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ORIGINAL ARTICLE

Chemotherapy-associated treatment burden in breast cancer patients receiving lipegfilgrastim or pegfilgrastim: secondary efficacy data from a phase III study

Oleg A. Gladkov[1] · **Anton Buchner**[2] · **Peter Bias**[3] · **Udo Müller**[3] · **Reiner Elsässer**[3]

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Abstract
Purpose Lipegfilgrastim is a once-per-cycle glycoPEGylated granulocyte colony-stimulating factor (G-CSF). Noninferiority of lipegfilgrastim versus pegfilgrastim was demonstrated in a phase III trial in chemotherapy (CTx)-naïve breast cancer patients. Secondary outcomes relating to treatment burden are reported here.
Methods Patients with high-risk stage II, III, or IV breast cancer were randomized to receive lipegfilgrastim 6 mg (n=101) or pegfilgrastim 6 mg (n=101) subcutaneously on day 2 of each CTx cycle. Doxorubicin 60 mg/m^2 plus docetaxel 75 mg/m^2 commenced on day 1, for up to four cycles. Secondary end points included days in the hospital or intensive care unit (ICU), use of intravenous antibiotics for febrile neutropenia (FN) or related infections, and measures of CTx delivery (dose delays, reductions, and omissions).
Results One lipegfilgrastim recipient and two pegfilgrastim recipients were hospitalized in cycle 1 because of FN or associated infection. The lipegfilgrastim-treated patient spent 1 day in the ICU for FN, and the two pegfilgrastim-treated patients were hospitalized for FN for 5 and 6 days, respectively. All hospitalized patients received antibiotics. An additional pegfilgrastim-treated patient received antibiotics but was not hospitalized. Most patients received CTx as scheduled; over 98 % received their planned doxorubicin and docetaxel doses in all cycles. In the lipegfilgrastim group, no patients had a CTx dose reduced or omitted; eight patients in the pegfilgrastim group had a CTx dose reduced or omitted during cycles 2–4.
Conclusions The burden of treatment associated with myelosuppressive CTx was similar in breast cancer patients treated with lipegfilgrastim or pegfilgrastim.

Keywords Granulocyte colony-stimulating factor · Antibiotics · Febrile neutropenia · Breast neoplasms · Hospitalization

Introduction

Myelosuppressive chemotherapy (CTx) frequently results in neutropenia, which adds to the overall burden of disease and treatment in patients with cancer [1, 2]. The development of neutropenia increases the risk of infection and febrile neutropenia (FN), which requires hospitalization and intravenous (IV) antibiotic treatment [1]; these complications may cause dose reductions or delays in subsequent CTx cycles [1]. Prophylactic therapy with granulocyte colony-stimulating factors (G-CSFs) is recommended to ameliorate CTx-related neutropenia [3–5]. Current treatment guidelines from the American Society of Clinical Oncology, the National Comprehensive Cancer Network, the European Organisation for Research and Treatment of Cancer, and the European Society for Medical Oncology recommend G-CSF prophylaxis in patients receiving CTx whose risk of developing FN is 20 % or higher [4–7].

Filgrastim (Neupogen®; Amgen Inc., Thousand Oaks, California) was the first G-CSF introduced into clinical practice (in 1991), providing a means of preventing and managing FN but requiring daily subcutaneous (SC) injections [8]. The covalent attachment of polyethylene glycol (PEG) extends the

✉ Oleg A. Gladkov
gladkov_o@rambler.ru

[1] Chelyabinsk Regional Clinical Oncology Dispensary, 42 Blukhera str, Chelyabinsk 454087, Russian Federation

[2] Merckle GmbH, Graf-Arco-Strasse 3, 89079 Ulm, Germany

[3] Teva Ratiopharm, Graf-Arco-Strasse 3, 89079, Ulm, Germany

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half-life of G-CSFs, and PEGylated G-CSFs such as pegfilgrastim (Neulasta®; Amgen Inc.) require less-frequent, once-per-cycle administration [9, 10]. Lipegfilgrastim (Lonquex®; Teva Pharmaceuticals Industries Ltd, Petach Tikva, Israel) is a new, long-acting, once-per-cycle glycoPEGylated G-CSF recently approved by the European Medicines Agency for reducing the duration of neutropenia and the incidence of FN in patients receiving myelosuppressive CTx [11]. In a phase III noninferiority trial conducted in CTx-naïve patients with breast cancer, lipegfilgrastim was noninferior to pegfilgrastim with respect to duration of severe neutropenia (absolute neutrophil count [ANC] $<0.5\times10^9$/L) in cycle 1 (0.7 vs. 0.8 days, respectively; least-squares mean difference, −0.218, 95 % confidence interval, −0.498, 0.062) [12]. Severe neutropenia also occurred at a similar rate in both treatment groups: 44 % with lipegfilgrastim and 51 % with pegfilgrastim. The safety profiles were similar between the two regimens, with most treatment-emergent adverse events consistent with the effects of CTx or the underlying disease. The rates of bone pain–related symptoms, commonly associated with G-CSF therapy, were also similar (23.8 % with lipegfilgrastim and 16.8 % with pegfilgrastim).

The objective of the analysis described here was to examine the burden of treatment experienced by patients receiving lipegfilgrastim or pegfilgrastim who participated in this phase III trial, based on the incidence and duration of hospitalizations related to FN, IV antibiotic use, and CTx dose delays, reductions, or omissions.

Methods

This was a multinational, multicenter, randomized, double-blind, active-controlled, phase III trial. Full details of the study design, patient population, treatment procedures, and schedule of assessments have been reported elsewhere [12].

Study population

In brief, the patient population included CTx-naïve men and women aged ≥18 years with high-risk stage II, III, or IV breast cancer and eligible to receive four cycles of docetaxel/doxorubicin. An Eastern Cooperative Oncology Group (ECOG) performance status ≤2, ANC 1.5×10^9/L, platelet count $\geq100\times10^9$/L, and adequate hepatic (alanine aminotransferase and aspartate aminotransferase <2.5 times upper limit of normal [ULN], alkaline phosphatase <5 times ULN, and bilirubin <ULN), cardiac (left ventricular ejection fraction ≥50 % as assessed by echocardiography or equivalent method within 4 weeks prior to randomization), and renal function (creatinine <1.5 times ULN) were also required. Key exclusion criteria included previous exposure to a G-CSF <6 months before randomization, treatment with systemically active antibiotics within 72 h before CTx, chronic use of oral corticosteroids or planned use of lithium during the study, radiation therapy or tumor surgery ≤4 weeks prior to randomization, history of malignancy (except basal or squamous cell carcinoma) ≤5 years prior to randomization, and previous bone marrow or stem cell transplantation.

Treatments

Each patient could receive up to four CTx cycles (3 weeks per cycle). On day 1 of each cycle, patients received 60 mg/m^2 doxorubicin as an IV bolus injection followed 1 h later by 75 mg/m^2 docetaxel administered as an IV infusion over at least 1 h. On day 2 of each cycle, patients received a single dose of either lipegfilgrastim 6 mg SC or pegfilgrastim 6 mg SC (each in 0.6 mL sterile solution) in the abdomen, upper arm, or thigh. Each drug was administered at room temperature, after blood sampling for ANC and measurement of body temperature.

In the event of FN and/or ANC 0.5×10^9/L lasting longer than 1 week, the docetaxel dose was reduced to 60 mg/m^2 and the doxorubicin dose to 45 mg/m^2. Docetaxel dose reduction to 45 mg/m^2 was also warranted for severe or cumulative cutaneous toxicity or grade 3 or 4 peripheral neuropathy, with both docetaxel and doxorubicin dose reductions of 25 % for platelet count $<20\times10^9$/L and/or failure to recover to $\geq100\times10^9$/L at day 21 of a cycle. Treatment discontinuation with study withdrawal was warranted for patients with continued reactions at these lower doses and for any occurrences of symptomatic pleural effusion, liver enzyme elevations above those specified for study enrollment, signs and symptoms of worsening cardiac function, treatment delays beyond 2 weeks, or clear clinical and/or radiologic evidence of progressive disease.

Prophylaxis with systemically (i.e., IV, intramuscular, or oral) active antibiotics was not permitted during the study, except for patients with an individual high risk of infection as determined by the investigator. If clinically necessary, antibiotic therapy was allowed for any increased temperature of >38.5 °C orally if associated with neutropenia (i.e., ANC value $<0.5\times10^9$/L), as well as for any other microbiologically, clinically, or radiologically documented infection or medically relevant infection. Antibiotics were stopped at least 72 h before the next CTx cycle. If longer antibiotic treatment was necessary, the next CTx cycle was postponed.

Efficacy assessments and analysis

Several secondary end points were used to assess burden of treatment in this study, and the following are reported here: number of patients hospitalized and amount of time (days) in the hospital and in the intensive care unit (ICU) due to FN or related infections; number of patients treated with IV

antibiotics because of FN or related infections; actual versus scheduled cumulative CTx dose delivered per patient, per CTx cycle; the proportion of patients with reduced, omitted, or delayed CTx doses; and the duration of CTx delays.

Efficacy assessments were analyzed using both the intent-to-treat (ITT) population, comprising all patients randomized to study treatment at baseline, and the per-protocol population, comprising all randomized patients without any major protocol violation. Results from the per-protocol population are not reported in this article. The secondary end points reported here were summarized using descriptive statistics, including frequency counts, mean, standard deviation, range, and minimum and maximum values.

Results

Full results of the primary efficacy and safety analyses have been reported elsewhere [12].

Patients

A total of 202 patients were randomized to either lipegfilgrastim (n=101) or pegfilgrastim (n=101); 95 and 98 patients, respectively, completed the trial. Of the nine patients who discontinued (lipegfilgrastim n=6; pegfilgrastim n=3), reasons for discontinuation were withdrawal of consent (lipegfilgrastim n=2; pegfilgrastim n=1), adverse events (lipegfilgrastim n=1, pegfilgrastim n=2), and one case each of death, disease progression, and "other" (all in the lipegfilgrastim group).

Baseline demographic and clinical characteristics were comparable between the lipegfilgrastim and pegfilgrastim groups (Table 1). All patients were white women with a good ECOG performance status (0 or 1), 50 % were postmenopausal, 83 % had stage III or high-risk stage II breast cancer, and 74 % were receiving docetaxel/doxorubicin as adjuvant CTx.

Hospitalizations, ICU care, and antibiotic use

In the ITT population, three patients were hospitalized during cycle 1 due to FN or related infection: one patient (for a duration of 1 day) in the lipegfilgrastim group and two patients (for durations of 5 and 6 days, respectively) in the pegfilgrastim group (Table 2) [12]. There were no hospitalizations in either group during cycles 2, 3, or 4. The patient in the lipegfilgrastim group who was hospitalized due to FN was admitted to the ICU for a duration of 1 day due to an ANC $<0.5\times10^9$/L for the previous 3 days and later died of FN 9 days after the first cycle of CTx (8 days after the first and only dose of study medication). An autopsy was performed, and enterocolitis was proven as the cause of death.

Table 1 Baseline demographics and clinical characteristics (ITT population)

Variable	Lipegfilgrastim 6 mg (n=101)	Pegfilgrastim 6 mg (n=101)
Mean age (SD), years	49.9 (10.1)	51.1 (9.4)
≤64 years, n (%)	94 (93.1)	94 (93.1)
65–74 years, n (%)	7 (6.9)	7 (6.9)
Female, n (%)	101 (100)	101 (100)
White, n (%)	101 (100)	101 (100)
Reason for chemotherapy, n (%)		
Adjuvant therapy	75 (74.3)	74 (73.3)
Metastatic disease	26 (25.7)	27 (26.7)
Stage, n (%)		
High-risk stage II	39 (38.6)	36 (35.6)
Stage III	48 (47.5)	45 (44.6)
Stage IV	14 (13.9)	20 (19.8)
ECOG performance status, n (%)		
0	45 (44.6)	47 (46.5)
1	56 (55.4)	54 (53.5)
2	0	0

Adapted with permission from Bondarenko et al [12]

ECOG Eastern Cooperative Oncology Group, *ITT* intent-to-treat, *SD* standard deviation

All three patients who were hospitalized for FN received IV antibiotics, and the lipegfilgrastim recipient was also managed with antipyretics [12]. An additional patient in the pegfilgrastim group who was not hospitalized also received IV antibiotics for FN in cycle 1 [12].

CTx density, intensity, and planned versus actual dosing

The proportions of patients in each group with CTx dose delays, reductions, or omissions are summarized in Table 3. The majority of patients in both treatment groups received their CTx as scheduled. Fewer than 20 % of patients in either group experienced a CTx dose delay, and dose delays were brief,

Table 2 Incidence and duration of FN-related hospitalizations and ICU care in chemotherapy cycle 1 (ITT population)

	Lipegfilgrastim 6 mg (n=101)	Pegfilgrastim 6 mg (n=101)
Hospitalization, n (%)	1 (1.0)[a]	2 (2.0)
Time in hospital, days, mean (SD)	1 (0)	5.5 (0.7)
ICU care, n (%)	1 (1.0)	0
Time in ICU, days, mean (SD)	1 (0)	0

FN febrile neutropenia, *ICU* intensive care unit, *ITT* intent-to-treat, *SD* standard deviation

[a] No patients were hospitalized or admitted to the ICU during chemotherapy cycles 2, 3, or 4

Table 3 Incidence of chemotherapy dose delays, reductions, or omissions (ITT population)

	Lipegfilgrastim 6 mg	Pegfilgrastim 6 mg
Patients with chemotherapy delays, *n* (%)[a]		
Cycle 2	16 (16.2)	15 (15.0)
Cycle 3	14 (14.3)	17 (17.3)
Cycle 4	4 (4.2)	9 (9.2)
Duration of chemotherapy delays across cycles, days		
Mean (SD)	1.9 (3.5)	2.2 (4.1)
Median (range)	0.0 (0.0–14.0)	0.0 (0.0–29.0)
Patients with chemotherapy dose reductions/omissions, *n* (%)[a]		
Cycle 2	0	4 (4.0)
Cycle 3	0	2 (2.0)
Cycle 4	0	2 (2.0)

ITT intent-to-treat, *SD* standard deviation

[a] Data shown based on the ITT patients remaining enrolled in the study at each cycle; lipegfilgrastim group: cycle 1, *n*=101; cycle 2, *n*=99; cycle 3, *n*=98; cycle 4, *n*=95; pegfilgrastim group: cycle 1, *n*=101; cycle 2, *n*=100; cycles 3 and 4, *n*=98

Table 4 Percentage of planned chemotherapy dose actually administered (ITT population)

	Lipegfilgrastim 6 mg	Pegfilgrastim 6 mg
Mean percentage of planned doxorubicin dose administered (SD)[a]		
Cycle 1	99.1 (1.9)	99.3 (1.8)
Cycle 2	98.7 (2.9)	98.2 (5.1)
Cycle 3	98.8 (2.9)	98.3 (5.2)
Cycle 4	98.9 (2.9)	98.4 (5.1)
Mean percentage of planned docetaxel dose administered (SD)[a]		
Cycle 1	99.3 (1.6)	99.2 (2.3)
Cycle 2	98.9 (2.7)	98.2 (4.8)
Cycle 3	98.9 (2.8)	98.3 (4.7)
Cycle 4	98.9 (2.8)	98.3 (4.8)

ITT intent-to-treat, *SD* standard deviation

[a] Data shown based on the ITT patients remaining enrolled in the study at each cycle; lipegfilgrastim group: cycle 1, *n*=101; cycle 2, *n*=99; cycle 3, *n*=98; cycle 4, *n*=95; pegfilgrastim group: cycle 1, *n*=101; cycle 2, *n*=100; cycles 3 and 4, *n*=98

with a mean delay of 1.9 days for the lipegfilgrastim group and 2.2 days for the pegfilgrastim group (Table 3). In the lipegfilgrastim group, no patients had a CTx dose reduced or omitted; eight patients in the pegfilgrastim group had a CTx dose reduced or omitted during cycles 2–4. For patients with a CTx dose reduction, the mean doxorubicin dose was reduced to 45.0 mg/m^2 and the mean docetaxel dose was reduced to 58.0 or 59.0 mg/m^2.

In both the lipegfilgrastim and pegfilgrastim groups, >98 % of the planned doses of doxorubicin and docetaxel were administered in each CTx cycle (Table 4).

Discussion

In this phase III study, patients with breast cancer undergoing CTx with doxorubicin and docetaxel and receiving lipegfilgrastim or pegfilgrastim as prophylaxis for neutropenia experienced comparable low incidences and durations of FN-related hospitalizations and IV antibiotic treatment. Chemotherapy treatment delays were infrequent and brief in both groups and few patients required dose reductions or omissions.

A prior dose-finding phase II study of lipegfilgrastim 3, 4.5, or 6 mg in a doxorubicin/docetaxel-treated breast cancer population identified the 6-mg dose as optimal, having efficacy and safety profiles comparable with those of pegfilgrastim 6 mg [13]. Pegfilgrastim was selected as an appropriate active control arm in that study and the current phase III study, with ethical considerations precluding the use of a placebo comparator for a CTx regimen associated with a FN rate of approximately 40 % in the present study. A number of prospective studies of the efficacy and safety of pegfilgrastim were conducted exclusively in breast cancer populations or had study populations that had a high proportion of patients with breast cancer, given the frequent use of myelosuppressive regimens such as taxane-based combinations in this setting [14–18]. Some of these studies and additional prospective trials and retrospective series in a variety of different populations (including but not limited to breast cancer) collectively demonstrate that pegfilgrastim treatment significantly reduces FN [17–21] and/or significantly reduces rates of associated hospitalization [18, 19, 21–23] relative to its predecessor, filgrastim. A review of available literature for these two particular G-CSFs for preventing chemotherapy-induced FN found that in studies of patients with breast cancer, pegfilgrastim was significantly more effective than filgrastim in terms of FN incidence (except in a study in which it was given on day 1), with additional evidence of reduced hospitalizations and cost-effectiveness for pegfilgrastim [24]. One early study of weight-based dosing of pegfilgrastim versus filgrastim was conducted in patients with high-risk stage II or III/IV breast cancer receiving the same CTx combination used in the present study, up to four cycles of doxorubicin 60 mg/m^2 plus docetaxel 75 mg/m^2 [20]. In that study, the primary end point of duration of severe neutropenia (DSN) in cycle 1 was similar between the two groups; however, DSN was significantly shorter with pegfilgrastim in cycles 2–4 and the incidence of FN with pegfilgrastim was half that with filgrastim, a significant difference (9 vs. 18 %; P=0.029). Data for the outcomes of hospitalization, antibiotic use, and

CTx delivery for lipegfilgrastim versus pegfilgrastim were not available for the previous phase II lipegfilgrastim study. Subsequently, a placebo-controlled phase III trial evaluated pegfilgrastim 6 mg (as used for the control regimen of the current study) among breast cancer patients receiving up to four cycles of docetaxel 100 mg/m^2 every 3 weeks, a regimen for which the expected incidence of FN is in the range of 10 to 20 % [25]. Pegfilgrastim was initiated the day after the first cycle, with the proportions of patients requiring FN-related hospitalization, receiving IV antibiotics, and maintaining the planned CTx dose for cycles 2–4 as the secondary end points. Pegfilgrastim was associated with incidences of FN (primary end point), FN-related hospitalization, and IV antibiotic use of 1, 1, and 2 %, respectively, all of which were significantly ($P<0.001$) lower than the corresponding rates in the placebo group (17, 14, and 10 %, respectively). Although both groups had a similar proportion of patients without CTx delays (80 % with pegfilgrastim versus 78 % with placebo), this was likely a reflection of the study design, as patients with FN during the double-blind treatment period were to receive open-label pegfilgrastim for the remaining cycles. Our results support the use of long-acting glycoPEGylated products in reducing the risk of not only FN but also hospitalizations and antibiotic use, with no differences between lipegfilgrastim and pegfilgrastim in any of these outcomes, based on observations to date. Given the costs and risk of mortality that are inherently associated with neutropenia-related hospitalization [26], long-acting glycoPEGylated products hold potential for influencing real-world outcomes from a broader perspective than that typically considered as part of the regulatory approval of these products.

Patient preferences and potential out-of-pocket costs are key considerations that may influence clinical decision-making in routine oncology practice, especially in the current era in which there is a continually growing list of treatment options. A recent US survey of preferences among patients with breast cancer found that while patients prefer G-CSF regimens with the lowest out-of-pocket cost, they also prefer those that confer improved clinical outcomes (in the form of keeping to their scheduled CTx regimen and reducing infection-related hospitalization risk) and greater convenience (in the form of single injections per cycle) [27]. Factors that were associated with a willingness to pay higher out-of-pocket costs included the ability to reduce the risks of a CTx delay and infection-related hospitalization, as well as the number of per-cycle G-CSF injections from 11 to 1. Considering that cost of treatment may be the paramount factor from a patient perspective, the potential out-of-pocket costs that may arise from a FN-related complication and/or hospitalization are an important part of the overall equation when discussing the available options for G-CSF prophylaxis, and may help to guide the selection of glycoPEGylated products. In the context of this cost discussion, it is important to keep in mind the difference in the number of clinic visits that are required for use of filgrastim relative to longer-acting products that require only a single visit, which has been shown to translate into lower human resource costs [28].

Limitations of this analysis include the relatively small sample size, consisting of about 200 patients between the two arms, and the lack of formal statistical comparisons. This study also provides no insight into the relative efficacy of these products in patients receiving other types of myelosuppressive CTx regimens for breast cancer or other common malignancies. Additionally, given the strict guidelines for detecting and managing FN that are outlined as part of clinical trial protocols, these results are not necessarily representative of what might be expected in routine practice. Future investigations should include a continued focus on developing increasingly reliable predictive models to identify patients at the highest risk of FN who may remain susceptible despite the use of glycoPEGylated products and would benefit from added preventative measures, such as closer monitoring and broader antibiotic coverage [29]. Such models may largely rely on the ability to quantify patient-to-patient variability in CTx exposure, which is inherently challenging.

In conclusion, these findings demonstrate that patients with breast cancer undergoing CTx and receiving lipegfilgrastim or pegfilgrastim experience similarly low burdens of treatment related to FN, with no clinically relevant differences in CTx dose density or intensity.

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Conflict of interest Oleg A. Gladkov declares that he has no conflict of interest. Anton Buchner is an employee of Merckle GmbH. Peter Bias, Udo Müller, and Reiner Elsässer are employees of Teva Ratiopharm.

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