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ORIGINAL ARTICLE

Febrile neutropenia (FN) and pegfilgrastim prophylaxis in breast cancer and non-Hodgkin's lymphoma patients receiving high (> 20%) FN-risk chemotherapy: results from a prospective observational study

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Abstract

Purpose Prophylaxis for febrile neutropenia (FN) is recommended for the duration of myelosuppressive chemotherapy in high-risk patients; yet, granulocyte-colony-stimulating factor (G-CSF) discontinuation occurs frequently in clinical practice. The objective of this study was to investigate the incidence of FN in real-world settings and the extent and impact of early pegfilgrastim discontinuation.

Methods This prospective, observational study enrolled patients with any-stage non-Hodgkin's lymphoma (NHL) or breast cancer initiating a new chemotherapy course with a high (> 20%) FN risk, with pegfilgrastim in cycle 1. During routine clinical visits, data were collected on FN events, discontinuation of pegfilgrastim (defined as administration of G-CSF other than pegfilgrastim for ≥ 1 cycle) and all G-CSF (and reasons), neutropenic complications and adverse drug reactions (ADRs).

Results Overall, 943 patients were enrolled; 844 met the eligibility criteria (full analysis set) and 814 (86%) completed the study. Twenty-eight patients (3%) had 31 FN events (NHL, $n = 17$; breast cancer, $n = 11$). Twenty-six patients (3%) discontinued pegfilgrastim. Forty-four patients (5%) discontinued G-CSF. The most common reason for pegfilgrastim discontinuation was physician preference for daily G-CSF ($n = 14$ [2%]), and for discontinuation of all G-CSFs was reduced FN risk ($n = 14$ [2%]). Patients who continued G-CSF prophylaxis were less likely to experience neutropenic complications (odds ratio [95% confidence interval]: 0.26 [0.09–0.80]). Suspected ADRs to pegfilgrastim occurred in 43 patients (5%) and serious ADRs in 5 (1%).

Conclusions FN rates were consistent with previous reports with pegfilgrastim in clinical practice. No new ADRs were observed. G-CSF discontinuation was uncommon but appeared to increase the likelihood of neutropenic complications.

Keywords Pegfilgrastim · Granulocyte-colony-stimulating factor · Prophylaxis · Discontinuation · Febrile neutropenia

Introduction

Febrile neutropenia (FN) is a serious, yet common complication of myelosuppressive chemotherapy associated with substantial morbidity and in-patient mortality rates of up to 11% [1, 2]. Among cancer patients receiving chemotherapy, occurrence of FN has been shown to be associated with a 15% greater risk of dying compared with patients who do not experience FN [3]. Complications of neutropenia, including fever and opportunistic infection, require urgent hospitalisation and often prolonged monitoring and treatment [1, 2, 4]. Occurrence of FN can therefore cause delays to subsequent cycles of chemotherapy or lead to reductions in the dose delivered. These decreases in relative dose intensity (RDI) have been associated with poorer outcomes and worse survival in patients with lymphoma or breast cancer compared with those receiving intended dose regimens [5, 6].

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Prophylaxis with granulocyte-colony-stimulating factor (G-CSF), including the once-per-cycle pegfilgrastim or once-daily filgrastim, started a day after chemotherapy, has been shown to reduce the incidence and duration of neutropenia and decrease the number of hospitalisations caused by FN among patients with different tumour types, chemotherapy regimens and varying background characteristics [7–11]. Additionally, more patients receive their planned RDI of chemotherapy if they are prophylactically treated with G-CSF [6, 12]; accordingly, prophylaxis with G-CSF has been associated with improvements in overall survival [13]. A phase 3 study in patients with breast cancer evaluated the importance of continuing G-CSF prophylaxis across all cycles of chemotherapy and reported a higher incidence of FN in patients who received prophylactic G-CSF for the first two cycles only, compared with those who received prophylaxis for the entire chemotherapy regimen [14].

International guidelines recommend that a risk assessment of chemotherapy-induced FN should be conducted prior to initiation of treatment and should evaluate cancer type, chemotherapeutic regimen and patient-related risk factors, such as age, stage of disease, comorbidities and prior history of FN [15–17]. Patients are considered to be at high risk if there is a > 20% risk of developing FN [15–17], and prophylactic administration of G-CSF is recommended for these patients, starting in the first cycle and continuing for all subsequent cycles of chemotherapy [15–18]. However, several studies have demonstrated that these guidelines are not routinely followed, resulting in suboptimal prophylactic use of G-CSF. A large observational study of routine clinical practice in Europe, Australia and Canada found that up to 80% of patients with solid tumours considered at high risk of FN did not receive G-CSF prophylaxis in line with management guidelines [19]. Another study of patients with breast cancer or non-Hodgkin's lymphoma (NHL) reported that around 16% and 44% of patients, respectively, did not receive prophylactic G-CSF in cycle 1 [20]. Furthermore, although G-CSF administration at every cycle of chemotherapy is recommended, early discontinuation has been reported [19]. A US study found that, among patients receiving chemotherapy for either breast cancer or NHL who were hospitalised for FN, 41% had not received prophylactic G-CSF in that cycle [21]. There is also evidence to suggest that stopping G-CSF prophylaxis before the completion of all cycles of chemotherapy may increase the risk of FN in subsequent cycles [14, 22].

While it is apparent that current guidelines for the management of FN with G-CSF are not always followed, the reasons for not doing so are unclear. Also, the full extent of the withdrawal of G-CSF prophylaxis before chemotherapy is completed in the real-world setting is not known. This prospective observational study was designed to investigate the incidence of FN, and the extent and impact of early pegfilgrastim discontinuation, in patients with breast cancer or NHL at high risk of FN in European clinical practice. We also explored whether the occurrence of FN and complications of neutropenia were different in patients who discontinued G-CSF prophylaxis.

Patients and methods

Study design and patients

In this prospective observational study, eligible patients were aged ≥ 18 years and were diagnosed with any stage NHL or breast cancer. Patients must have received the first cycle of a permitted standard-dose chemotherapy regimen with an estimated high (> 20%) FN risk according to published data or guidelines (Online Resource: Table S1). Recruitment was limited to NHL and breast cancer patients with > 20% FN risk to ensure that only individuals with a clear need for continued pegfilgrastim primary prophylaxis, per guideline recommendations, were included. The population was limited to patients with confirmed high FN risk to allow us to study the group of patients in clinical practice who are most likely to experience the negative effects of G-CSF discontinuation. Dose modifications ± 10% were allowed in cycle 1. Patients must also have initiated pegfilgrastim in cycle 1 according to the pegfilgrastim Summary of Product Characteristics [23]. Enrolment must have occurred after the first pegfilgrastim dosing in cycle 1 and before the second day of cycle 2 (Online Resource: Fig. S1). The observation period was until the end of the last cycle of planned primary chemotherapy (up to a maximum of 8 cycles) or withdrawal from the study, whichever was sooner. The eligibility criteria for this study were kept broad to minimise selection bias and to reflect a real-world setting.

Study data were collected retrospectively from the first chemotherapy administration in cycle 1 to enrolment and were collected prospectively from enrolment to the end of study. Data on outcomes including FN events and FN-related hospitalisations, other neutropenia-related complications, reasons for discontinuation of pegfilgrastim or other G-CSF prophylaxis and safety data (adverse drug reactions (ADRs) and/or serious ADRs, other safety findings) were collected during routine clinical practice visits. FN was defined as an absolute neutrophil count (ANC) of $< 0.5 \times 10^9$/L, or $< 1.0 \times 10^9$/L predicted to fall below 0.5×10^9/L within 48 h, with fever or clinical signs of sepsis [15]. Fever and ANC were measured on the same day or within ± 1 calendar day.

Study outcomes

The primary outcome was the proportion of patients who experienced FN during the study period. Secondary outcomes included the proportion of patients who discontinued

pegfilgrastim prophylaxis and discontinued all G-CSF prophylaxis and the reasons for discontinuation of pegfilgrastim prophylaxis or all G-CSF prophylaxis. Discontinuations of both pegfilgrastim and all G-CSF were estimated to investigate differences in the reasons for changing or withdrawing prophylaxis and the resulting consequences. Additional secondary endpoints were the proportion of patients who experienced complications of neutropenia and ADRs to pegfilgrastim. An exploratory aim was to explore the association between discontinuation of G-CSF prophylaxis and the occurrence of FN and complications of neutropenia.

G-CSF prophylaxis was defined as G-CSF administered after the end of chemotherapy in a cycle (but not in the form of treatment provided after an event of severe neutropenia or FN). Discontinuation of pegfilgrastim prophylaxis was defined as the administration of a G-CSF other than pegfilgrastim as prophylaxis in at least one cycle. Discontinuation could be temporary (prophylaxis resumed in a later cycle) or permanent (no further prophylaxis). Discontinuation of all G-CSF prophylaxis was defined as no G-CSF prophylaxis in at least one cycle. Discontinuation could be temporary or permanent. Neutropenic complications were defined as FN-related hospitalisations and death and neutropenia-related chemotherapy dose delays and dose reductions.

Statistical analysis

It was calculated that a sample size of 500 patients each for the breast cancer and NHL groups would ensure that the half-width of the 95% confidence interval (CI) for an observed proportion of subjects with FN of ≤ 10% would be no larger than three percentage points. Previous observational studies with pegfilgrastim prophylaxis have shown a discontinuation rate of 11% in breast cancer and 14% in NHL patients ([19], Amgen data on file); similar discontinuation rates were expected to occur in this study.

Results are reported for the full analysis set, which included all enrolled patients who met the eligibility criteria. Data were summarised using descriptive statistics and subgroup analyses were presented by tumour type. Two-sided 95% CIs were calculated using Wilson's method.

The relationships between baseline factors and discontinuation of pegfilgrastim prophylaxis or discontinuation of G-CSF prophylaxis were explored using bivariate and multivariate logistic regression models. Patients were included in the models according to whether they experienced an event (FN or complications of FN) after discontinuation. Baseline covariates were predefined based on known risk factors for FN. Stepwise logistic regression analyses explored the association between discontinuation of G-CSF prophylaxis and the occurrence of neutropenic complications, adjusting for a prespecified set of potential confounding factors which were forced into the models (age [< 65 vs ≥ 65 years], sex [male vs female], tumour type [breast vs NHL] and disease stage [I–III vs IV]. Odds ratios (ORs) and 95% CIs for ORs were calculated for each covariate in the final model. The Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 or later was used to code all ADRs according to maximum severity.

Results

Patient characteristics and chemotherapy regimens

Between July 2014 and October 2016, patients were recruited from 66 centres across nine countries: Austria, Belgium, Bulgaria, Czech Republic, France, Germany, Greece, Poland and Romania. In total, 943 patients were enrolled, of whom 844 met the eligibility criteria and were included in the full analysis set (654 with breast cancer, 190 with NHL; Online Resource: Fig. S2). Most of the recorded protocol deviations identified post-enrolment were related to the permitted chemotherapy regimen. Of the 844 patients included in the analysis, a further 30 patients discontinued the study because of death ($n = 13$), loss to follow-up ($n = 10$) and withdrawal of consent ($n = 7$).

Patient baseline characteristics are shown in Table 1. Overall, 723 patients (86%) were female and mean patient age was 57.2 years. In total, 190 patients (23%) had NHL and 654 (77%) had breast cancer. One third of the patients (33%) were ≥ 65 years old: 124/190 patients (65%) in the NHL cohort and 157/654 (24%) in the breast cancer group. Patients with NHL were older with later-stage disease, poorer performance status and more comorbidities than patients with breast cancer (Table 1). Five patients, all from the NHL group, had a history of FN. Overall, 673 patients (80%) were white.

The most common chemotherapy regimens in NHL were R-CHOP-21 (in patients aged ≥ 65 years) (55% of patients), DHAP ± R (16%) and R-FC (10%) and in breast cancer were FEC-Doc (30%), ddAC/EC-Pac (27%) and ADoc (15%) (Online Resource: Table S2). Treatment intent was curative or to prolong life in 186 (98%) patients with NHL and 611 (93%) breast cancer patients. Average follow-up time was 4.1 months.

Neutropenia outcomes

Of the 844 patients in the full analysis set, 28 (3%) experienced 31 events of FN (Table 2). FN was more common in NHL patients ($n = 17$ [9%]) than breast cancer patients ($n = 11$ [2%]) and occurred most often during cycle 1 (16 patients in total [2%]). One patient (1%) in the NHL group had two FN events and one patient (1%) in the NHL group had three FN events. FN was most commonly managed by hospitalisation (21 of 31 events; Table 2).

Table 1 Baseline characteristics

	Total $N = 844$	NHL $N = 190$	Breast cancer $N = 654$
Sex, *n* (%)			
Female	723 (85.7)	74 (38.9)	649 (99.2)
Age (years)			
Mean (SD)	57.2 (12.2)	65.5 (10.5)	54.8 (11.6)
Median (Min, Max)	59.0 (21, 86)	68.0 (22, 86)	56.0 (21, 83)
Age group, *n* (%)			
≥ 65 years	281 (33.3)	124 (65.3)	157 (24.0)
Baseline comorbidities, *n* (%)	286 (33.9)	89 (46.8)	197 (30.1)
Liver disease	18 (2.1)	9 (4.7)	9 (1.4)
Cardiovascular disease	211 (25.0)	67 (35.3)	144 (22.0)
Diabetes mellitus	75 (8.9)	27 (14.2)	48 (7.3)
COPD/pulmonary disease	41 (4.9)	8 (4.2)	33 (5.0)
Renal disease	16 (1.9)	12 (6.3)	4 (0.6)
Current infection	8 (0.9)	4 (2.1)	4 (0.6)
Open wound	3 (0.4)	0	3 (0.5)
Disease stage, *n* (%)			
Stage I	110 (13.0)	15 (7.9)	95 (14.5)
Stage II	295 (35.0)	23 (12.1)	272 (41.6)
Stage III	241 (28.6)	50 (26.3)	191 (29.2)
Stage IV	161 (19.1)	90 (47.4)	71 (10.9)
Stage not available/not staged	33 (3.9)	12 (6.3)	21 (3.2)
Missing	4 (0.5)	0	4 (0.6)
ECOG performance status, *n* (%)			
0	645 (76.4)	106 (55.8)	539 (82.4)
1	129 (15.3)	61 (32.1)	68 (10.4)
≥ 2	21 (2.5)	15 (7.9)	6 (0.9)
Missing	49 (5.8)	8 (4.2)	41 (6.3)
History of febrile neutropenia, *n* (%)			
Yes	5 (0.6)	5 (2.6)	0

n number of patients, *COPD* chronic obstructive pulmonary disease, *ECOG* Eastern Cooperative Oncology Group, *NHL* non-Hodgkin's lymphoma, *SD* standard deviation

Overall, there were 124 neutropenic complications in 57 patients (7%; Table 2). Neutropenic complications were observed more frequently in NHL patients (15%) than in breast cancer patients (4%). The most common complication was neutropenia-related dose delay to chemotherapy in both NHL (9%) and breast cancer (3%) patients. There were no FN-related deaths (Table 2).

Discontinuation of pegfilgrastim or G-CSF prophylaxis

Permanent discontinuation of pegfilgrastim and all G-CSFs was low (3% and 5% of patients, respectively, Table 3). Permanent or temporary discontinuation of pegfilgrastim was more common in patients with NHL (8%) than breast cancer patients (2%), and discontinuation was more likely to be permanent than temporary (3% vs 1% overall). This pattern was similar for discontinuation of all G-CSF prophylaxis (Table 3). The highest proportion of discontinuation of pegfilgrastim prophylaxis was in cycle 3 (13 of 803 cycles, 2%) and the highest proportion of discontinuation of all G-CSF prophylaxis was in cycle 8 (19 of 226 cycles, 8%). The most common reason for temporarily or permanently discontinuing pegfilgrastim was to give daily G-CSF (2%) and the most common reason for discontinuing all G-CSF was that the patient was no longer considered at high risk of FN (2%) (Table 3). Three of the 14 patients who discontinued G-CSF due to no longer being considered at high risk of FN had received a reduced dose of chemotherapy.

Multivariate analysis showed higher odds of discontinuation of pegfilgrastim for patients with later disease stage (OR [95% CI]: 2.58 [1.02–6.54]), fewer number of planned cycles (0.62 [0.44–0.86]) and 1–2 comorbidities versus none (2.37 [1.01–5.60]).

Table 2 Febrile neutropenia and complications of neutropenia

	Total $N = 844$	NHL $N = 190$	Breast cancer $N = 654$
FN in any cycle, *n* (%)	28 (3.3)	17 (8.9)	11 (1.7)
[95% CI]	[2.3–4.8]	[5.7–13.9]	[0.9–3.0]
FN in cycle 1, *n* (%)	16 (1.9)	8 (4.2)	8 (1.2)
Primary management of FN[a], *n* (%)			
Hospitalised	21 (2.5)	15 (7.9)	6 (0.9)
Outpatient visit	1 (0.1)	0	1 (0.2)
Home care	3 (0.4)	0	3 (0.5)
No action	3 (0.4)	2 (1.1)	1 (0.2)
Unknown	1 (0.1)	1 (0.5)	0
Neutropenic complications[b], *n* (%)	57 (6.8)	28 (14.7)	29 (4.4)
FN-related hospitalisation	21 (2.5)	15 (7.9)	6 (0.9)
FN-related death	0	0	0
Neutropenia-related dose reduction	23 (2.7)	6 (3.2)	17 (2.6)
Neutropenia-related dose delay	34 (4.0)	17 (8.9)	17 (2.6)

n number of patients, *CI* confidence interval, *FN* febrile neutropenia, *NHL* non-Hodgkin's lymphoma

[a] One patient with NHL had multiple events of FN that were managed in different settings

[b] Patients could be included in more than one category

Table 3 Pegfilgrastim or all G-CSF discontinuation

	Total $N = 844$	NHL $N = 190$	Breast cancer $N = 654$
Discontinuation of pegfilgrastim prophylaxis, *n* (%)	26 (3.1)	15 (7.9)	11 (1.7)
Temporary	4 (0.5)	2 (1.1)	2 (0.3)
Permanent	22 (2.6)	13 (6.8)	9 (1.4)
Reasons for permanent or temporary discontinuation of pegfilgrastim prophylaxis[a], *n* (%)			
Daily G-CSF preferred to once-per-cycle G-CSF	14 (1.7)	11 (5.8)	3 (0.5)
Adverse reaction to G-CSF	6 (0.7)	1 (0.5)	5 (0.8)
Following protocol of hospital or country/region	2 (0.2)	1 (0.5)	1 (0.2)
Cost	1 (0.1)	1 (0.5)	0
Chemotherapy dose intensity reduced	0	0	0
Patient no longer considered at high risk of FN	0	0	0
Other	3 (0.4)	1 (0.5)	2 (0.3)
Discontinuation of all G-CSF prophylaxis, *n* (%)	44 (5.2)	13 (6.8)	31 (4.7)
Temporary	9 (1.1)	5 (2.6)	4 (0.6)
Permanent	35 (4.1)	8 (4.2)	27 (4.1)
Reasons for permanent or temporary discontinuation of all G-CSF prophylaxis[a], *n* (%)			
Patient no longer considered at high risk of FN	14 (1.7)	4 (2.1)	10 (1.5)
Chemotherapy dose intensity reduced	9 (1.1)	6 (3.2)	3 (0.5)
Adverse reaction to G-CSF	3 (0.4)	0	3 (0.5)
Cost	3 (0.4)	3 (1.6)	0
Following protocol of hospital or country/region	2 (0.2)	1 (0.5)	1 (0.2)
Other	22 (2.6)	5 (2.6)	17 (2.6)

n number of patients, *G-CSF* granulocyte-colony stimulating factor, *FN* febrile neutropenia, *NHL* non-Hodgkin's lymphoma

[a] Patients could be included in more than one category

Association between discontinuation of G-CSF prophylaxis and FN or complications of neutropenia

There were two events of FN and three events of neutropenic complications in 105 cycles during which G-CSF was discontinued, and 29 events of FN and 121 events of neutropenic complications in 4944 cycles in which prophylactic G-CSF was administered. Stepwise logistic regression analyses explored the association between patients who discontinued G-CSF prophylaxis and the subsequent occurrence of FN or neutropenic complications, adjusting for a prespecified set of potentially confounding factors. The very low number of FN events meant it was not possible to obtain reliable results from the exploration of factors associated with FN; therefore, results from this analysis are not reported. Complications of neutropenia were more likely in patients who discontinued G-CSF prophylaxis, with lower odds of an event occurring in patients who continued with G-CSF prophylaxis (OR [95% CI]: 0.26 [0.09–0.80]). Other factors more common among patients who experienced complications of neutropenia were female sex, NHL tumour type, later disease stage, prior history of FN and planned dose-dense regimen (Table 4).

Table 4 Association between G-CSF discontinuation/other factors and occurrence of complications of neutropenia[a]

Factor	Neutropenic complications[b]: odds ratio [95% CI]
Discontinuation of G-CSF prophylaxis	
Yes	Reference
No	0.26 [0.09–0.80]
Age	
< 65	Reference
≥ 65	0.81 [0.36–1.84]
Sex	
Male	Reference
Female	4.12 [1.38–12.27]
Tumour type	
Breast cancer	Reference
NHL	8.55 [3.19–22.91]
Disease stage	
Stage I–III	Reference
Stage IV	2.46 [1.04–5.79]
History of FN	
Yes	Reference
No	0.06 [0.01–0.53]
Planned chemotherapy regimen	
Dose-dense	Reference
Non-dose-dense	0.41 [0.17–0.99]

CI confidence interval, *FN* febrile neutropenia, *G-CSF* granulocyte-colony-stimulating factor, *NHL* non-Hodgkin's lymphoma

[a] Stepwise logistic regression with age (< 65 vs ≥ 65 years), sex (male vs female), tumour type (breast vs NHL) and disease stage (I–III vs IV) forced into the model. The following factors were considered in the stepwise procedure: anti-infective prophylaxis in cycle 1 (yes vs no), planned chemotherapy regimen (dose-dense vs non-dose-dense), number of planned cycles, ECOG performance status (0–1 vs 2–4), number of prior lines of chemotherapy (0–1 vs ≥ 2), number of comorbidities (0 vs 1–2 vs ≥ 3), history of FN (yes vs no), baseline ANC (< 3×10^9 /L vs ≥ 3×10^9 /L) and baseline haemoglobin (< 12 g/dL vs ≥ 12 g/dL)

[b] Neutropenic complications were defined as FN-related hospitalisations and death, and neutropenia-related chemotherapy dose delays and dose reductions

Safety

Forty-three patients (5%) had a suspected ADR to pegfilgrastim and there were five grade 3 events and one grade 4 event (Table 5). Serious ADRs to pegfilgrastim were reported in five patients (1%): three patients with FN, one patient with abdominal pain and vomiting and one patient with back and abdominal pain. In total, 13 patients (1%) died during the study. None of the deaths were considered related to FN or pegfilgrastim administration. Overall, 56 subjects (7%) had grade 3 or 4 neutropenia and 40 subjects (5%) had grade 4 neutropenia. There were no substantial changes from baseline in other laboratory analytes tested.

Discussion

Despite advances in treatment, FN remains one of the most frequent and life-threatening complications of myelosuppressive chemotherapy [17]. Onset of FN can necessitate reduction of treatment intensity in subsequent treatment cycles, further jeopardising patient outcomes [5, 6]. Therefore, the use of G-CSF has become an essential component of high FN-risk chemotherapy, allowing the continuation of treatment while mitigating the risks of FN [15–18]. In general, our results indicate that the efficacy of G-CSF observed in clinical studies is achieved in clinical practice, and adherence to G-CSF is maintained in high-risk patients.

Real-world studies suggest that the incidence of FN is higher in clinical practice than in clinical trials [24–26]. Our results show that 3% of patients (9% in the NHL group and 2% in the breast cancer group) had FN events following myelosuppressive chemotherapy. These findings are broadly similar to those previously reported in observational studies involving G-CSF-treated patients who had a wider range of FN risk (10% to ≥ 20%), a broader range of tumour types and who were receiving a more diverse set of chemotherapy regimens than the patients in our study [20, 27–31]. FN events and neutropenic complications were more frequent in NHL than in breast cancer, probably because patients with NHL were older, with later-stage disease, more bone marrow involvement, poorer performance status and more comorbidities than patients with breast cancer.

Table 5 Safety summary

	Total ($N = 844$) n (%)
Suspected ADRs to pegfilgrastim[a]	43 (5.1)
CTCAE grade 1	20 (2.4)
CTCAE grade 2	17 (2.0)
CTCAE grade 3	5 (0.6)
CTCAE grade 4	1 (0.1)
CTCAE grade 5	0
Serious ADR	5 (0.6)
Fatal ADR	0
Grade 3/4 neutropenia	56 (6.6)
Grade 4 neutropenia	40 (4.7)

ADR adverse drug reaction, *CTCAE* Common Terminology Criteria for Adverse Events

[a] Maximum CTCAE grade per patient is reported

Of the 44 patients who discontinued G-CSF prophylaxis, 5% experienced FN and 7% had complications of FN. As expected, FN occurred most frequently during cycle 1 (57% of all FN events) and was more common in the NHL group than in the breast cancer group (4% in the NHL group, 1% in the breast cancer group). These findings are broadly in line with other observational studies among patients at high risk of FN receiving G-CSF prophylaxis. A prospective, observational study of G-CSF guideline adherence versus chemotherapy delivery in patients with lymphomas or a range of solid tumours identified an FN incidence of 3% in patients who received pegfilgrastim as primary prophylaxis, with 51% of all FN events occurring during treatment cycle 1 [27]. Another prospective, observational study of pegfilgrastim primary prophylaxis in Polish patients with lymphoma, breast, lung or ovarian cancer at high risk of FN found that FN occurred in 4% of patients. In total, 50% of all FN events were observed during the first cycle of chemotherapy [29]. A sub-analysis of breast cancer patients enrolled in the IMPACT solid study who received higher FN-risk regimens (≥ 10%) found that only half received G-CSF prophylaxis and the majority of FN events (56%) occurred when prophylactic G-CSF was not administered [30].

The importance of continuing G-CSF prophylaxis during all chemotherapy cycles has been recognised in clinical management guidelines [15–18, 32] and clinical studies [14]. Among patients who receive G-CSF in cycle 1 and remain on the chemotherapy regimen, the majority appear to continue prophylaxis as indicated. Yet, in observational studies of clinical practice, discontinuation of G-CSF primary prophylaxis is observed, generally in later cycles when the risk of FN is considered lower but sometimes immediately after the first cycle of treatment [22]. In a retrospective database study, Weycker et al. found that among cancer patients who received FN prophylaxis during cycle 1, 9% did not receive further FN prophylaxis during cycle 2. Compared with matched cohorts who continued pegfilgrastim, patients who discontinued were at a 2–4-fold higher risk of FN, with similar results observed for subsequent cycles [31]. A comparable discontinuation rate was observed during another retrospective US database study. Among patients treated for breast cancer or NHL who received pegfilgrastim prophylaxis during cycle 1, approximately 90% continued to receive pegfilgrastim prophylaxis by cycle 4. Among patients with breast cancer or NHL who continued chemotherapy without G-CSF, the proportion with infection or FN ranged from 0 to 14% [20]. In our study, rates of discontinuation were comparatively low (3% discontinued pegfilgrastim prophylaxis [< 1% temporarily, 3% permanently]; 5% discontinued any G-CSF prophylaxis [1% temporarily, 4%, permanently]), with the highest proportion of discontinuation seen during cycle 3 for pegfilgrastim and cycle 8 for all G-CSFs. The low rate of discontinuation in our study compared with the previous studies described above may be due to the FN risk of the regimens (> 20% vs > 10%) and the prospective nature of the study which meant that all physicians knew they were being observed. The most frequent reasons for discontinuation were physician preference for daily over once-per-cycle G-CSF (among patients receiving pegfilgrastim) and the patient no longer being considered at high risk of FN (among patients receiving any G-CSF). Discontinuations were higher among NHL patients which, although initially counterintuitive given their higher incidence of FN compared with breast cancer patients, may be accounted for by the baseline characteristics of these patients and the necessity to reduce chemotherapy dose intensity in some patients who may have been impaired by other side effects or the presence of comorbidities. It was anticipated that financial costs might be cited as a reason for discontinuation (hence, this was included in the pre-specified list of options); however, less than 1% of patients discontinued G-CSF because of cost, suggesting that clinical considerations may be more important for physicians. Although factors associated with administering pegfilgrastim in cycle 1 have previously been reported [28, 29], to our knowledge, reasons for discontinuing pegfilgrastim have not.

Exploratory multivariate analyses were also performed in this study, with the aim of investigating the association between discontinuation of G-CSF prophylaxis and the occurrence of neutropenic complications. These analyses suggested that patients who discontinued G-CSF prophylaxis, as well those with other patient-related factors (female sex, NHL tumour type, later disease stage, prior history of FN and planned dose-dense regimen), were more likely to experience these complications than those who did not discontinue. Based on calculated ORs, the most strongly associated factors were NHL tumour type (versus breast cancer tumour type) and history of FN (versus no history of FN). Due to the relatively low number of neutropenic complications observed during the study, the small proportion of subjects who discontinued G-CSF prophylaxis, and the fact that residual confounding may have remained after adjustments, the findings from these

exploratory analyses should be interpreted with caution. However, it is noteworthy that the association between neutropenic complications and each of the factors identified in our analyses is already well known [15–18, 32].

Limitations of this study were recognised early in the process when it became apparent that 1:1 enrolment of patients with NHL and breast cancer would not be achievable. We suspect that the 3:1 (breast cancer/NHL) trend emerged due largely to clinical practice and pegfilgrastim prescribing patterns in the participating study countries. Similarly, enrolment may have been influenced by differences in incidence of breast cancer and NHL. An increase in enrolment was attempted by adding more permitted regimens for NHL, including some dose-dense regimens where pegfilgrastim use would be more likely.

Overall, the main findings of our study are aligned with those of others, including some involving patients with a broader range of tumour types and FN risk. They also show similar incidences of FN with pegfilgrastim primary prophylaxis and a similar impact of discontinuation on subsequent events related to neutropenia. For this reason, we consider our results to be generalisable to a broader population of cancer patients and that, in accordance with guidelines, pegfilgrastim should be continued in high-risk patients, especially those aged over 65 years, with later disease stage, receiving dose-dense regimens and/or with prior FN.

In conclusion, guideline recommendations appeared to be followed for patients receiving standard regimens with known high risk of FN: the number of patients who discontinued pegfilgrastim or G-CSF prophylaxis was low, and the incidence of FN was also relatively low for a population at high risk of FN. The rates of FN were consistent with those previously reported in patients who receive pegfilgrastim in clinical practice and no new or unexpected ADRs were observed. The findings from this study are consistent with the established benefit/risk profile of pegfilgrastim.

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Compliance with ethical standards

Conflict of interest This study was sponsored by Amgen. All authors had full access to the study data.

Lucy DeCosta, James O'Kelly, Yohann Omnes and Sally Wetten are employees of and shareholders in Amgen. Charisios Karanikiotis, Martin Smakal, Jean Paul Salmon and Marek Wojtukiewicz have no conflicts of interest to disclose.

Data sharing statement There is a plan to share data. This may include de-identified individual patient data for variables necessary to address the specific research question in an approved data-sharing request; also related data dictionaries, study protocol, statistical analysis plan, informed consent form and/or clinical study report. Data sharing requests relating to data in this manuscript will be considered after the publication date and (1) this product and indication (or other new use) have been granted marketing authorization in both the US and Europe, or (2) clinical development discontinues and the data will not be submitted to regulatory authorities. There is no end date for eligibility to submit a data sharing request for these data. Qualified researchers may submit a request containing the research objectives, the Amgen product(s) and Amgen study/studies in scope, endpoints/outcomes of interest, statistical analysis plan, data requirements, publication plan and qualifications of the researcher(s). In general, Amgen does not grant external requests for individual patient data for the purpose of re-evaluating safety and efficacy issues already addressed in the product labeling. A committee of internal advisors reviews requests. If not approved, a Data Sharing Independent Review Panel will arbitrate and make the final decision. Upon approval, information necessary to address the research question will be provided under the terms of a data sharing agreement. This may include anonymized individual patient data and/or available supporting documents, containing fragments of analysis code where provided in analysis specifications. Further details are available at the following: http://www.amgen.com/datasharing.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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