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Prophylaxis of Neutropenia with Lipegfilgrastim in Breast Cancer Patients with Dose-Dense Chemotherapy: Results of a Noninterventional Study on Therapeutic Routine in Germany (NADENS)

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Keywords
Breast cancer · Dose-dense chemotherapy · Chemotherapy-induced neutropenia · Febrile neutropenia · Lipegfilgrastim

Abstract
Introduction: Noninterventional study (NIS) on application and effectiveness of primary G-CSF prophylaxis with lipegfilgrastim in primary breast cancer patients undergoing dose-dense (dd) or intense-dose-dense (idd) chemotherapy (CTx) regimen in daily clinical practice. ***Methods:*** Prospective, multicenter, single-arm, NIS in 41 private practices and 27 hospitals in Germany. ***Results:*** Data analysis of 282 patients with a mean age of 49 years (93.6% of patients <65 years) was performed. Hormone receptor status was triple negative in 29.8% of patients, and 81.9% of patients were HER2 negative. A total of 73.8% of patients received "EC dd → taxane CTx." Patients received lipegfilgrastim prophylaxis in 97.5% of 1,121 documented dd/idd cycles. Overall, the study registered 275 events of SN (CTCAE grade 3 or 4) and 9 events of FN. During the first dd cycle, SN occurred in 33.3% and FN in 1.1% of patients. CTx delay or dose reduction due to neutropenia was required in 2.5% of patients during the 4 dd cycles with lipegfilgrastim support. Overall, 314 adverse events (AEs) were reported from 107 patients and 27 serious AEs from 21 patients. None of the SAEs was "fatal," and CTCAE grade was mostly (89.6%) assessed as "1" or "2." According to the treating physicians, 99.3% of all patients benefitted from lipegfilgrastim prophylaxis, and tolerability was mostly rated "very good" or "good." ***Conclusion:*** These results suggest that primary lipegfilgrastim prophylaxis is effective and safe in clinical routine and is beneficial in primary breast cancer patients undergoing dd/idd-ETC CTx.

Introduction

Breast cancer is the most common type of cancer affecting women in industrialized countries. Worldwide, there are about 1,000,000 new cases of breast cancer per year [1]. According to current guidelines, dose-dense chemotherapy (ddCTx) is the recognized standard of care for high-risk breast cancer patients [2, 3]. It has significantly improved both overall survival and disease-free survival of early breast cancer patients [4]. A recent meta-analysis including 26 RCTs shows that ddCTx significantly reduces the 10-year risk of recurrence and breast cancer mortality without increasing the risk of death from other causes [5]. The principle of most ddCTx regi-

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mens is to shorten the treatment interval from 3 weeks to 1–2 weeks in order to increase the cytotoxic effect by shortening the recovery time of the proliferating tumor cells [6]. ddCTx is possible by the introduction of primary prophylaxis with granulocyte colony-stimulating factors (G-CSFs), i.e., G-CSF administration in the first cycle of chemotherapy (CTx) [7]. G-CSFs stimulate the growth and differentiation of neutrophil precursor cells and can contribute to reduce frequency, duration, and severity of febrile neutropenia (FN) in patients receiving CTx [8]. Severe neutropenia (SN) and FN are serious complications of myelosuppressive CTx and may compromise its therapeutic success [1, 9, 10]. Possible consequences of neutropenia include the patients' hospitalization, administration of intravenous antibiotic therapy, and intensive care. Furthermore, dose reduction or postponement of CTx cycles is often necessary, considerably impairing the success of treatment [11–14]. In addition, neutropenia, particularly FN, is associated with a substantial reduction in the quality of life of the patients [15]. Avoiding FN episodes is therefore an important therapeutic goal in chemotherapeutic treatment.

Prophylaxis with G-CSF significantly reduces the occurrence of FN episodes in breast cancer patients undergoing CTx. Prophylaxis with G-CSF significantly reduces the occurrence of FN episodes in breast cancer patients undergoing CTx, allowing maintenance of dose density and treatment success. A systematic review including 20 RCTs shows that primary prophylaxis with G-CSF in ddCTX improves survival in breast cancer patients [16]. Accordingly, primary prophylaxis with G-CSF represents an essential pillar of the treatment strategy and helps to improve CTx success and the survival of patients. According to current guidelines of the AGO, EORTC, and ASCO, primary prophylaxis with G-CSF is recommended for breast cancer patients with ddCTx [1, 17, 18]. To date, however, only very limited real-world data are available for this patient group. The aim of this noninterventional study (NIS) was to prospectively investigate the administration and effects of primary G-CSF prophylaxis with lipegfilgrastim in breast cancer patients with ddCTx in daily clinical practice.

Materials and Methods

This was a multicenter, single-arm, NIS conducted in private practices and hospitals in Germany. The study protocol was approved by the Ethics Committee of the Technical University Munich, Medical Department, and patients have given their written informed consent to participate in the study. Inclusion criteria were age above 18 years and primary breast cancer treated with ddCTx or intense-dose-dense (idd)-ETC CTx regimen given in a two-weekly schedule and supported by primary prophylaxis with Lonquex® (lipegfilgrastim) (Teva GmbH, Ulm, Germany). Lipegfilgrastim prophylaxis was prescribed to the best clinical judgment of the participating physicians and had to be administered according to the summary of product characteristics. Major exclusion criteria were pregnancy or lactation, advanced breast cancer (stage IV), and planned myelosuppressive or myeloablative therapy with stem cell support. The objective of this NIS was to monitor and further explore the management and outcome of patients with primary breast cancer treated with a dd two-weekly CTx regimen supported by primary prophylaxis with lipegfilgrastim in terms of clinical relevant neutropenia-induced complications as well as quality of life and health economics – under conditions of standard clinical practice. The primary endpoints were the occurrence of incidence of SN (NCI CTCAE grades 3–4) and FN within the first CTx cycle. Secondary objectives included (1) description of patient management under real-life conditions: reduction, delays, and omissions of the CTx dose in CTx treatment interval; (2) and resource utilization (i.e., days of hospitalization, days in intensive care unit, blood transfusion, antibiotic use). Data were collected as part of routine treatment and transferred pseudonymously from the medical records to electronic documentation forms by the respective center. Data were recorded at baseline (before start of the first dd cycle), 2-weekly during dd cycles 1–4, as well as 6–8 weeks after the last documented dd cycle and included the following: demographic data (including age, height, weight, ECOG status, breast cancer stage, and tumor biology), breast cancer history, concomitant diseases, CTx details, details of lipegfilgrastim prophylaxis, SN and FN episodes during CTx cycles 1–4, administration of anti-infectives and antibiotics, days of hospitalization, days in intensive care unit, and adverse drug reactions and other drug safety related issues. The analysis set includes all patients who meet all inclusion and none of the exclusion criteria and whose documentation has been performed and completed according to the protocol. An explorative data analysis was performed on a cycle basis and on a patient basis and included the number of observations, mean value, standard deviation, and the 95% confidence interval of the mean, as well as minimum, lower quartile (q1), median, up-

Table 1. Patient demographics and baseline breast cancer characteristics (n = 282)

Patient demographics	
Age, years; median (q1; q3)	50.0 (42; 57)
≥65 years, *n* (%)	18 (6.4)
Overweight/obesity, *n* (%)	150 (53.2)
ECOG/WHO status "0," *n* (%)	249 (88.3)
Breast cancer characteristics	
Stage (UICC) at baseline, *n* (%)	
0	2 (0.7)
I	46 (16.3)
IIA	89 (31.6)
IIB	61 (21.6)
IIIA	55 (19.5)
IIIB	11 (3.9)
IIIC	18 (6.4)
ER/PR status, *n* (%)	
ER–/PR–	110 (39.0)
ER–/PR+	7 (2.5)
ER+/PR–	32 (11.3)
ER+/PR+	131 (46.5)
HER2 status, *n* (%)	
Negative	231 (81.9)
Positive	50 (17.7)
TNBC, *n* (%)	84 (29.8)

Table 2. CTx characteristics on patient basis (n = 282)

CTx intention, *n* (%)	
Adjuvant	89 (31.6)
Neoadjuvant	193 (68.4)
Start of the first dd cycle	
Time since initial breast cancer diagnosis, days; median (q1; q3)	33.5 (23; 52)
In patients with adjuvant therapy	56 (44; 56)
In patients with neoadjuvant therapy	28 (20; 28)
CTx courses, *n* (%)	
EC dd → taxane	208 (73.8)
AC dd → taxane	7 (2.5)
A dd → taxane → C dd	2 (0.7)
Taxane → EC dd	14 (5.0)
Taxane → AC dd	1 (0.4)
E idd → taxane → C idd	50 (17.7)

per quartile (q3), and maximum for continuously scaled variables. For categorical characteristics, the absolute and relative frequencies were given.

Results

The study enrolled 328 patients from 27 hospitals and 41 private practices. Of these, 282 patients were included in the analysis set. Table 1 summarizes patient demographics and baseline disease characteristics. Mean patient age was 49 years with 93.6% of patients being younger than 65 years at enrollment. Median body mass index was 25.8, with 31.6% of all patients being overweight and 21.6% obese. The vast majority of patients (88.3%) did not report restrictions on quality of life (ECOG performance status "0"). For 45.4% of all patients, between 1 and 6 concomitant diseases were documented. Most commonly reported disease was "hypertension" (19.1% of all patients) followed by "hypothyroidism" (9.2%) and "depression" (3.9%). Surgery was performed in 35.8% of all patients prior to study enrollment, and 2.5% had received radiotherapy. Table 1 summarizes tumor staging and hormone receptor status. In this study, 18.1% of the tumors were HER2-enriched, and 29.8% were triple negative.

The first dd/idd-ETC cycle of current CTx started in median 33.5 days after initial cancer diagnosis (adjuvant patients: 56 days/neoadjuvant patients 28 days). Almost 1/3 of all patients (31.6%) underwent CTx with adjuvant intent, while 68.4% received CTx with neoadjuvant intent. The most common regimen was EC dd → taxane (73.8% of all patients). Table 2 summarizes further CTx regimens. Epirubicin was given to 96.4% of the patients, with only 3.6% receiving "doxorubicin." CTx plans included between 6 and 20 cycles, usually including 4 dd cycles (81.2%) or 6 idd cycles (17.7%). The study documented 1,121 dd/idd cycles, including 97.5% supported by lipegfilgrastim administered on the 2nd day of the cycle in 81.6% of the patients. Lipegfilgrastim was mostly administered subcutaneously (98.8%), by the patients themselves (56.5%) and preferably at home (63.9%).

Table 3. Incidence of severe and FN

	dd cycle 1	dd cycle 1–4
SN (CTCAE grade 3 or 4)		
Patients, *n* (%)	94 (33.3)	131 (46.5)
[95% CI]	[27.9; 39.2]	[40.5; 52.5]
SN events, *n*		275
FN		
Patients, *n* (%)	3 (1.1)	6 (2.1)
[95% CI]	[0.2; 3.1]	[0.8; 4.6]
		9

Incidence of SN and FN

Overall, 275 events of SN (CTCAE grade 3 or 4) and 9 events of FN occurred in this study during the 1,121 documented ddCTx cycles (Table 3). At least one SN occurred in 46.5% of the patients, 33.3% during the first cycle, 22.1% in cycle 2, 22.9% in cycle 3, and 19.8% in cycle 4. Table 3 summarizes the incidence of incidence of SN and FN.

CTx Modifications

CTx modifications such as delay of the CTx cycle, dose reduction, premature termination of CTx, or change to other CTx were documented at least once in 66 patients (23.4% of all patients; 95% CI: 18.6%; 28.8%) during 4 observed dd/idd-ETC cycles. For these 66 patients, 79 therapy modifications were documented. "Delay of cycle" was the most frequently documented modification on a patient basis with at least one entry in 48 patients (17% of all patients), followed by "dose reduction" (7 patients/2.5%). During the 4 cycles of CTx, neutropenia was the reason for delay of the CTx cycle or dose reduction in 2.5% of patients (on a per-cycle basis: 0.6% of all 1,121 dd

cycles). The proportion of CTx cycles with any therapy modifications was highest in cycle 4 (13.3%), followed by cycle 3 (8.2%) and cycle 2 (6.4%).

Resource Utilization

A total of 12.4% of patients were hospitalized, with 51 single hospitalizations having been documented. Median total duration of all hospitalizations per patient was 7 days, whereas each separate hospitalization event lasted in median 5 days. The following reasons were given for hospitalization: "Febrile neutropenia" (6 events), "other neutropenic complications" (5 events), and "infections" (7 events), while most frequently mentioned reasons were "other" (24 events) and "other toxicities in relation with CTx" (9 events). There were no admissions to the intensive care unit, and 15 blood transfusions occurred, resulting in one adverse event (AE) (4.3%). Overall, 34% of all patients received at least one anti-infective agent at least once during the observational period (218 documented treatments). The vast majority of patients (75% of patients with anti-infective treatment/25.5% of all patients) received "ciprofloxacin," followed by "cefuroxime" (14.6%/5.0%) as well as "sulfamethoxazole and trimethoprim" and "acyclovir" (each 4.2%/1.4%). The median cumulative dose during the observational period was 5 mg for "ciprofloxacin" and 6 mg for "cefuroxime."

Final Evaluation of Lipegfilgrastim Prophylaxis

At the end of the study, physicians evaluated efficacy and tolerability of lipegfilgrastim. According to the treating physicians, 99.3% of all patients benefitted from lipegfilgrastim prophylaxis. The main achievements most frequently mentioned were "adherence to scheduled treatment plan" (82.6% of all patients), "prevention of (febrile) neutropenia" (75.9%), and "prevention of infections" (44.3%). The tolerability of the lipegfilgrastim treatment was most often rated "very good" (53.9%) or "good" (42.6%) by the treating physicians, and "moderate" was documented for 2.8% and "poor" for 0.7% of all patients.

Safety

For 37.9% of patients (107/282), at least one AE was reported during the observational period (number of AE events: 314); for 7.4% of patients (21/282), at least one serious AE was observed (number of serious AE events: 27). None of these 314 documented AEs was "fatal," CTCAE grade was mostly assessed as "1" (43.8%) or "2" (45.8%), and only 3.6% of all AE events were rated as CTCAE grade "4." Overall, 58 patients experienced 88 ADRs with probable or possible causal relationship with at least one suspected drug including lipegfilgrastim, resulting in an ADR incidence of 20.6%. The most frequently reported ADRs fall under the system organ class "musculoskeletal and connective tissue disorders" (52 cases in 35 patients, 12.4% of all patients). At least one ADR was assessed as serious in 3.4% of all patients.

Discussion

In recent years, studies focusing on real-world populations of patients attracted increasing recognition. Real-world settings offer the advantage to recruit a broad range of patients including those that could never be included in a phase III trial, given the clear set of strict inclusion or exclusion criteria; another benefit of many noninterventional studies is the fact that they take into account the reality of how oncologists practice medicine [19]. The aim of the NIS NADENS was to monitor and further explore the management and outcome of patients with primary breast cancer treated with a dd two-weekly CTx regimen supported by primary prophylaxis with lipegfilgrastim in a real-world setting. The primary endpoints were the occurrence of the incidence of SN (NCI CTCAE grades 3–4) and FN within the first CTx cycle. Within 1,121 documented dd cycles, only 9 cases of FN and 275 cases of SN occurred.

The respective incidences for patients with FN were 1.1% (dd cycle 1) and 2.1% (all 4 dd cycles). Compared to the results from a meta-analysis of two RCTs assessing primary prophylaxis with lipegfilgrastim in breast cancer patients, the FN rate in cycle 1 is higher (1.1% vs. 0.7%). The higher FN rate within NADENS may be due to the more intense CTx regimen applied, the unselected patient population, and/or the prophylactic use of systemically active antibiotics in one RCT for patients at high risk for infection [20]. A recently published real-world study in BC patients (Protroca) showed for the subgroup of patients with primary prophylaxis comparable results: the observed rate of FN across up to 4 cycles of CTx is 2.25% versus 2.1% in NADENS [21]. SN was experienced in 33.3% of patients during the first dd cycle and in 46.5% of patients during the entire 4 documented dd cycles in NADENS. In the pivotal study, in which patients with stage II–IV BC received up to 4 cycles of doxorubicin and docetaxel, SN rates of 51.5% in cycle 1 and 58.5% over all CT cycles occurred. Overall, during 4 observed dd/idd-ETC cycles, a CTx modification (dose reduction, delay of cycle, premature termination of CTx, change to other CTx) occurred at least once in 66 patients, which accounts for 23.4% of all patients. A "delay of cycle" occurred in 17% of patients. Delay in CTx or dose reduction due to neutropenia was required during the 4 dd cycles with lipegfilgrastim support for 2.5% of all patients (0.6% of all dd cycles). In Protroca, 9.5% of patients with primary prophylaxis had dose reductions; in the pivotal trial, 30.7% had delayed CT treatment [22]. Investigators de-

cided on cycle delay or dose reduction in the NADENS study and in Protroca. In the pivotal trial, CTx was repeated on day 22 following the previous cycle and then hematologic parameters have recovered (ANC $\geq 1.5 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L). Overall, the drug-related AEs incidence was 20.6%, and drug-related SAEs occurred in 3.6% of the patients. Most frequently, these ADRs fall under the system organ class "musculoskeletal and connective tissue disorders" (12.4%) and "blood and lymphatic system disorders" (1.4%). Protroca showed 14.4% ADRs and 0.9% SADRs in patients with primary prophylaxis, most frequently documented as bone pain and thrombocytopenia with 10.9% and 3.6% of patients, respectively. RCTs in BC patients reported rates for bone pain as 20.0% and 23.8% in patients using lipegfilgrastim prophylaxis [22, 23]. Both noninterventional studies reported adverse drug reactions, and in addition, in routine clinical practice due to nonsystematic documentation, an underreporting of adverse drug reactions might occur. A positive assessment of lipegfilgrastim tolerability by the treating physician's, the low rate of AE with probable or possible causal relationship to lipegfilgrastim, and the physicians' evaluation that 99% of all patients benefitted from lipegfilgrastim treatment round up a positive overall assessment of lipegfilgrastim prophylaxis in daily clinical practice. Overall, lipegfilgrastim was effective and safe in this NIS, and results fall in the range of those observed in randomized clinical trials [22]. In conclusion, primary prophylaxis with lipegfilgrastim contributes to safe and effective ddCTx in the daily clinical treatment routine in hospitals and especially in outpatient centers. Observed adverse drug reactions were in line with the lipegfilgrastim summary of product characteristics. In addition, no new toxicities were identified.

Statement of Ethics

This noninterventional study was assessed by the Ethics Committee of the Technical University Munich, Medical Department (approval number 468/16 S) and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. All registered patients gave written informed consent for study participation.

Conflict of Interest Statement

M.K.: renumeration: Springer Press, Biermann Press, Celgene, AstraZeneca, Myriad Genetics, Teva, and Eli Lilly; consultant/advisory role: Myriad Genetics, Bavarian KVB, DKMS Life, BLAEK, and Teva; equity owner: Therawis Diagnostics GmbH and AIM GmbH; funding: SphingoTec, German Cancer Aid, German Research Council, BMBF, Senator Roesner Foundation, Dr. Pommer-Jung Foundation, Waltraut Bergmann Foundation, and Bavarian State Ministry of Economy. C.S., U.K.: advisory/consultancy/speaker bureau from Teva. D.L.: honoraria for advisory board activities and/or oral presentations from Amgen, AstraZeneca, Celgene, Lilly, L'Oreal, MSD, Mundipharma, Mylan, Novartis, Pfizer, Roche, Teva, and Tesaro. J.H.: employee of Teva. E.S: medical writer at Mediveritas.

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Author Contributions

Marion Kiechle, Joachim Hipp, and Eva Stetzer substantially contributed to the conception or design of the work; Marion Kiechle, Christian Schem, and Uwe Köhler contributed to the data acquisition. Marion Kiechle, Diana Lüftner, and Eva Stetzer contributed to analysis and interpretation of data for the work. Marion Kiechle and Eva Stetzer drafted the work and revised it critically for important intellectual content. All the authors finally approved the version to be published.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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