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Efficacy and Safety of Lipegfilgrastim in Lung Cancer Patients Receiving Myelosuppressive Chemotherapy in a Real-World Setting: Results of an Analysis of Pooled Data from Two Non-Interventional European Studies

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Keywords

Lipegfilgrastim · Granulocyte colony-stimulating factor · Chemotherapy-induced neutropenia · Febrile neutropenia · Real-world clinical practice

Abstract

Background/Aim: Chemotherapy-induced neutropenia is a common and serious complication in cancer patients receiving myelosuppressive chemotherapy. This analysis was undertaken to evaluate the effectiveness and safety of prophylaxis with lipegfilgrastim, a glycoPEGylated granulocyte colony-stimulating factor, in lung cancer patients undergoing chemotherapy in real-world clinical practice. ***Methods:*** Data from two European non-interventional studies (NIS NADIR and NIS LEOS) investigating lipegfilgrastim for primary and secondary prophylaxis were pooled. Outcomes included the incidence of chemotherapy-induced neutropenia and febrile neutropenia (FN), use of anti-infectives and antimycotics, and adverse events and their relationship to lipegfilgrastim. ***Results:*** The safety population included 361 patients with lung cancer (median age, 66 years [range, 36–88]), of whom 322 had received 2 or more consecutive cycles of lipegfilgrastim (efficacy population [primary prophylaxis, 75.5%; secondary prophylaxis, 16.5%]). Almost 40% of the patients were considered to have a high risk (>20%) of FN, and around 60% had an intermediate risk (10–20%). For all cycles, FN was reported in 3 patients (0.9%), neutropenia in 14 (4.3%), and grade 4 neutropenia in 9 (2.8%). Anti-infectives were used in 27 patients (8.4%) and antimycotics in 6 (1.9%). The incidence rates were lower for the patients' first cycle (FN, 0.4%; neutropenia, 0.8%; grade 4 neutropenia, 0.8%; anti-infectives, 0.6%; antimycotics, 0.6%). Adverse drug reactions considered lipegfilgrastim related were reported in 35 patients (9.7%), and serious adverse drug reactions in 10 (2.8%). None of the fatal events reported in 28 patients (7.8%) were lipegfilgrastim related. ***Conclusion:*** Lipegfilgrastim administered to patients with lung cancer undergoing chemotherapy in real-world clinical practice showed similar effectiveness and safety to that reported in published pivotal trials.

Introduction

Chemotherapy-induced neutropenia is a common and serious complication experienced by cancer patients treated with myelosuppressive chemotherapy [1]. It increases the risk of potentially life-threatening infections, which may require hospitalization, and frequently leads to chemotherapy delays or reductions in dose intensity, which may compromise treatment outcomes [2–6]. Because neutropenia does not usually cause any signs and symptoms, patients typically present with only fever [2]. Risk factors for development of febrile neutropenia (FN) include intensive chemotherapy regimens and patient-related factors such as advanced age, advanced disease

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stage, previous episode of FN, and comorbid conditions [6, 7]. Prophylactic use of granulocyte colony-stimulating factor (G-CSF) is recommended in cancer patients considered to be at high risk of chemotherapy-induced FN [6–9].

Lipegfilgrastim (Lonquex®; Teva Pharmaceuticals Industries Ltd, Petah Tikva, Israel) is a long-acting (once-per-cycle) G-CSF for the prevention of chemotherapy-induced neutropenia approved by the European Medicines Agency in 2013 [10]. It is glycoPEGylated in a site-specific manner, resulting in greater structural homogeneity, with pharmacological properties distinct from those of conventionally PEGylated G-CSFs [11–14]. Phase III trials of chemotherapy-naïve patients with breast cancer show lipegfilgrastim to be noninferior to pegfilgrastim with respect to duration of severe neutropenia, with similar incidence and duration of FN-related dose reductions, hospitalizations, and antibiotic use [15, 16]. The safety profile of lipegfilgrastim is similar to that of pegfilgrastim, and both drugs show similar rates of bone pain-related symptoms [15, 17, 18].

The majority of large randomized controlled trials investigating the efficacy and safety of G-CSFs have been conducted in breast cancer patients; however, lipegfilgrastim has also been studied in a randomized placebo-controlled phase III clinical trial in patients with advanced non-small cell lung cancer (NSCLC) receiving cisplatin/etoposide [19, 20]. Post hoc analyses suggested that the incidence of FN during cycle 1 in patients aged ≤65 years was similar in the lipegfilgrastim and placebo groups; however, in patients >65 years, administration of lipegfilgrastim reduced the incidence of FN [19, 20]. In both age groups, lipegfilgrastim reduced the incidence and duration of severe neutropenia, the time to absolute neutrophil count recovery, and the depth of the absolute neutrophil count nadir [20].

"Real-world" data are needed to complement the results of randomized controlled trials. In NADIR, a non-interventional study including 2,489 patients with different tumor types undergoing chemotherapy in routine clinical practice, lipegfilgrastim showed similar effectiveness and safety to that reported in pivotal trials [21]. We report a pooled analysis of efficacy and safety data from patients with lung cancer who were included in NADIR and in LEOS, another non-interventional study with lipegfilgrastim conducted in Europe [22].

Patients and Methods

Both the NADIR study (German Clinical Trials Register ID DRKS00005711) and the LEOS study (Lonquex Observational Cohort Study) were phase IV multicenter prospective observational cohort studies of cancer patients receiving cytotoxic chemotherapy and lipegfilgrastim. The NADIR study was conducted in 201 centers in Germany from December 2013 to September 2016. The LEOS study was conducted from January 2015 to December 2017 in 114 centers in 9 European countries (Austria, Belgium, Czech Republic, Italy, Luxemburg, The Netherlands, Poland, Slovakia, and Spain). Ethics committee approval was obtained in each country.

The studies enrolled patients with different tumor types, including both solid tumors and hematological malignancies. Male and female cancer patients who were aged ≥18 years, who were receiving cytotoxic chemotherapy for lung cancer and G-CSF treatment with lipegfilgrastim, and who provided written informed consent were included in this analysis. The patients were followed up during the chemotherapy regimen until 6–8 weeks after the last dose of lipegfilgrastim. They were receiving chemotherapy treatment as per standard clinical practice in their countries, and as per the decision of treating physicians. Lipegfilgrastim was also administered as per standard clinical practice based on the decision of the treating physician, within approved marketing authorization.

The following data were collected in both studies: demographics (age, gender, and ethnicity) and baseline data (overall risk of FN, estimated by the treating physician as low [<10%], intermediate [10–20%], or high [>20%]; individual patient-related risk factors; planned chemotherapy and/or biological treatment and their setting; previous treatment; history of FN; nutritional deficiency; and intended use of lipegfilgrastim [primary or secondary prophylaxis]). At each chemotherapy cycle visit, information on the incidence of neutropenia and FN, as well as on the use of anti-infectives and antimycotics, was recorded.

Data on adverse events (AEs) were collected throughout both studies. AEs, serious AEs (SAEs), adverse drug reactions (ADRs), and serious ADRs (SADRs) were coded using the Medical Dictionary for Regulatory Affairs (MedRA) version 20.0 and are shown by the preferred term.

Statistical Analysis

The data from NADIR and LEOS were merged and analyzed using descriptive statistics. Continuous variables are shown as means (±standard deviation [SD]) or median (range); discrete variables are shown as frequencies and percentages. IBM SPSS Statistics (version 21.0 and eventual updates/upgrades) and StatXact (version 6.0) were used for the statistical analyses. Missing values were neither replaced nor extrapolated.

Results

Patient Disposition

Data are available for a total of 361 patients with lung cancer who had received lipegfilgrastim at least once during their respective study (safety population). Of these, a total of 322 patients, who had at least 2 consecutive chemotherapy cycles with lipegfilgrastim, constituted the efficacy population.

In the safety population, a conclusion visit was available for 359 patients (99.4%). The conclusion visit dates ran from April 10, 2014, to September 12, 2017. Among the 359 patients with a conclusion visit, 225 patients (62.7%) received lipegfilgrastim during each of their chemotherapy cycles and 134 patients (37.3%) did not. The reasons for not receiving lipegfilgrastim during all che-

motherapy cycles were: patient decision to withdraw (n = 14; 10.4%); physician decision (n = 5; 3.7%); AEs (n = 6; 4.5%); or other reasons (n = 109; 81.3%). For "other reasons," additional information was available from 33 patients. The most common other reason was that chemotherapy had been terminated, interrupted, or changed (n = 16), and among these patients, in several cases, other forms of treatment were planned, including radiotherapy (n = 5), resection (n = 1), or biological therapy (bevacizumab; n = 1). Other reasons included progression of disease (n = 5), doctor/medical decision (n = 2), patient's wish (n = 1), loss to follow-up (n = 1), hospitalization (n = 1), that the patient was transferred to a palliative care unit (n = 1), or renal insufficiency (n = 1).

The mean total duration of treatment (from inclusion visit to end-of-study visit) was 3.69 (±1.71) months in the safety population and 3.89 (±1.54) months in the efficacy population.

Patient Demographics and Baseline Characteristics

Demographics and baseline characteristics were similar for the patients in the safety and efficacy populations (Table 1). The median age was 66 years, ranging from 36 to 88 years. Approximately two-thirds of the patients were male, and the median time since the diagnosis of cancer was less than 1 year (range 0–13).

The distribution of patients by tumor type and stage was similar in the safety and the efficacy population. Approximately 40% of the patients were reported as having NSCLC or SCLC, respectively, and more than 50% had stage IV tumors. Eastern Cooperative Oncology Group (ECOG) performance status was 0 or 1 in three-quarters of the patients in both populations, and the majority of patients were assessed by the investigator to be at intermediate risk (around 60%) or high risk (almost 40%) of FN, as defined in the NCCN guidelines [7] (Table 1). The overall number of risk factors and numbers of patients with individual risk factors for FN are also shown in Table 1.

The majority of patients had previously received chemotherapy (around 85%), almost one-third (around 31%) had previously received radiotherapy, and a few had received immunotherapy, targeted therapy or biological therapy (around 2%), or hormonal therapy (0.6%).

Of the patients in the safety population in whom comorbidities had been evaluated (n = 360), 291 (80.9%) had at least one comorbidity, and the mean number of comorbidities per patient was 1.89 (±1.40) (range 0–6). Similar values were seen among the patients in the efficacy population in whom comorbidities had been evaluated (n = 321). Overall, 256 patients (79.8%) had at least one comorbidity, and the mean number of comorbidities per patient was 1.87 (±1.41) (range 0–6). The number of system organ classes (SOCs) affected by comorbidities is summarized in Table 1.

Table 1. Demographics and baseline characteristics of the safety and efficacy populations

Variable	Safety population (N = 361)	Efficacy population (N = 322)
Age, years	66 (36–88)	66 (36–88)
Male	227 (62.9)	202 (62.7)
Duration of cancer, years	0.20 (0–13.34)	0.18 (0–13.34)
Lung cancer type		
SCLC	154 (42.7)	144 (44.7)
NSCLC	143 (39.6)	127 (39.4)
Other	64 (17.7)	51 (15.8)
Tumor stage		
I or II	31 (8.6)	27 (8.4)
III	63 (17.5)	55 (17.1)
IV	192 (53.2)	170 (52.8)
Missing	75 (20.8)	70 (21.7)
Risk of FN[a, b]		
Low (<10%)	7 (1.9)	7 (2.2)
Intermediate (10–20%)	214 (59.3)	194 (60.2)
High (>20%)	140 (38.8)	121 (37.6)
Individual risk factors for FN (%)[c]		
Age >65 years	187 (51.8)	166 (51.6)
History of prior FN	166 (46.0)	146 (45.3)
Female gender	134 (37.1)	120 (37.3)
Hemoglobin level <12 g/dL	35 (9.7)	28 (8.7)
Poor nutritional status	16 (4.4)	14 (4.3)
Poor performance status	11 (3.0)	8 (2.5)
Overall number of individual risk factors for FN	1.52±0.98	1.50±0.97
ECOG performance status		
0	110 (30.5)	99 (30.7)
1	162 (44.9)	147 (45.7)
2+	48 (13.3)	39 (12.1)
Missing	41 (11.4)	37 (11.5)
Previous cancer treatments		
Chemotherapy	307 (85.0)	277 (86.0)
Radiotherapy	115 (31.9)	100 (31.1)
Other	11 (3.0)	9 (2.8)
Number of system organ classes affected by comorbidities		
1	80 (22.2)	70 (21.8)
2	95 (26.4)	86 (26.8)
≥3	116 (32.2)	100 (31.2)
Missing	1 (0.3)	1 (0.3)
Use of lipegfilgrastim		
Primary prophylaxis	269 (74.5)	243 (75.5)
Secondary prophylaxis	61 (16.9)	53 (16.5)
Missing	31 (8.6)	26 (8.1)

Values are presented as median (range), mean ± SD, or n (%). ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; FN, febrile neutropenia; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; SD, standard deviation. [a] Estimated by the treating physician, considering the FN risk associated with chemotherapy and individual risk factors. [b] Risk categories as defined in the NCCN guidelines [7]. [c] Risk factors for FN included in the EORTC guidelines [6].

Table 2. Most frequent chemotherapy regimens (planned use in ≥10 patients in either population)

Chemotherapy regimen	Safety population (*N* = 361)	Efficacy population (*N* = 322)	FN risk (%) associated with chemotherapy regimen [Ref.][a]
Carboplatin/etoposide or cisplatin/etoposide	135 (37.4)	125 (38.8)	5–18 [33, 34]
Carboplatin/paclitaxel (±bevacizumab)	36 (10.0)	34 (10.6)	2–9 [35–38]
Topotecan	25 (6.9)	21 (6.5)	5 (oral) [39] 28 (second line) [40]
Cisplatin/pemetrexed (±bevacizumab)	24 (6.6)	23 (7.1)	1 [41]
Cisplatin/vinorelbine	22 (6.1)	19 (5.9)	4.5 [42] 9 (adjuvant) [42]
Cyclophosphamide/doxorubicin/vincristine	16 (4.4)	13 (4.0)	13.8 [44]
Docetaxel	11 (3.0)	8 (2.5)	12.7 [45]

Values are presented as *n* (%). FN, febrile neutropenia. [a] FN risk associated with the chemotherapy regimen derived from the literature.

Chemotherapy was planned for all patients and was in a palliative setting in the majority of cases (64.5% and 70.5% in the safety and the efficacy population, respectively). The most frequently planned chemotherapy regimens are shown in Table 2 [33–45]. Carboplatin/etoposide was the regimen planned most frequently (for 29.9% and 30.7% of the patients in the safety and the efficacy population, respectively).

Lipegfilgrastim Administration

In the safety population, a total of 1,414 cycles with lipegfilgrastim were administered (mean 3.92 cycles/patient). In the efficacy population, 1,375 cycles of lipegfilgrastim were administered (mean 4.27 cycles/patient). Indications for lipegfilgrastim were primary prophylaxis in 1,093 cycles (79.5%)/243 patients (75.5%) and secondary prophylaxis in 198 cycles (14.4%)/53 patients (16.5%). Information was missing for 84 cycles (6.1%)/26 patients (8.0%). In the patients' first cycle, lipegfilgrastim was administered for primary prophylaxis to 243 patients (75.5%) and for secondary prophylaxis to 53 patients (16.5%). Information was missing for 26 cycles (8.0%) in 26 patients (8.0%).

Efficacy of Lipegfilgrastim

Reported episodes of FN, neutropenia, and grade 3 and 4 neutropenia for all cycles using lipegfilgrastim as well as for the patients' first cycle (for all cycles and also for cycles used as primary and secondary prophylaxis, separately) are summarized in Table 3, together with the frequency of use of anti-infectives and antimycotics after the cycles. For all cycles using lipegfilgrastim, FN was observed after 4 cycles (0.3%) in 3 patients (0.9%) and neutropenia after 21 cycles (1.5%) in 14 patients (4.3%). Two of the cases of neutropenia were of grade 3 (in 2 patients [0.6%]) and 12 cases were of grade 4 (in 9 patients [2.8%]). Carboplatin/etoposide was the only chemotherapy regimen associated with neutropenia in ≥1 patient (3 patients with SCLC and 1 patient with NSCLC). No chemotherapy regimen was associated with FN in more than a single patient. Anti-infectives were used after 35 cycles (2.5%) in 27 patients (8.4%), and antimycotics were used after 6 cycles (0.4%) in 6 patients (1.9%). When known, the most common reason for their use was prophylaxis/infection prophylaxis. For all first cycles using lipegfilgrastim, FN was observed after 2 cycles (0.6%) and neutropenia after 3 cycles (0.9%). All 3 cases of neutropenia were of grade 4. Anti-infectives were used in 2 patients (0.6%) and antimycotics in 6 patients (1.9%). When known, the most common reason for their use was prophylaxis/infection prophylaxis. Across all cycles and for all first cycles, the incidence of FN and neutropenia was lower when lipegfilgrastim was used as primary prophylaxis than when it was used as secondary prophylaxis (Table 3).

Safety of Lipegfilgrastim

Overall, 1,130 AEs were recorded in 255 of the 361 patients (70.6%) of the safety population. The most frequent AEs, reported in ≥3% of patients by SOC, were: anemia (18.6%), thrombocytopenia (16.1%), neutropenia (15.0%), leukopenia (14.4%), and leukocytosis (4.4%) in the SOC "blood and lymphatic system disorders"; nausea (7.5%), diarrhea (7.2%), and constipation (3.0%) in the SOC "gastrointestinal disorders"; fatigue (8.0%), general physical health deterioration (5.8%), pain (4.4%), and pyrexia (4.2%) in the SOC "general disorders and administration site conditions"; pneumonia (4.2%) and infection

Table 3. Incidence of chemotherapy-induced FN and neutropenia, anti-infective use, and antimycotic use in lipegfilgrastim-treated patients (efficacy population)

	For all cycles		For patients' first cycle
	patients	cycles	
All cycles, N	322	1,375	322
FN	3 (0.9)	4 (0.3)	2 (0.6)
Neutropenia	14 (4.3)	21 (1.5)	3 (0.9)
Grade 3	2 (0.6)	2 (0.1)	0
Grade 4	9 (2.8)	12 (0.9)	3 (0.9)
Anti-infectives	27 (8.4)	35 (2.5)	2 (0.6)
Oral	24	30	2
IV	3	4	0
Antimycotics	6 (1.9)	6 (0.4)	2 (0.6)
Oral	4	4	2
IV	1	1	0
Primary prophylaxis, N	243	1,093	243
FN	2 (0.8)	3 (0.3)	1 (0.4)
Neutropenia	9 (3.7)	15 (1.4)	2 (0.8)
Grade 3	2 (0.8)	2 (0.2)	0
Grade 4	8 (3.3)	11 (1.0)	2 (0.8)
Anti-infectives	22 (9.1)	30 (2.7)	2 (0.8)
Oral	21	27	2
IV	2	3	0
Antimycotics	4 (1.6)	4 (0.4)	2 (0.8)
Oral	2	2	1
IV	1	1	1
Secondary prophylaxis, N	53	198	53
FN	1 (1.9)	1 (0.5)	1 (1.9)
Neutropenia	5 (9.4)	6 (3.0)	1 (1.9)
Grade 3	0	0	0
Grade 4	1 (1.9)	1 (0.5)	1 (1.9)
Anti-infectives	5 (9.4)	5 (2.5)	0
Oral	3	3	0
IV	1	1	0
Antimycotics	1 (1.9)	1 (0.5)	0
Oral	1	1	0
IV	0	0	0

Values are presented as *n* (%). FN, febrile neutropenia.

(3.9%) in the SOC "infections and infestations"; back pain (3.0%) in the SOC "musculoskeletal and connective tissue disorders"; and dyspnea (5.8%) and cough (5.0%) in the SOC "respiratory, thoracic and mediastinal disorders." All other AEs had a frequency <3%, including all bone pain-related symptoms (bone pain 1.9%, arthralgia 0.3%, musculoskeletal chest pain 0.6%, musculoskeletal pain 0.3%, neck pain 0.3%, pain in extremity 0.6%, and spinal pain 0.8%).

The treating physician provided a causality relationship for all AEs (yes/no), and a relationship to lipegfilgrastim was indicated for 79 ADRs (7.0%) in 35 patients (9.7%). All ADRs are listed (as preferred terms, within each SOC) in Table 4. The most frequent ADRs (occurring in ≥1% of patients) were thrombocytopenia (1.7%), anemia (1.4%), and asthenia (1.1%). All other ADRs occurred in <1% of patients, including bone pain-related symptoms (bone pain 0.8%, back pain 0.6%, arthralgia 0.3%, pain in extremity 0.3%, and spinal pain 0.3%).

Overall, 176 SAEs were recorded in 96 patients (26.6%). Sixteen of the SAEs (in 10 patients) were considered by the treating physician to be related to lipegfilgrastim. The SADRs are summarized in Table 5. No SADR was reported in more than a single patient. Nine patients (2.5%) discontinued the study as a consequence of ADRs or SADRs. Of the SAEs that led to death in 28 patients, none was considered to be related to lipegfilgrastim.

Discussion

This pooled analysis of data from two non-interventional studies was undertaken to assess the effectiveness and safety of lipegfilgrastim, administered at the discretion of the treating physician, in the prevention of chemotherapy-induced neutropenia and FN in patients receiving treatment for lung cancer in real-world clinical practice. FN was reported in 0.9% of patients across all treatment cycles and in 0.4% of patients in cycle 1. These values are comparable to those reported in a pivotal randomized placebo-controlled phase III trial of lipegfilgrastim in patients with NSCLC [19], which reported an incidence of FN of 2.4% in cycle 1, and of 0.5, 0.5, and 1.2% in cycles 2, 3, and 4, respectively. The AEs reported in the current pooled analysis were consistent with the underlying disease and the chemotherapy regimen received. The incidence of bone pain-related symptoms, which are typically associated with G-CSF therapy, was low and comparable with that reported in the phase III NSCLC trial [19]. The overall incidence of AEs considered by the treating physician to have a causal relationship to lipegfilgrastim (i.e., ADRs) was also similar to that in the phase III NSCLC trial [19]: 79 ADRs were reported in 35 patients (9.7%) and mortality (7.8%) was low. Moreover, it is notable that among the conditions that were reported as ADRs and SADRs, some of the reported reactions (such as FN, neutropenia, diarrhea, asthenia, fatigue, infection, and dehydration) are not listed in the current Summary of Product Characteristics of lipegfilgrastim [10], suggesting that these were more likely caused by the chemotherapy regimen received or the underlying malignancy. Importantly, none of the deaths reported in the current analysis was considered to be related to lipegfilgrastim.

The findings of the current pooled analysis of data for lung cancer patients in the NADIR and LEOS studies are comparable to the results of the overall final anal-

Table 4. Frequency of ADRs occurring in >1 patient coded by MedRA system organ class and preferred terms (safety population, $N = 361$)

System organ class	Preferred term	Patients	ADRs
Any ADR		35 (9.7)	79 (100)
Blood and lymphatic system disorders	Thrombocytopenia	6 (1.7)	10 (12.3)
	Anemia[a]	5 (1.4)	6 (7.4)
	Leukocytosis	3 (0.8)	3 (3.7)
	Neutropenia[a]	2 (0.6)	3 (3.7)
Gastrointestinal disorders	Nausea	3 (0.8)	3 (3.7)
General disorders and administration site condition	Asthenia[a]	4 (1.1)	5 (6.2)
	Pyrexia	3 (0.8)	4 (4.9)
	Malaise[a]	2 (0.6)	2 (2.5)
Musculoskeletal and connective tissue disorders	Bone pain	3 (0.8)	3 (3.7)
	Back pain	2 (0.6)	2 (2.5)
Respiratory, thoracic and mediastinal disorders	Dyspnea	2 (0.6)	2 (2.5)

Values are shown as *n* (%). ADR, adverse drug reaction. [a] These conditions were reported as ADRs by the treating physicians. However, they are not listed in the current Summary of Product Characteristics of lipegfilgrastim [10], and their likely cause is considered in the Discussion section of this article.

Table 5. Frequency of SADRs reported by the treating physicians, coded by MedRA preferred terms (safety population, $N = 361$)

SADR	Patients	Events
Any SADR	10 (2.8)	16 (100)
Neutropenia[a]	1 (0.3)	2 (12.6)
Febrile neutropenia[a]	1 (0.3)	1 (6.3)
Thrombocytopenia	1 (0.3)	1 (6.3)
Diarrhea[a]	1 (0.3)	1 (6.3)
Nausea	1 (0.3)	1 (6.3)
Asthenia[a]	1 (0.3)	1 (6.3)
Disease progression[a]	1 (0.3)	1 (6.3)
Malaise[a]	1 (0.3)	1 (6.3)
Infection[a]	1 (0.3)	1 (6.3)
Infectious pleural effusion[a]	1 (0.3)	1 (6.3)
Pneumonia[a]	1 (0.3)	1 (6.3)
Dehydration[a]	1 (0.3)	1 (6.3)
Back pain	1 (0.3)	1 (6.3)
Renal failure	1 (0.3)	1 (6.3)
Pneumonitis	1 (0.3)	1 (6.3)

Values are shown as *n* (%). SADR, serious adverse drug reaction. [a] These conditions were reported as SADRs by the treating physicians. However, they are not listed in the current Summary of Product Characteristics of lipegfilgrastim [10], and their likely cause is considered in the Discussion section of this article.

yses of the individual studies [21, 22]. The NADIR study included 2,489 patients with different tumor types, including breast cancer, non-Hodgkin lymphoma, and prostate cancer, in addition to the lung cancer patients included in the current pooled analysis [21]. The LEOS study included 1,313 patients, with breast cancer and lymphoma being the most common tumor types [22]. The rates of FN seen in the current pooled analysis are also similar to those reported in randomized controlled trials of lipegfilgrastim in patients with breast cancer [15, 16, 23]. Overall, these results suggest that, when administered to patients with lung cancer undergoing chemotherapy in routine clinical practice, lipegfilgrastim showed an effectiveness and safety broadly comparable to that seen in randomized clinical trials [15, 16, 19, 23].

The incidence of FN reported with lipegfilgrastim in the current analysis is considerably lower than that reported in some observational studies of patients with a number of different tumor types who were undergoing myelosuppressive chemotherapy and receiving prophylaxis with another long-acting (once-per-cycle) G-CSF, pegfilgrastim. These studies often included substantial numbers of lung cancer patients, but in several of the studies, the incidence of FN by individual tumor type was not reported. A study reported by Fiegl et al. [24] included 335 evaluable patients (75 with lung cancer), of whom the majority (63.9%) were assessed as being at intermediate risk of FN (low risk 21.2%, high risk 14.9%) and 80.3% received pegfilgrastim for primary prophylaxis. The overall rate of FN among patients who received pegfilgrastim was 5.7% [24]. Of a total of 2,112 patients in a study reported by Ozer et al. [25], 265 had NSCLC and 76 SCLC. Overall, FN occurred in 3.6% of patients in the first cycle and 6.3% across all cycles [25]. The OPERa study included 333 patients, of whom 4% had lung cancer, and the

overall incidence of FN was 3% among patients who received pegfilgrastim for primary prophylaxis compared with 12% among patients who did not receive pegfilgrastim [26].

The rate of FN has also been reported for observational studies of pegfilgrastim in patients with different tumor types [27, 28]. In a study of 1,072 patients, including 127 patients (12%) with lung cancer (median age of 65 years, similar to the current analysis), the overall incidence of FN was 5% [27]. As observed in the current pooled analysis, the incidence of FN was substantially lower in the setting of primary prophylaxis (3%) than in secondary prophylaxis (13%) [27]. The incidence of FN across all cycles in patients with lung cancer was 6%, ranging from 3 to 7% across different cancer types [27]. In another study in which pegfilgrastim was used for primary prophylaxis only, the overall incidence of FN was 4% [28]. The incidence of FN was lowest in lung and ovarian cancer (both 0%), and highest in lymphoma (non-Hodgkin lymphoma 10% and Hodgkin lymphoma 13%) [28]. The molecular structure of lipegfilgrastim differs from that of pegfilgrastim, due to the different glycoPEGylating technologies used in their production [29]. They also differ in their pharmacokinetic and pharmacodynamic properties, with lipegfilgrastim having a longer half-life in vitro [29]. The results of a recent study in patients with non-Hodgkin lymphoma indicate that lipegfilgrastim may be more efficient than pegfilgrastim for mobilization of CD34+ cells after chemotherapy, resulting in more rapid hematologic recovery [30].

Current guidelines recommend primary prophylaxis with G-CSF if the risk of FN is high (≥20%) or intermediate (10–20%) with additional risk factors [6–9]. In the current pooled analysis, lipegfilgrastim was also administered to patients receiving chemotherapy regimens associated with a lower risk of FN. This is not unexpected and has been observed in other studies assessing adherence to G-CSF guidelines in real-world settings [31, 32]. These findings would appear to suggest there may be a need for the development of predictive tools to better define high-risk patients as well as educational activities to offer guidance on the most effective ways to use G-CSFs in routine clinical practice.

Conclusion

Lipegfilgrastim administered to patients with lung cancer undergoing chemotherapy in routine practice settings shows similar effectiveness and safety to that reported in published pivotal clinical trials.

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Statement of Ethics

The review board at each participating institution approved the trial protocol for the original studies LEOS and NADIR. These trials were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent to participate.

Conflict of Interest Statement

C.G. has received honoraria for participating in advisory boards and providing academic talks from AstraZeneca, Berlin Chemie, BMS, Boehringer Ingelheim, Chiesi, GSK, MSD, Novartis, Pfizer, Roche, Sanofi, and Teva. K.P. has no conflicts of interest to declare. N.F. has received personal fees from AstraZeneca, BMS, Boehringer Ingelheim, MSD, Novartis, Pfizer, Roche, and Takeda, and has received nonfinancial support from BMS, Boehringer Ingelheim, and Takeda.

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Author Contributions

All authors participated meaningfully in the analysis, critically reviewed the manuscript for important intellectual content, and approved the final submitted version of the manuscript.

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