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ORIGINAL ARTICLE

Risk of chemotherapy-induced febrile neutropenia with early discontinuation of pegfilgrastim prophylaxis in US clinical practice

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Abstract
Purpose Accumulating evidence suggests that not all cancer chemotherapy patients who receive first-cycle pegfilgrastim prophylaxis continue to receive it in subsequent cycles and that these patients may be subsequently at higher risk of febrile neutropenia (FN). Additional evidence from US clinical practice is warranted.
Methods Data from two US private healthcare claims repositories were employed. The source population comprised adults who received "intermediate-risk" or "high-risk" chemotherapy regimens for solid cancers or non-Hodgkin's lymphoma and first-cycle pegfilgrastim prophylaxis. From the source population, all patients who did not receive second-cycle pegfilgrastim prophylaxis ("comparison patients") were matched (1:1) to those who received it ("pegfilgrastim patients") based on cancer, regimen, and propensity score. Odds ratios (OR) for FN—broad and narrow definitions—during the second chemotherapy cycle were estimated for comparison patients versus pegfilgrastim patients using generalized estimating equations.
Results A total of 2245 comparison patients (5.3 % of source population) were matched to pegfilgrastim patients; cohorts were well-balanced on baseline characteristics. Second-cycle FN incidence proportions for comparison and pegfilgrastim patients were 3.8 versus 2.2 % based on broad definition and 2.6 versus 0.8 % based on narrow definition; corresponding OR were 1.7 (95 % CI 1.2–2.5, p=0.002) and 3.5 (95 % CI 2.0–6.0, p<0.001). Results were similar within cancer/regimen-subgroups and were robust when using alternative methods for confounding adjustment.
Conclusions In this retrospective evaluation of cancer chemotherapy patients who received first-cycle pegfilgrastim prophylaxis in US clinical practice, a clinically relevant minority did not receive second-cycle prophylaxis. Second-cycle FN odds among this subset were significantly higher than they were among those who continued prophylaxis.

Keywords Febrile neutropenia · Pegfilgrastim · Neulasta · Granulocyte colony-stimulating factor

Introduction

Neutropenia is a common side effect of myelosuppressive chemotherapy that increases the risk of infection. When neutropenic patients develop fever (i.e., febrile neutropenia [FN]), the cardinal signs of an opportunistic infection typically necessitate hospitalization for urgent evaluation, ongoing monitoring, and administration of intravenous (IV) antibiotics [1, 2]. FN, as well as severe or prolonged neutropenia, can lead to dose delays, dose reductions, and/or chemotherapy discontinuations, interfering with the delivery of optimal treatment and possibly adversely affecting patient outcomes [1, 3–7].

Clinical practice guidelines recommend prophylaxis with a colony-stimulating factor (CSF) when FN risk is high (>20 %) based on either chemotherapy regimen risk alone or a combination of regimen risk and patient risk factors [8]. Among the CSFs that are commercially available in the USA, pegfilgrastim is by far the agent most widely used in clinical practice as, unlike others agents, it requires only a single dose

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in each chemotherapy cycle [9–12]. There is an abundance of evidence from clinical trials that primary prophylaxis with pegfilgrastim (i.e., planned administration in the first and all subsequent chemotherapy cycles) reduces FN risk during the chemotherapy course. Accumulating evidence from clinical practice suggests, however, that not all cancer chemotherapy patients who receive pegfilgrastim prophylaxis in the first cycle (when FN risk is highest) continue to receive it in subsequent cycles (when FN risk in any of these cycles is typically lower than first-cycle FN risk) [9, 13–20].

The impact of abbreviated pegfilgrastim prophylaxis (i.e., early discontinuation of pegfilgrastim prophylaxis) on FN risk was recently evaluated in a randomized open-label multicenter trial of breast cancer patients with projected FN risk >20 % receiving tri-weekly polychemotherapy in the Netherlands [21]. Eligible patients were randomly assigned to either primary pegfilgrastim prophylaxis throughout all chemotherapy cycles ("standard arm") or to primary prophylaxis during the first two cycles only ("experimental arm"). Notably, after 167 subjects were enrolled (out of the 230 planned), the random assignment of subjects was prematurely stopped based on the recommendation of the Independent Data Monitoring Committee because of an unexpectedly high FN rate during the course in the experimental arm (36 vs. 10 % in the standard arm; adjusted odds ratio=5.8 [95 % CI 2.5–13.8]). FN risk in the experimental arm was highest (24 %) in the first cycle without prophylaxis (i.e., the third cycle of chemotherapy). While available literature suggests that the use of abbreviated CSF prophylaxis schedules—especially those limiting CSF to the first cycle of chemotherapy—is gaining popularity in clinical practice due to cost concerns, its use, and impact in this setting has not been formally and thoroughly examined [13, 14, 22]. We thus undertook a study to provide real-world evidence on the use and potential implications of abbreviated pegfilgrastim prophylaxis schedules in US clinical practice.

Methods

Study design

A retrospective cohort design and data from two large US healthcare claims repositories were employed. To minimize healthy survivor bias and other (e.g., selection) biases that would likely occur in such an observational study if it were designed to mimic the above-described trial by Aarts and colleagues, the evaluation was limited to receipt or no receipt of pegfilgrastim prophylaxis during the second chemotherapy cycle among a cohort of patients who all received first-cycle pegfilgrastim prophylaxis. A detailed description of study design and study methods may be found in the online supplement (Online Resource A).

Data source

Data from the two US healthcare claims repositories spanned January 1, 2006 through December 31, 2013, and were pooled for analyses. The two study repositories, the Truven Health Analytics MarketScan® Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits Databases ("MarketScan Database"), and the IMS LifeLink™ PharMetrics Plus Health Plan Claims Database ("LifeLink Database"), comprise medical (i.e., facility and professional service) and outpatient pharmacy claims from a large number of participating private US health plans. Formal approval for this study from an Institutional Review Board (IRB) was not required because the design was retrospective in nature, and subjects in the study databases could not be identified—directly or indirectly—through variables linked to their claims and/or enrollment records. Use of the study databases for health services research is fully compliant with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule and federal guidance on Public Welfare and the Protection of Human Subjects [23].

Source and study populations

The source population comprised all patients aged ≥18 years who, from July 2006 to June 2013, received a course of myelosuppressive chemotherapy of at least two cycles duration for a single primary solid tumor or non-Hodgkin's lymphoma (NHL). For each patient in the source population, the first observed course of chemotherapy and the first two cycles of chemotherapy within that course were characterized. Only patients who received first-cycle pegfilgrastim prophylaxis had continuous health benefits for ≥6 months prior to chemotherapy, did not have evidence of reactive CSF use or FN in cycle 1, did not receive prophylaxis with other CSF agents (filgrastim, sargramostim) or antimicrobials in either cycle 1 or cycle 2, and met all other selection criteria (as described in the online supplement) that were retained in the source population. Prophylactic use of pegfilgrastim was defined as receipt 1–3 days following completion of myelosuppressive chemotherapy administration in a given chemotherapy cycle, which is consistent with the indicated administration schedule and National Comprehensive Cancer Network (NCCN) guidelines [8, 9]. Use of pegfilgrastim was identified based on medical claims with corresponding Healthcare Common Procedure Coding System (HCPCS) Level II codes (C9119, S0135, J2505). From the source population, all patients who did not receive pegfilgrastim prophylaxis in their second cycle of chemotherapy ("comparison patients") were matched to those who received it ("pegfilgrastim patients").

Matching was implemented for each patient in the source population who did not receive second-cycle pegfilgrastim prophylaxis by first identifying all "candidate" patients who

received second-cycle pegfilgrastim prophylaxis and had the same cancer type and chemotherapy regimen. From all such candidates for each patient, the candidate with the closest propensity score to the comparison patient was selected as the matched patient using a fixed 1:1 ratio and nearest-neighbor approach [24]. Propensity scores represent the conditional probability of assignment to the exposure group and may be used to control for multiple observed covariates that are associated with exposure and outcome [25, 26]. Propensity scores for receipt of second-cycle pegfilgrastim prophylaxis were estimated using multivariate logistic regression; independent variables included all patient, cancer, and treatment characteristics described below. The study population was limited to patients who received intermediate/high-risk chemotherapy regimens for non-metastatic breast cancer, non-metastatic colorectal cancer, non-metastatic lung cancer, or NHL, and for which the number of patients who discontinued pegfilgrastim prophylaxis in cycle 2 was ≥100 (Table 1).

FN episodes

FN episodes were ascertained beginning 4 days after completion of myelosuppressive chemotherapy administration in the second cycle of chemotherapy and ending on the last day of that cycle, and were identified using a "broad" definition, as follows [27]. FN episodes requiring inpatient care were identified based on hospital admissions with a principal or secondary diagnosis of neutropenia (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] 288.0), or fever (780.6), or infection (codes in Online Resource A). FN episodes requiring outpatient care only were identified based on ambulatory encounters (e.g., those in a physician's office, emergency department, or home) with a diagnosis of neutropenia, or fever, or infection and—on the same date—a HCPCS Level I (i.e., Current Procedural Terminology [CPT]) code for IV administration of antimicrobial therapy. Such encounters that preceded or followed an FN-related hospitalization during the same cycle of chemotherapy were not considered as a separate outpatient episode (i.e., they were classified as part of the episode of FN requiring inpatient care). An alternative ("narrow") definition for FN comprising inpatient encounters with a principal or secondary diagnosis of neutropenia, and outpatient encounters with a diagnosis of neutropenia and evidence of IV antimicrobial therapy, was also evaluated [27].

Patient, cancer, and treatment characteristics

Patient characteristics included many of those listed by the American Society of Clinical Oncology (ASCO) and NCCN as important risk factors for FN and thus those that could confound the estimated relationship between prophylaxis discontinuation and FN risk. Patient characteristics were evaluated based on evidence during the period beginning up to 12 months prior to the date of chemotherapy initiation and ending 3 days after completion of chemotherapy in the second cycle (unless otherwise noted in the online supplement).

Characteristics included the following: age; sex; presence of selected chronic comorbidities (cardiovascular disease, diabetes, liver disease, lung disease, renal disease, osteoarthritis, rheumatoid disease, thyroid disorder); body weight/nutritional status (obesity, underweight, malnutrition); proxies for health status (hospice/skilled nursing facility [SNF] care) and physical function (use of hospital bed, supplemental oxygen, walking aid, wheelchair); use of immunosuppressive therapy; history of blood disorders (anemia, neutropenia, other), infection, recent surgery (i.e., ≤90 days prechemotherapy), hospitalization (all-cause and FN-related, respectively), chemotherapy, and radiation therapy; total healthcare expenditures in the baseline period; presence of metastatic disease; and calendar year of chemotherapy initiation.

Table 1 Intermediate/high-risk regimens for non-metastatic breast cancer, non-metastatic colorectal cancer, non-metastatic lung cancer, or NHL

Primary	Chemotherapy regimen	Standard dosing periodicity	Exclusion criteria for first-cycle duration
Non-metastatic breast cancer	TC	Q3W	Q4W
	TAC	Q3W	Q4W
	TCH	Q3W	Q4W
	AC and AC-T (Dose Dense)	Q2W	Q3W/Q4W
Non-metastatic colorectal cancer	FOLFOX	Q2W	Q3W/Q4W
Non-Hodgkin's lymphoma	CHOP	Q2W/Q3W	Q4W
	CHOP-R	Q2W/Q3W	Q4W
Non-metastatic lung cancer	CAR+PAC	Q3W	Q4W

TC docetaxel+cyclophosphamide, *TAC* docetaxel+doxorubicin+cyclophosphamide, *TCH* docetaxel+carboplatin+trastuzumab, *AC and AC-T* doxorubicn+cyclophosphamide, with or without subsequent docetaxel or paclitaxel, *FOLFOX* folinic acid+fluorouracil+oxaliplatin, *CHOP* cyclophosphamide+doxorubicin+vincristine+prednisone with rituximab (R), CAR+PAC carboplatin+paclitaxel, *PEG* pegfilgrastim, *Q2W* once every 2 weeks, *Q3W* once every 3 weeks, *Q4W* once every 4 weeks

Statistical analyses

The adequacy of the matching procedure in terms of patients' baseline characteristics was evaluated using standardized differences; a value <0.1 was assumed to indicate a negligible difference in the characteristic between comparison patients and pegfilgrastim patients [28, 29]. Comparisons of second-cycle FN odds between comparison patients and pegfilgrastim patients were evaluated on an overall basis and within cancer- and regimen-specific subgroups using generalized estimating equation (GEE) regression models; a binomial distribution and logistic link function were specified for all GEE models, and the models were fitted using an exchangeable correlation structure. GEE models were used to account for the matched-pairs design; additional covariates were not included in the models (since groups were well-balanced on their baseline characteristics).

All statistical tests were two-sided and were performed at a significance level of α=0.05. Assuming an approximate 50 % increase in second-cycle FN risk among patients not receiving pegfilgrastim prophylaxis in that cycle (6.4 vs. 4.2 % for those receiving pegfilgrastim prophylaxis) and assuming further that the minimum sample size for each group would be at least 2000 (4000 in total), we calculated that the beta (β) for this evaluation would be <20 % (two-sided α=0.05) and thus the study should have adequate power (>80 %) to evaluate the primary objective [13].

The sensitivity of study results to alternative methods for confounding adjustment (i.e., using all patients qualifying for inclusion in the source population and multivariate regression) and alternative methods for propensity-score matching (i.e., 1:3 ratio and sequential) were evaluated. In multivariate regression analyses, all patients in the source population with a qualifying cancer-regimen combination were included, and the second-cycle FN odds ratio for comparison patients versus pegfilgrastim patients was estimated using a logistic model including all potential confounders as independent variables.

Results

A total of 68,442 adult patients underwent a course of myelosuppressive chemotherapy of at least two cycle duration for a single primary solid tumor or NHL from July 2006 to June 2013 and were administered first-cycle pegfilgrastim prophylaxis; 42,314 (62 %) received one of the intermediate/high-risk regimens of interest for one of the cancer types of interest and met all other criteria for inclusion in the source population. Of these patients, 2245 (5.3 %) were not administered second-cycle pegfilgrastim prophylaxis ("comparison patients") and were matched to those who did ("pegfilgrastim patients"). A description of the numbers of patients qualifying for inclusion in the source and study populations may be found in the online supplement (Online Resource B).

Among matched patients, 78 % had breast cancer (50 % received docetaxel+cyclophosphamide [TC], 30 % received doxorubicin+cyclophosphamide with or without subsequent docetaxel or paclitaxel [AC/AC-T, dose-dense]), 8 % had colorectal cancer (folinic acid+fluorouracil+oxaliplatin [FOLFOX]), 8 % had NHL (cyclophosphamide+doxorubicin+vincristine+prednisone with rituximab [R-CHOP]), and 6 % had lung cancer (carboplatin+paclitaxel [CAR+PAC]) (Table 2). With one exception, matched comparison and pegfilgrastim patients were well-balanced on their baseline characteristics; only day of pegfilgrastim administration in cycle 1 was somewhat different between groups (next day after chemotherapy administration: 78 vs. 82 %, standard difference=0.1). Characteristics of comparison patients and pegfilgrastim patients within cancer- and regimen-specific subgroups were largely comparable and are set forth in the online supplement.

On an overall basis, second-cycle incidence proportion for FN (broad definition) among comparison patients was 3.8 versus 2.2 % among pegfilgrastim patients; the corresponding odds ratio was 1.7 (95 % CI=1.2–2.5, p value=0.002) (Table 3). Second-cycle incidence proportion for FN based on the narrow definition was 2.6 versus 0.8 %, and the corresponding odds ratio was 3.5 (95 % CI=2.0–6.0; p value< 0.001). Across subgroups defined on the basis of cancer type and chemotherapy regimen, results were generally comparable with a few exceptions.

Second-cycle FN odds ratios for comparison patients versus pegfilgrastim patients, overall and by cancer/regimen combination, that were estimated using multivariate logistic regression are presented in Table 3 and were similar to those from the matched sample analysis. Results from analyses using an alternative approach to matching were also comparable (online supplement).

Discussion

The results of this study, based on a retrospective cohort design and two large US healthcare claims repositories, suggest that an important minority of cancer chemotherapy patients who receive first-cycle pegfilgrastim prophylaxis do not receive second-cycle pegfilgrastim prophylaxis in clinical practice. While our study focused on prophylaxis discontinuation after the first cycle, the cumulative incidence of prophylaxis discontinuation at any time during the chemotherapy course was notably higher: Among the 42,314 patients who received pegfilgrastim prophylaxis in

Table 2 Characteristics of patients who received pegfilgrastim prophylaxis in cycle 1 only and patients who received pegfilgrastim prophylaxis in cycles 1 and 2 (matched and all patients)

	All cancer types				
	Pegfilgrastim in cycle 1 only (n=2245)	Pegfilgrastim in cycles 1 and 2			
		Matched subjects (n=2245)		All subjects (n=40,069)	
		% or mean (SD)	Stand. diff.[a] (vs. PEG in cycle 1 only)	% or mean (SD)	p value (vs. PEG in cycle 1 only)
Patient					
Age (years)					
Mean (SD)	55.2 (10.9)	55.1 (10.7)	0.011	54.6 (10.7)	0.019
Male, %	11.9	12.4	0.015	10.4	0.023
Chronic comorbidities, %					
Liver disease	3.3	3.8	0.027	3.0	0.408
Lung disease	5.1	5.4	0.012	3.6	0.000
Renal disease	2.1	1.8	0.022	1.5	0.014
Osteoarthritis	6.4	6.5	0.004	6.6	0.714
Rheumatoid disease	1.0	1.1	0.004	1.0	0.923
Thyroid disorder	12.1	13.1	0.031	11.5	0.410
Body weight and nutritional status, %					
Obese	4.5	4.0	0.024	4.3	0.677
Underweight	0.1	0.1	0.000	0.0	0.134
Malnutrition	0.4	0.2	0.039	0.5	0.725
Proxies for health status, %					
Hospice care	0.2	0.2	0.000	0.3	0.618
SNF	0.6	0.7	0.011	0.6	0.859
Hospice or SNF	0.8	0.9	0.009	0.8	0.991
Proxies for physical function, %					
Use of hospital bed	0.1	0.3	0.038	0.2	0.427
Use of supplemental oxygen	2.6	2.6	0.003	2.5	0.848
Use of walking aid	1.6	1.5	0.004	1.2	0.176
Use of wheel chair	0.3	0.3	0.008	0.3	0.917
Any of above	4.3	4.4	0.004	3.9	0.346
Use of immunosuppressive drugs, %	4.1	3.4	0.033	4.8	0.114
History of other conditions/events, %					
Anemia	15.2	15.8	0.015	14.9	0.639
Neutropenia	6.2	6.0	0.007	6.6	0.404
Other blood disorders	6.0	4.9	0.049	6.0	0.991
Infection	35.0	34.8	0.004	32.8	0.030
Recent surgery (prior 90 days)	69.1	69.1	0.001	66.7	0.018
History of hospitalization for any reason	38.2	37.2	0.020	34.9	0.001
History of chemotherapy	0.1	0.0	0.042	0.2	0.422
History of radiation therapy	3.8	4.1	0.016	4.2	0.446
Prechemotherapy expenditures ($), mean±SD	34,015 (31, 232)	33,855 (27, 606)	0.005	32,989 (25, 395)	0.066
Cancer, primary site, %					
Female breast	78.3	78.3	–	81.6	<0.0001
Colon/rectum	7.8	7.8	–	3.2	
Lung	6.4	6.4	–	3.4	
Non-Hodgkin's lymphoma	7.5	7.5	–	11.8	

Table 2 (continued)

	All cancer types				
	Pegfilgrastim in cycle 1 only (n=2245)	Pegfilgrastim in cycles 1 and 2			
		Matched subjects (n=2245)		All subjects (n=40,069)	
		% or mean (SD)	Stand. diff.[a] (vs. PEG in cycle 1 only)	% or mean (SD)	p value (vs. PEG in cycle 1 only)
Chemotherapy and supportive care					
Chemotherapy Regimen, %					
Breast cancer					
TC	49.5	49.5	–	30.5	<0.0001
TAC	6.3	6.3	–	11.6	
AC and AC-T (dose dense)	30.4	30.4	–	45.9	
TCH	13.8	13.8	–	12.0	
Colorectal cancer					
FOLFOX	100.0	100.0	–	100.0	–
Non-Hodgkin's lymphoma					
CHOP	91.1	89.9	–	91.3	0.9380
CHOP-R	8.9	10.1	–	100.0	–
Lung cancer					
CAR+PAC	100.0	100.0	–	100.0	–
Number of myelosuppressive drugs, %					
1	0.0	0.0	0.000	0.0	<0.001
2	76.7	76.7	0.000	69.0	<0.001
≥3	23.3	23.3	0.000	31.0	<0.001
Year of chemotherapy, %					
2006–2008	30.4	31.6	0.026	27.9	<0.001
2009–2010	34.3	33.1	0.025	30.8	<0.001
2011–2013	35.3	35.3	0.001	41.3	<0.001
Day of pegfilgrastim prophylaxis (relative to last day of chemotherapy)					
Cycle 1					
Day +1	77.8	81.8	0.100	85.7	<0.001
Day +2	12.3	9.6	0.086	7.3	<0.001
Day +3	9.9	8.6	0.046	7.0	<0.001
Cycle 2					
Day +1	0.0	82.0	–	86.8	–
Day +2	0.0	10.5	–	7.4	–
Day +3	0.0	7.4	–	5.8	–

PEG pegfilgrastim, *SD* standard deviation, *SNF* skilled nursing facility, *TC* docetaxel+cyclophosphamide, *TAC* docetaxel+doxorubicin+cyclophosphamide, *TCH* docetaxel+carboplatin+trastuzumab, *AC and AC-T* doxorubicin+cyclophosphamide, with or without subsequent docetaxel or paclitaxel, *FOLFOX* folinic acid+fluorouracil+oxaliplatin, *CHOP* cyclophosphamide+doxorubicin+vincristine+prednisone with rituximab (R), *CAR+PAC* carboplatin+paclitaxel

[a] Standard difference: values <0.1 assumed to indicate negligible difference

the first cycle, 16 % did not receive it in one or more subsequent cycles during their course. Notwithstanding differences in study designs, study populations, and study methods, this finding is consistent with evidence from the published literature [13, 14].

More notably, the results of this study also suggest that the odds of second-cycle FN are significantly higher among this subset (i.e., those who discontinue prophylaxis in the second cycle) versus patients who continue to receive prophylaxis. These results were found to be robust when using an

Table 3 Odds ratios for febrile neutropenia during second cycle of chemotherapy among patients who received pegfilgrastim prophylaxis in cycle 1 only versus patients who received pegfilgrastim prophylaxis in cycle 1 and cycle 2, overall and within cancer/regimen-specific subgroups[a]

	FN-broad definition[b], inpatient+outpatient			FN-narrow definiton[c], inpatient+outpatient		
	n (%)	OR (95 % CI)	*p* value	*n* (%)	OR (95 % CI)	*p* value
All cancer types						
Matched patients						
PEG in cycle 1 only (*n*=2245)	86 (3.8)	1.7 (1.2–2.5)	0.002	58 (2.6)	3.5 (2.0–6.0)	<0.001
PEG in cycles 1 and 2—matched (*n*=2245)	50 (2.2)			17 (0.8)		
All patients[†]						
PEG in cycle 1 only (*n*=2245)	86 (3.8)	2.3 (1.8–2.9)	<0.001	58 (2.6)	4.5 (3.3–6.0)	<0.001
PEG in cycles 1 and 2—all (*n*=40,069)	760 (1.9)			309 (0.8)		
Non-metastatic breast cancer						
TC						
Matched patients						
PEG in cycle 1 only (*n*=870)	33 (3.8)	2.2 (1.2–4.2)	0.011	27 (3.1)	9.3 (2.8–30.7)	<0.001
PEG in cycles 1 and 2—matched (*n*=870)	15 (1.7)			3 (0.3)		
All patients[†]						
PEG in cycle 1 only (*n*=870)	33 (3.8)	3.0 (2.0–4.5)	<0.001	27 (3.1)	10.8 (6.4–18.3)	<0.001
PEG in cycles 1 and 2—all (*n*=9972)	138 (1.4)			32 (03)		<0.001
TAC						
Matched patients						
PEG in cycle 1 only (*n*=110)	5 (4.5)	2.6 (0.5–13.9)	0.272	5 (4.5)	–	–
PEG in cycles 1 and 2—matched (*n*=110)	2 (1.8)			0 (0.0)		
All patients[†]						
PEG in cycle 1 only (*n*=110)	5 (4.5)	2.8 (1.1–7.3)	0.034	5 (4.5)	7.4 (2.6–20.7)	<0.001
PEG in cycles 1 and 2—all (*n*=3801)	74 (1.9)			29 (0.8)		
TCH						
Matched patients						
PEG in cycle 1 only (*n*=243)	10 (4.1)	3.4 (0.9–12.8)	0.066	6 (2.5)	–	–
PEG in cycles 1 and 2—matched (*n*=243)	3 (1.2)			0 (0.0)		
All patients[†]						
PEG in cycle 1 only (*n*=243)	10 (4.1)	3.2 (1.6–6.5)	0.002	6 (2.5)	21.0 (5.4–81.2)	<0.001
PEG in cycles 1 and 2—all (*n*=3904)	55 (1.4)			5 (0.1)		
AC and AC-T (dose dense)						
Matched patients						
PEG in cycle 1 only (*n*=534)	17 (3.2)	1.0 (0.5–2.0)	1.000	12 (2.2)	1.1 (0.5–2.5)	0.835
PEG in cycles 1 and 2—matched (*n*=534)	17 (3.2)			11 (2.1)		
All patients[†]						
PEG in cycle 1 only (*n*=534)	17 (3.2)	1.6 (1.0–2.7)	0.054	12 (2.2)	2.0 (1.1–3.6)	0.029
PEG in cycles 1 and 2—all (*n*=15,005)	289 (1.9)			168 (1.1)		
Non-metastatic colorectal cancer-FOLFOX						
Matched patients						
PEG in cycle 1 only (*n*=175)	4 (2.3)	–	–	1 (0.6)	–	–
PEG in cycles 1 and 2—matched (*n*=175)	0 (0.0)	–	–	0 (0.0)		
All patients[†]						
PEG in cycle 1 only (*n*=175)	4 (2.3)	3.3 (0.9–11.7)	0.063	1 (0.6)	–	–
PEG in cycles 1 and 2—all (*n*=1297)	13 (1.0)			1 (0.1)	–	–
Non-Hodgkin's lymphoma CHOP and CHOP-R						
Matched patients						
PEG in cycle 1 only (*n*=169)	11 (6.5)	1.6 (0.6–4.1)	0.320	5 (3.0)	1.7 (0.5–6.0)	0.419

Table 3 (continued)

	FN-broad definition[b], inpatient+outpatient			FN-narrow definiton[c], inpatient+outpatient		
	n (%)	OR (95 % CI)	*p* value	*n* (%)	OR (95 % CI)	*p* value
PEG in cycles 1 and 2—matched (*n*=169)	7 (4.1)			3 (1.8)		
All patients[†]						
PEG in cycle 1 only (*n*=169)	11 (6.5)	2.1 (1.0–4.0)	0.019	5 (3.0)	2.0 (0.7–5.3)	0.171
PEG in cycles 1 and 2—all (*n*=4722)	152 (3.2)			72 (1.5)		
Non-metastatic lung cancer-CAR+PAC						
Matched patients						
PEG in cycle 1 only (*n*=144)	6 (4.2)	1.0 (0.3–2.9)	1.000	2 (1.4)	–	–
PEG in cycles 1 and 2—matched (*n*=144)	6 (4.2)			0 (0.0)		
All patients[†]						
PEG in cycle 1 only (*n*=144)	6 (4.2)	1.6 (0.7–4.1)	0.299	2 (1.4)	–	–
PEG in cycles 1 and 2—all (*n*=1368)	39 (2.9)			2 (0.1)		

OR odds ratio, *CI* confidence interval, *PEG* pegfilgrastim, *TC* docetaxel+cyclophosphamide, *TAC* docetaxel+doxorubicin+cyclophosphamide, *TCH* docetaxel+carboplatin+trastuzumab, *AC and AC-T* doxorubicin+cyclophosphamide, with or without subsequent docetaxel or paclitaxel, *FOLFOX* folinic aci+fluorouracil+oxaliplatin, *CHOP* cyclophosphamide+doxorubicin+vincristine+prednisone with rituximab (R), *CAR+PAC* carboplatin+paclitaxel

[a] Odds ratios could not be estimated for subgroups in which number of events was small ($n \leq 2$)

[b] Hospital admission with diagnosis of neutropenia, infection, or fever, or outpatient encounter with such a diagnosis and IV antimicrobial therapy

[c] Hospital admission with diagnosis of neutropenia or outpatient encounter with such diagnosis and IV antimicrobial therapy

[†] Odds ratios adjusted for potential confounders via multivariate regression

alternative definition for FN, an alternative matching design, and all patients qualifying for inclusion in the source population (with adjustment for confounding via multivariate regression), and are directionally consistent with those from the aforementioned multicenter trial of breast cancer patients in the Netherlands, notwithstanding differences in study design and methods [21]. We note that because follow-up in our study was limited to the second cycle of chemotherapy and did not extend through the end of the chemotherapy course as in the study by Aarts et al., reported FN incidence proportions should be interpreted accordingly. We also note that caution should be exercised in generalizing the results of our study since incidence proportions, and FN odds with versus without pegfilgrastim prophylaxis, may be different in later cycles.

While clinical practice guidelines recommend CSF prophylaxis when FN risk is high (>20 %) based on either chemotherapy regimen risk alone or a combination of regimen risk and patient risk factors, recent publications have reported widespread use of these agents in a manner that is inconsistent with guidelines [1, 8]. For this reason, and because of the relatively high cost of CSF agents, reducing the inappropriate use of CSF prophylaxis has been targeted as one of the key opportunities to reduce healthcare expenditures [30–33]. While the precise reasons for prophylaxis discontinuation in our study are unknown, the use of abbreviated prophylactic regimens should be carefully considered by providers, as the results of this study (and those from Aarts et al.) suggest that premature discontinuation could lead to additional FN events, which may require hospitalization and may be associated with severe consequences [2, 4, 21, 34–36].

We note a few limitations and possibilities for bias in the current study. In clinical practice, patients who receive pegfilgrastim prophylaxis in cycle 1 and cycle 2 may be systematically different than those who received it in cycle 1 only, and to the extent such differences are unobserved, study results may be biased. For example, underlying FN risk in cycle 2 may be higher among those receiving prophylaxis in cycle 2 versus those not receiving it in cycle 2 due to differences in absolute neutrophil count (ANC) and/or chemotherapy dose (both of which are unobservable in the study repositories), which would bias the study toward the null hypothesis (i.e., no difference in FN risk between groups).

Because there is no ICD-9-CM diagnosis code for FN, codes for neutropenia, fever, and infection were employed to identify inpatient and outpatient encounters that are assumed to be related to FN. Since patients are typically not given chemotherapy when they are neutropenic or have active infection, the appearance of codes for neutropenia, fever, or infection within a defined exposure period after receiving chemotherapy increases the likelihood that such outcomes are related to receipt of chemotherapy. While the sensitivity of the broad definition for FN used in this study is likely higher than that of the narrow definition using only the ICD-9-CM code for neutropenia, the specificity and positive predictive values are likely lower, chiefly due to the inclusion of infections occurring in

the absence of fever and neutropenia [27]. Some infection-related encounters during a given cycle may occur after chemotherapy-induced neutropenia has resolved, especially those that occur temporally later in the cycle (e.g., day 14 and later). In addition, because the study databases do not include information on the use of drugs in hospital, identification of FN episodes requiring inpatient care was based on diagnosis codes only. While the precise direction and magnitude of these limitations/biases are unknown, there is no reason to believe that they should disproportionately impact comparison patients versus pegfilgrastim patients.

Because the accuracy of algorithms/variables capturing the presence of acute and chronic conditions is undoubtedly less than perfect and because histories are left-truncated, some patients may be misclassified in terms of their comorbidity profile and/or prechemotherapy healthcare experience. Similarly, the accuracy of our algorithms for identifying the primary tumor type and presence of metastatic disease is unknown. Because the study population comprised (principally) cancer patients aged less than 65 years with coverage from private US health plans, the study population may not reflect US patients treated in clinical practice across the USA. Consequently, study results may not be generalizable to those with public health insurance, the uninsured, older patients, and patients residing outside of the USA. Finally, our study was sponsored by Amgen, a manufacturer of pegfilgrastim. We note, however, that our study was undertaken in response to the publication of findings from a randomized trial that was not sponsored by Amgen or any other biopharma organization and that also found prophylaxis discontinuation to be associated with a significantly higher risk of FN [21, 37]. Notwithstanding these corroborative findings, we believe that additional independent research evaluating the relationship between prophylaxis discontinuation and FN risk is warranted.

In summary, in this retrospective evaluation of cancer chemotherapy patients who received first-cycle pegfilgrastim prophylaxis in US clinical practice, a clinically relevant minority did not receive second-cycle prophylaxis. Second-cycle FN odds among this subset were substantially higher than they were among those who continued prophylaxis. Accordingly, the decision to use abbreviated pegfilgrastim prophylaxis schedules in clinical practice should be carefully considered against the associated risks.

Authors' contributions Authorship was designated based on the guidelines promulgated by the International Committee of Medical Journal Editors (2004). All persons who meet criteria for authorship are listed as authors on the title page. The contribution of each of these persons to this study is as follows: (1) conception and design (all authors), acquisition of data (X. Li, Weycker), analysis or interpretation of data (all authors); and (2) preparation of manuscript (X. Li, Weycker), critical review of manuscript (Kartashov, Figueredo, Barron, Y. Li, Reiner, Garcia, Tzivelekis). The study sponsor reviewed the study research plan and study manuscript; data management, processing, and analyses were conducted by PAI, and all final analytic decisions were made by study investigators. All authors have read and approved the final version of the manuscript.

Compliance with ethical standards

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