-filgrastim	63459091036	NDC
Tbo-filgrastim	63459091211	NDC
Tbo-filgrastim	63459091212	NDC
Tbo-filgrastim	63459091215	NDC
Tbo-filgrastim	63459091217	NDC
Tbo-filgrastim	63459091236	NDC
Tbo-filgrastim	J1446	HCPCS
Tbo-filgrastim	J1447	HCPCS

Abbreviations: G-CSF, granulocyte colony-stimulating factor; NDC, National Drug Code.

eAppendix 2. ICD-9-CM, CPT, and LOINC Codes Used to Identify Secondary Outcomes of G-CSF Use in Breast or Lung Cancer			
Outcome	ICD-9-CM Code	CPT Code	LOINC
Severe neutropenia defined by absolute neutrophil count			L0032013010104, L0032013010110, L0032013010204, L0032013010210, L0032013010304, L0032013010310, L0032013010404, L0032013010410, L0032013010504, L0032013010510, L0032013020104, L0032013020110, L0032013020204, L0032013020210, L0032013020304, L0032013020310, L0032013020404, L0032013020410, L0032013020504, L0032013020510, L0032013070104, L0032013070110, L0032013070204, L0032013070210, L0032013070304, L0032013070310, L0032013070404, L0032013070410, L0032013070504, L0032013070510
Anaphylaxis	995.2, 995.20, 995.27, 995.29, 995.3, 995.6×, 995.7, 995.0, 999.49		
Bone pain	730.×, 733.0×, 733.1×–733.9×, E934.×, E947.×		
Hyperleukocytosis	288.3, 288.4, 288.6, 288.8, 288.9		
Combined: glomerulonephritis, capillary leak syndrome, splenic rupture	580.×, 582.×, 448.9, 865.0, 865.1, 865.10, 865.12, 865.13, 865.14, 865.19	38100, 38101, 38102, 38815	

Abbreviation: G-CSF, granulocyte colony-stimulating factor; LOINC, Logical Observation Identifiers Names and Codes.

eAppendix 3. Covariates With Potential Impact on Receipt or Outcomes Associated With G-CSF Prophylaxis in Breast or Lung Cancer	
Combined comorbidity score	Metastatic liver cancer
Anaphylaxis	Metastatic disease
Anemia	Neutropenia
Arthritis	Peptic ulcer disease
Bone pain	Poor nutritional status
Bone marrow/stem cell transplant	Second cancer diagnosis
Cancer-related radiation	Splenic rupture
Capillary leak syndrome	Recent surgery/wounds
Congestive heart failure	Thyroid disorder
Chronic obstructive pulmonary disease	Chemotherapy regimens of interest[a]
Glomerulonephritis	Antibiotics
HIV/AIDS	Endocrine drug products
Hyperleukocytosis	Drug therapy for bone metastases (eg, bisphosphonates, denosumab)
Kidney disorder	Breast chemotherapy (regimen of interest) [breast cohort only]
Latex allergy	Other breast chemotherapy [breast cohort only]
Severe liver impairment	Other chemotherapy (not breast) [breast cohort only]
Lumpectomy/Mastectomy	Small cell lung cancer chemotherapy (regimen of interest) [small cell lung cancer cohort only]
Metastatic bone cancer	Other small cell lung chemotherapy [small cell lung cancer cohort only]
Metastatic brain cancer	Other chemotherapy (not lung) [small cell lung cancer cohort only]

Abbreviation: G-CSF, granulocyte colony-stimulating factor.
[a]Reported in Renner P, Milazzo S, Liu JP, et al. Primary prophylactic colony-stimulating factors for the prevention of chemotherapy-induced febrile neutropenia in breast cancer patients. Cochrane Database Syst Rev 2012;10:CD007913.