Efficacy and safety of lipegfilgrastim for prophylaxis of chemotherapy-induced neutropenia in breast cancer patients in Poland

Joanna Streb[1], Jakub Kucharz[2], Aurelia Lipa[3], Marcin Strzondała[3], Piotr J. Wysocki[1]

[1]Department of Oncology, Jagiellonian University Medical College, Krakow, Poland
[2]Department of Uro-Oncology, Maria Sklodowska-Curie, National Research Institute of Oncology, Warsaw, Poland
[3]Teva Pharmaceuticals Polska Sp. z o.o., Medical Department, Poland

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Corresponding author:
Jakub Kucharz
Department of Uro-Oncology
Maria Sklodowska-Curie
National Research Institute
of Oncology
Warsaw, Poland
E-mail: jakub.kucharz@pib-nio.pl

Abstract

Introduction: Lipegfilgrastim is a long-acting glycoPEGylated granulocyte-colony stimulating factor (G-CSF) used to prevent chemotherapy-induced neutropenia (CIN) and febrile neutropenia (FN). The aim of the current study was to obtain data on the drug efficacy and safety in real-world clinical practice.

Material and methods: This is an exploratory analysis of Polish breast cancer patients participating in a pan-European study of lipegfilgrastim in primary and secondary prophylaxis for patients receiving cytotoxic chemotherapy (Lonquex ObsErvational Cohort Study, LEOS). Patients were followed from the start of neutropenia prophylaxis until 6 to 8 weeks after the last dose of lipegfilgrastim. The efficacy measures were chemotherapy dose reductions, omissions, delays and the proportion of the planned cumulative dose actually delivered.

Results: A total of 45 patients, mostly at high risk of FN, were included in the analysis. Overall, 31 (14.6%) of 212 chemotherapy cycles were delayed in 19 (42.2%) patients. The cumulative dose of chemotherapy was reduced in 1.4% of the cycles in 4.4% of the patients. The mean percentage of planned cumulative dose actually administered was 99.95% across all cycles. Only 1 patient had FN. There were 15 episodes of neutropenia in 3 (6.7%) patients. A total of 69 adverse events were reported, of which 65% were drug-related. The most common were musculoskeletal pain (17.8%) and myalgia (11.1%). Four adverse events were serious and two of them were related to lipegfilgrastim.

Conclusions: Lipegfilgrastim proved to be effective and well tolerated for CIN prophylaxis in patients with breast cancer receiving myelosuppressive chemotherapy in a real-life setting.

Key words: granulocyte-colony stimulating factor, febrile neutropenia, cumulative dose, drug-related adverse event.

Introduction

Chemotherapy-induced neutropenia (CIN) is a significant dose-limiting toxicity of chemotherapy. It increases the risk of infectious complications and death. The severity of neutropenia is associated with the development of febrile neutropenia (FN), one of the most serious com-

plications of chemotherapy. Severe neutropenia and/or FN often result in dose reductions or treatment delays, which may compromise the efficacy of cancer therapy [1, 2].

Prophylactic use of granulocyte-colony stimulating factors (G-CSFs) was shown to be effective in reducing the severity and duration of severe neutropenia and FN, as well as all-cause mortality [3–6]. US and European guidelines recommend G-CSF therapy in primary prophylaxis in patients receiving high risk FN chemotherapy (> 20%). In patients treated with intermediate risk regimens (10–20%) other risk factors should be considered (e.g. age or coexisting diseases). Secondary prophylaxis is also important, i.e. in subsequent cycles in patients after a previous FN episode [1, 7].

Lipegfilgrastim (Lonquex; Teva Pharmaceuticals Industries Ltd, Petach Tikva, Israel) is a glyco-PEGylated, long-acting, fixed dose once per cycle, recombinant G-CSF, approved by the European Medicines Agency for reduction of the duration of neutropenia and the incidence of FN in adult patients treated with cytotoxic chemotherapy for malignancy (with the exception of chronic myeloid leukaemia and myelodysplastic syndromes) [8].

A phase III randomized trial comparing lipegfilgrastim and pegfilgrastim for prophylaxis of CIN in patients with breast cancer receiving doxorubicin/docetaxel chemotherapy demonstrated comparable efficacy in terms of duration of severe neutropenia and the incidence of FN and duration of FN-related hospitalization and antibiotic use [9, 10].

The objective of this exploratory analysis was to assess the efficacy and safety of lipegfilgrastim in real-world clinical practice in breast cancer patients in Poland.

Material and methods

Trial design and oversight

This was a multicentre, prospective, observational cohort study of cancer patients receiving cytotoxic chemotherapy and lipegfilgrastim (Lonquex) in outpatient and inpatient settings (Lonquex ObsErvational Cohort Study, LEOS). Lipegfilgrastim 6 mg was used in primary or secondary prophylaxis of chemotherapy-induced neutropenia. Patients were followed from the start of neutropenia prophylaxis with lipegfilgrastim until 6 to 8 weeks after the last dose of the drug. The study was conducted in European Union countries, including Poland. This is an exploratory analysis of Polish breast cancer patients. The trial was conducted in accordance with the Helsinki Declaration and the guidelines for Good Clinical Practice (GCP), Polish Pharmaceutical Law, Directive 2010/84/EU, Good Epidemiological Practice (GEP), Good Pharmacoepidemiology Practices and Good Pharmacovigilance Practices (GVP). The protocol was reviewed by the local ethics committee in Krakow, Poland. All patients provided written informed consent. The authors wrote the manuscript with the assistance of a medical writer funded by the sponsor.

Patients

Eligible subjects included male and female cancer patients ≥ 18 years of age treated with cytotoxic chemotherapy or biological therapy for solid and haematological malignancies, excluding chronic myeloid leukaemia and myelodysplastic syndromes, and receiving G-CSF treatment with lipegfilgrastim for primary or secondary prophylaxis of chemotherapy induced neutropenia. Only breast cancer patients were included in the present analysis.

Efficacy measurements

Primary efficacy measures included chemotherapy dose reductions, omissions, delays and mean percentages of planned cumulative doses actually administered. Among the secondary efficacy measures were frequencies of febrile neutropenia, neutropenia, hospitalisations, anti-infective treatments and blood transfusions.

Safety assessments

Adverse events were categorized using the Medical Dictionary for Regulatory Activities, version 20.1, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. Typical chemotherapy-induced adverse drug reactions were exempt from recording unless they were more severe or more frequent than expected from the treatment or the medical condition itself and included: nausea and vomiting, alopecia, diarrhoea and constipation, fatigue, asthenia, neuropathic pain, hand-foot-syndrome, swelling, mouth sores, appetite changes, nervous system effects and cognitive changes or dysfunction only if related to chemotherapy. The adverse event relation to study drug was determined by the treating physician.

Statistical analysis

This is an exploratory analysis. No formal statistical hypotheses were tested. Descriptive statistics methods were used. Ninety-five percent confidence intervals were calculated for efficacy and safety measures.

Results

Patients

From January 2015 to January 2016, a total of 45 breast cancer patients were enrolled and treat-

ed with chemotherapy at 6 sites in Poland. Patients' demographics and disease characteristics are summarized in Table I. The mean age of the patients was 56.6 years (range: 34.0–76.0). Forty percent of the patients were diagnosed with stage II, 33.3% with stage III and 11.1% with stage IV breast cancer. Two or more comorbidities were present in 28.8% of the patients. Over 50% of the patients were fully active (Eastern Cooperative Oncology Group performance status [ECOG-PS] 0) and 40% had ECOG-PS score of 1. The risk of febrile neutropenia was high (> 20%) in 62.2% of the patients.

Treatments

The majority of patients received adjuvant chemotherapy (68.9%). Most chemotherapy regimens were associated with intermediate or high risk of febrile neutropenia. In 80% of the patients lipegfilgrastim was used in primary prophylaxis. Patients received a total of 212 cycles. Lipegfilgrastim was used in 88.2% of the cycles. Chemotherapy regimens and FN prophylaxis are summarized in Table II.

Efficacy

Overall, 31 of 212 chemotherapy cycles (14.6%; 95% CI: 10.4–19.4%) were delayed in 19 patients (42.2%; 95% CI: 28.0–57.8). The median delay of the following cycle was 7.0 days (95% CI: 6.9–7.1). The mean percentage of planned cumulative dose actually administered was 99.95 ±2.02% across all cycles and 100 ±0.40% across all cycles and drugs. The cumulative dose of chemotherapy was reduced in 3 of 212 cycles (1.4%; 95% CI: 0.5–3.0%) in 2 (4.4%) patients. No chemotherapy cycle was omitted. Targeted treatment with trastuzumab was used in six cycles. None of the trastuzumab doses were reduced or omitted. Frequencies of chemotherapy cycles delays, dose reductions and omissions as well as the percentage of planned cumulative doses actually administered are summarized in Table III.

One patient had febrile neutropenia, which corresponds to an incidence of 2.2%. A total of 15 neutropenia episodes occurred across all cycles (7.1%) in 3 (6.7%) patients, with the exception of two severe (grade 4), while the rest were mild (grade 1). Anti-infectives were used 6 times, once intravenously for the treatment of febrile neutropenia and the other 5 orally for other infections (e.g. pharyngitis or wound infection). The median duration of anti-infective therapy was 4 days (range: 2–22). Two blood transfusions, one 2 and one 3 units, were used throughout the study.

There were three hospitalizations with a median duration of 8 days (range: 1–31). One hospital stay was due to febrile neutropenia and lasted 31 days. One patient had surgery to remove the breast implant due to wound infection, and in the third case it was a planned admission associat-

Table I. Patients demographics and disease characteristics (n = 45)

Characteristic	Results
Age [years], mean ± standard deviation	56.6 ±10.1
Caucasian race, *n* (%)	45 (100.0)
Stage of breast cancer*, *n* (%):	
IA	3 (6.7)
IB	0
IIA	12 (26.7)
IIB	6 (13.3)
IIIA	9 (20.0)
IIIB	4 (8.9)
IIIC	2 (4.4)
IV	5 (11.1)
Unknown	4 (8.9)
No. of co-morbidities, *n* (%):	
0	16 (35.6)
1	16 (35.6)
2	5 (11.1)
3	6 (13.3)
4	1 (2.2)
5	1 (2.2)
ECOG performance status, *n* (%):	
0	24 (53.3)
1	18 (40.0)
2	3 (6.7)
3	0
Febrile neutropenia risk, *n* (%):	
Low (< 10%)	1 (2.2)
Intermediate (10–20%)	16 (35.6)
High (> 20%)	28 (62.2)
Risk factors for febrile neutropenia, *n* (%):	
Advanced disease	13 (28.9)
Age above 65	10 (22.2)
History of prior FN	5 (11.1)
Poor performance status	3 (6.7)
Poor nutritional status	4 (8.9)
Female gender	45 (100.0)
Haemoglobin < 12 g/dl	6 (13.3)
Liver disease	2 (4.4)
Renal disease	0 (0.0)
Cardiovascular disease	17 (37.8)
Other	4 (8.9)

**According to AJCC Cancer Staging Manual, 8th Edition, 2017.*

Table II. Chemotherapy and FN prophylaxis (n = 45)

Treatment	Results
Chemotherapy setting, *n* (%):	
Adjuvant	31 (68.9)
Neoadjuvant	9 (20.0)
Metastatic disease	5 (11.1)
Chemotherapy regimen, *n* (%):	
Doxorubicin and docetaxel	11 (24.4)
Docetaxel and cyclophosphamide	6 (13.3)
Doxorubicin and cyclophosphamide	6 (13.3)
Doxorubicin, cyclophosphamide followed by docetaxel	4 (8.9)
Fluorouracil, epirubicin and cyclophosphamide (FEC)	4 (8.9)
Fluorouracil, epirubicin and cyclophosphamide followed by docetaxel (FEC-D)	3 (6.7)
Fluorouracil, doxorubicin and cyclophosphamide (FAC 50)	3 (7.7)
Doxorubicin, cyclophosphamide followed by paclitaxel (AC-T)	2 (4.4)
Doxorubicin and paclitaxel	1 (2.2)
Docetaxel, doxorubicin, and cyclophosphamide (TAC)	1 (2.2)
Docetaxel	1 (2.2)
Docetaxel followed by epirubicin	1 (2.2)
Paclitaxel	1 (2.2)
Docetaxel, carboplatin, trastuzumab (TCH)	1 (2.2)
No. of chemotherapy cycles (mean ± standard deviation)	212 (6.2 ±1.8)
No. of lipegfilgrastim doses (%)	187 (88.2)
Type of febrile neutropenia prophylaxis, *n* (%):	
Primary	36 (80.0)
Secondary	9 (20.0)

ed with the administration of zoledronic acid in a patient with bone metastasis. No hospital stay required an intensive care unit.

Safety

Overall, 69 adverse events were reported in 42.2% of the patients (95% confidence interval (CI) for the percentage: 28.9–57.2). Sixty-five percent of adverse events were drug-related. They occurred in 33.3% of the patients (95% CI: 22.2–48.6). None of the patients died during the study. Four adverse events reported in 6.7% of the patients (95% CI: 2.2–14.2) were serious (asthenia, hypersensitivity, wound infection, haemothorax), including two drug-related (hypersensitivity and wound infection) reported in 4.4% (95% CI: 0.0–9.0). All four severe adverse events reported in 4.4% of the patients were drug-related. They included hypersensitivity, skin toxicity, rash and wound infection. Two adverse events resulted in study drug discontinuation. Frequencies of adverse events are summarized in Table IV.

The most frequent adverse events overall were fatigue (14.5% of events) and musculoskeletal pain (11.6%), both reported in 6.7% of the patients. The most common drug-related adverse events were musculoskeletal pain (17.8% of drug-related events) and myalgia (11.1%), both in 6.7% of the patients, followed by fatigue (11.1%) in 4.4%. Adverse events overall and drug-related are summarized in Table V.

Discussion

This exploratory analysis from an observational study of lipegfilgrastim for the prophylaxis of chemotherapy-induced neutropenia in breast cancer patients in Poland showed that nearly 100% of the planned cumulative doses of various chemotherapy regimens across all cycles were administered. None of the patients required omissions of chemotherapy treatment and very few dose reductions were needed. Treatment delays were infrequent and their duration moderate.

In a phase III study of lipegfilgrastim versus pegfilgrastim in breast cancer patients treated with doxorubicin and docetaxel 98.8% to 99.3% of the planned chemotherapy doses were administered in the lipegfilgrastim group [10]. In our study doxorubicin/docetaxel accounted for almost 25% of chemotherapy regimens and the percentage of the planned doses actually administered across all regimens was even higher. The incidence of chemotherapy delays in a cycle was higher than in the phase III study (the highest 22.6% vs. 16.2%) (data not shown), and the average delay across all cycles was longer (median: 7.0, range: 1.0–77.0 vs. median: 0.0, range: 0.0–14.0 days) [10]. In the Protroca study, assessing the effectiveness and safety of lipegfilgrastim in non-selected breast cancer patients, the incidence of delay of chemotherapy was similar to our study [11]. Timmer-Bonte *et al.* reported higher rates of delay, but their study also included patients with haematological malignancies and solid tumours other than breast cancer [12]. Febrile neutropenia is rare with lipegfilgrastim. It was seen in approximately 1% of patients in another analysis of the already mentioned phase III study [9]. In turn, in the dose-finding phase II study of lipegfilgrastim 3.0, 4.5 or 6 mg in breast cancer patients treated with doxorubicin/docetaxel 3.9% and 6% of the patients experienced FN with 4.5 and 6.0 mg doses of lipegfilgrastim, respectively [13]. The incidence of FN in our analysis was 2.2%. Only two out of 15 episodes of neutropenia were severe,

Table III. Frequencies of chemotherapy cycles delays, dose reductions, omissions and percentages of planned cumulative dose actually administered

Variable	Patients (n = 45)/Cycles (n = 212)	95% confidence interval
No. of patients with delayed chemotherapy cycles (%)	19 (42.2)	28.0, 57.8
No. of delayed chemotherapy cycles (%)	31 (14.6)	10.4, 19.4
Duration of chemotherapy delays across all cycles [days]:		
Mean (± standard deviation)	10.3 (14.9)	
Median (range)	7.0 (1.0–77.0)	6.9, 7.1
Percentage of planned cumulative chemotherapy dose actually administered across all cycles*:		
Mean (± standard deviation)	99.9 (2.0)	
Median (range)	100 (78.1–118.7)	100.0, 100.0
Percentage of planned cumulative chemotherapy dose actually administered across all cycles and drugs**:		
Mean (± standard deviation)	100 (0.40)	
Median (range)	100 (98.6–102.1)	100.0, 100.0
No. of patients with chemotherapy cumulative dose reductions (%)	2 (4.4)	0.0, 9.0
No. of cycles with chemotherapy cumulative dose reductions (%)	3 (1.4)	0.5, 3.0
No. of patients with omitted cycles (%)	0	
No. of omitted cycles (%)	0	

**In each cycle for each patient the average percentage of planned dose actually administered across drugs was calculated. **For each patient the average planned dose actually administered across drugs and cycles was calculated.*

Table IV. Frequencies of adverse events

Variable	Adverse events overall	Drug-related adverse events
No. of patients with adverse event (%)	19 (42.2)	15 (33.3)
No. of adverse events (%)	69 (100.0)	45 (65.2)
No. of patients with serious adverse event* (%)	3 (6.7)	2 (4.4)
No. of serious adverse events (%)	4 (5.8)	2 (2.9)
No. of patients with severe adverse event** (%)	2 (4.4)	2 (4.4)
No. of severe adverse events (%)	4 (5.8)	4 (5.8)
No. of patients discontinued study drug due to adverse events (%)***	2 (4.4)	2 (4.4)

**Serious adverse event was an adverse event that resulted in death, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, or was a congenital anomaly/birth defect or was life-threatening or required medical intervention to prevent the above outcomes. **According to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) 'severe' refers to grade 3 severity of adverse events, which includes severe or medically significant but not immediately life-threatening events; indication for hospitalization or prolongation of hospitalization; disabling; limiting self-care activities of daily living, e.g., bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and not being bedridden. ***One observation was missing.*

which corresponds to an incidence of 4.4%. In the aforementioned phase II and III studies the incidence of severe neutropenia was substantially higher, i.e. depending on the cycle 8% to 38% (with a 6 mg dose of lipegfilgrastim) and 8.5% to 43.6% (50% across all cycles), respectively, with the highest values in cycle 1 [9, 13].

In our study typical chemotherapy-induced adverse drug reactions were recorded only if they were more severe or more frequent than expected from the treatment or the medical condition. Therefore, the majority of adverse events were drug-related. The incidence of drug-related adverse events (33.3%) was slightly higher than in the phase III study by Bondarenko *et al.* of breast cancer patients treated with lipegfilgrastim or pegfilgrastim in which drug-related adverse events occurred in 27.7% and 25.7% of the patients, re-

Table V. Adverse events overall and drug-related

Adverse event*	Number of patients (%)**	Number of events (%)	Number of patients (%)**	Number of events (%)
	Overall		Drug-related	
Fatigue	3 (6.7)	10 (14.5)	2 (4.4)	5 (11.1)
Musculoskeletal pain***	3 (6.7)	8 (11.6)	3 (6.7)	8 (17.8)
Pyrexia	2 (4.4)	6 (8.7)	1 (2.2)	1 (2.2)
Myalgia***	3 (6.7)	5 (7.2)	3 (6.7)	5 (11.1)
Headache	2 (4.4)	4 (5.8)	1 (2.2)	1 (2.2)
Arthralgia***	1 (2.2)	3 (4.3)	1 (2.2)	3 (6.7)
Spinal pain	1 (2.2)	3 (4.3)	0	0
Hyperaesthesia	1 (2.2)	3 (4.3)	1 (2.2)	3 (6.7)
Bone pain***	2 (4.4)	2 (2.9)	2 (4.4)	2 (4.4)
Asthenia	2 (4.4)	2 (2.9)	1 (2.2)	1 (2.2)
Chest pain	1 (2.2)	2 (2.9)	0	0
Immune thrombocytopenic purpura	1 (2.2)	1 (1.4)	0	0
Vomiting	1 (2.2)	1 (1.4)	1 (2.2)	1 (2.2)
Influenza-like illness	1 (2.2)	1 (1.4)	1 (2.2)	1 (2.2)
Malaise	1 (2.2)	1 (1.4)	0	0
Hypersensitivity	1 (2.2)	1 (1.4)	1 (2.2)	1 (2.2)
Face oedema	1 (2.2)	1 (1.4)	1 (2.2)	1 (2.2)
Infection	1 (2.2)	1 (1.4)	1 (2.2)	1 (2.2)
Periodontitis	1 (2.2)	1 (1.4)	1 (2.2)	1 (2.2)
Pharyngitis	1 (2.2)	1 (1.4)	0	0
Rhinitis	1 (2.2)	1 (1.4)	0	0
Wound infection	1 (2.2)	1 (1.4)	1 (2.2)	1 (2.2)
Body temperature increased	1 (2.2)	1 (1.4)	1 (2.2)	1 (2.2)
Back pain***	1 (2.2)	1 (1.4)	1 (2.2)	1 (2.2)
Pain in extremity***	1 (2.2)	1 (1.4)	1 (2.2)	1 (2.2)
Insomnia	1 (2.2)	1 (1.4)	1 (2.2)	1 (2.2)
Haemothorax	1 (2.2)	1 (1.4)	0	0
Rash	1 (2.2)	1 (1.4)	1 (2.2)	1 (2.2)
Papular rash	1 (2.2)	1 (1.4)	1 (2.2)	1 (2.2)
Skin exfoliation	1 (2.2)	1 (1.4)	1 (2.2)	1 (2.2)
Skin toxicity	1 (2.2)	1 (1.4)	1 (2.2)	1 (2.2)
Exfoliative rash	1 (2.2)	1 (1.4)	1 (2.2)	1 (2.2)

**Typical chemotherapy-induced adverse drug reactions were exempt from recording unless they were more severe or more frequent than expected from the treatment, summary of product characteristics, or the medical condition. **Patients could have more than one adverse event. ***Bone pain-related symptoms occurred in a total of 7 (15.6%) patients with drug-related adverse events. All bone pain-related symptoms were classified as drug-related.*

spectively [9]. The incidence of severe drug-related adverse events was low (4.4%), but also slightly higher than in the phase III study (1.0%) [9].

The observed safety profile was typical for G-CSFs with musculoskeletal pain, myalgia and fatigue as the most commonly observed adverse events. Bone pain-related symptoms are commonly associated with G-CSF therapy [14]. Overall, musculoskeletal pain (17.8% of events), myalgia (11.1%), arthralgia (6.7%), bone pain (4.4%), back pain and pain in an extremity (2.2% each) accounted for 44.4% of drug-related adverse events reported in 15.6% of the patients. All bone pain-related symptoms were classified as drug-related. The incidence of bone pain-related symptoms was slightly lower compared to that observed in randomized trials. In an integrated analysis from phase II [13] and III [9] studies in patients with breast cancer treated with lipegfilgrastim or pegfilgrastim, the incidence of bone pain-related adverse events was 25.2% and 21.9%, respectively, and bone pain-related events

associated with G-CSF 18.5% and 16.8%, respectively [15]. Nonsteroidal anti-inflammatory drugs and/or acetaminophen were used to manage the symptoms, or they resolved without treatment. In one case, musculoskeletal pain resulted in study drug discontinuation.

The limitation of the presented analysis is the relatively small sample size of 45 patients. Patients were enrolled in various cycles, as some patients had no indication for G-CSF therapy from the first chemotherapy cycle, and thus drug exposure may have been lower than in clinical trials.

In conclusion, lipegfilgrastim proved to be effective and well tolerated for CIN prophylaxis in patients with breast cancer receiving myelosuppressive chemotherapy in a real-life setting. The average cumulative dose was nearly 100%, although the dose intensity may have been slightly lower compared to previous experience due to longer delays. One FN and very rare severe neutropenia were observed. The safety profile was consistent with that of a G-CSF therapy.

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Conflict of interest

Streb J and Kucharz J were investigators in the LEOS study. Lipa A, Strzondała M are employees of Teva Pharmaceuticals Polska Sp. z o.o. Wysocki PJ declares no conflict of interest.

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