Prophylaxis of chemotherapy-induced neutropenia with Lipegfilgrastim in patients with breast cancer: Results from an interim analysis of the non-interventional study NADIR

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INTRODUCTION

Anthracycline and/or taxane-based chemotherapies are among the most effective treatments in breast cancer. However, many of the currently applied protocols, in particular dose-dense protocols increasingly applied in the (neo-) adjuvant setting with treatment intervals of ≤ 2 weeks, are associated with a significant incidence of febrile neutropenia thus necessitating a primary prophylaxis using granulocyte colony-stimulating factors (G-CSFs)[1].

Lipegfilgrastim is a glyco-pegylated G-CSF approved to reduce the duration of neutropenia and the incidence of febrile neutropenia. In the pivotal study by Bondarenko et al., the incidence of severe neutropenia (CTCAE grade 4) in breast cancer patients receiving Lipegfilgrastim prophylaxis was 50.0% while no patient (of 94 patients in the per protocol population) developed febrile neutropenia[2].

In 2014, NADIR, a large-scaled non-interventional study was initiated to obtain detailed information on the value of Lipegfilgrastim in order to prevent both febrile neutropenia and severe neutropenia in a real-world setting. Here we report on results from an interim analysis focusing on the subset of patients with breast cancer.

METHODS

Objectives

Evaluation of effectiveness (incidence of severe neutropenia (NCI CTCAE grade 3/4) and febrile neutropenia) and safety of Lipegfilgrastim use in 2,500 patients with different tumor entities subjected to chemotherapy in routine clinical practice.

Study design

NADIR is a non-interventional, prospective, multicenter study carried out in 270 outpatient centers and hospitals across Germany.

Patient population

- Cancer patients treated with chemotherapy receiving Lipegfilgrastim, without any other G-CSF support prior to Lipegfilgrastim in the current chemotherapy line.
- This was an interim analysis of the NADIR study and here the results for the subgroup of patients with breast cancer are presented.
- At time of data cut-off for this interim analysis patient enrollment was ongoing.

Treatment

- Dose dense regimens were defined as regimens with treatment intervals of 2 weeks containing at least one of the following substances: Epirubicin, cyclophosphamide, taxane.

Observational period

- Starting with the first administration of Lipegfilgrastim, patients were observed for a maximum of 6 subsequent cycles of chemotherapy.

Assessments

- Incidence of severe neutropenia (NCI CTCAE grade 3/4) was determined by assessing the neutrophil count.
- Incidence of febrile neutropenia was determined according to investigator's assessment.
- Severity of adverse events was graded according to CTCAE V4.03.

Statistical analysis

- The analysis population for the interim analysis included all patients who received at least one dose of Lipegfilgrastim and finished the observation period.
- All parameters were analyzed descriptively; for continuous parameters mean, standard deviation, median, quartiles, minimum and maximum were calculated, categorical parameters were presented using frequency tables together with a 95% confidence interval if primary endpoint.

RESULTS

Patient characteristics

- At the time of data cut-off for this interim analysis (March 2016), 2,422 patients had been enrolled at 198 sites. Of 1,556 evaluable patients, 741 patients were diagnosed with breast cancer, of which 274 were treated with dose-dense regimens (Figure 1). Patient characteristics are listed in Table 1.
- 89.1 and 97.1% of breast cancer patients and those receiving dose-dense regimens, respectively, were treated in a (neo-)adjuvant setting; 96.1% of breast cancer patients received an anthracycline and / or taxane based regimen (Table 2).

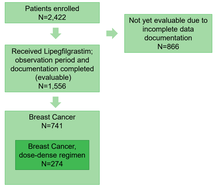

Figure 1: Flow chart of analysis population.

Lipegfilgrastim administration

- For 741 patients with breast cancer and 274 patients with breast cancer receiving dose-dense regimens a total of 3,410 and 1,294 chemotherapy cycles, respectively, were documented.
- 83.7 and 98.5% of breast cancer patients and those receiving dose-dense regimens received their first Lipegfilgrastim administration as primary prophylaxis, respectively (Figure 2).
- 94.6% (3,225 of 3,410) and 96.1% (1,243 of 1,294) of observed chemotherapy cycles in breast cancer patients and those receiving dose-dense regimens, respectively, were supported by Lipegfilgrastim.
- Most patients (76.0 and 81.6% of breast cancer patients and those receiving dose-dense regimens, respectively) received their first Lipegfilgrastim administration on the day following chemotherapy administration (Figure 3).

Table 1: Patient characteristics.

	Breast Cancer (n = 741)	Breast Cancer, dose-dense regimen (n = 274)
Median age, years (range)	53.9 (25.7 - 81.1)	51.3 (25.7 - 76.8)
ECOG, n (%)		
0	513 (69.2)	239 (87.2)
1	168 (22.7)	25 (9.1)
2	28 (3.8)	4 (1.5)
3	1 (0.1)	-
Missing	31 (4.2)	6 (2.2)
At least one concomitant disease, n (%)	376 (50.7)	114 (41.6)

Table 2: Chemotherapy setting and details on chemotherapy regimens.

	Breast Cancer (n = 741)	Breast Cancer, dose-dense regimen (n = 274)
Chemotherapy setting, n (%)		
Adjuvant*	392 (52.9)	126 (46.0)
Neo-adjuvant	268 (36.2)	140 (51.1)
Palliative	75 (10.1)	5 (1.8)
Missing	6 (0.8)	3 (1.1)
Chemotherapy regimen, n (%)#		
Anthracycline + Taxane regimen#	320 (43.1)	135 (49.3)
Anthracycline regimen#	269 (36.3)	139 (47.4)
Taxane regimen#	123 (16.6)	9 (3.3)
Other	29 (3.9)	-

*For one patient receiving a dose-dense regimen, chemotherapy setting was stated "curative" by site; #for sequential chemotherapy regimens, only documentation of one sequence supported by lipegfilgrastim was requested.

Table 3: Febrile neutropenia risk prior to first administration of Lipegfilgrastim according to investigator's assessment.

Febrile Neutropenia risk, n (%)	Breast Cancer (n = 741)	Breast Cancer, dose-dense regimen (n = 274)
> 20%	414 (55.9)	188 (68.6)
10 - 20%	314 (42.4)	82 (29.9)
< 10%	12 (1.6)	4 (1.5)
Missing	1 (0.1)	-

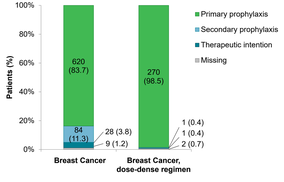

Figure 2: Intention of first Lipegfilgrastim administration, n (%).

Primary prophylaxis: Lipegfilgrastim was administered from the first cycle on to prevent neutropenia.

Secondary Prophylaxis: Lipegfilgrastim was administered for prophylaxis after prior occurrence of a neutropenic event.

Therapeutic intention: Lipegfilgrastim was administered to cure a neutropenic event.

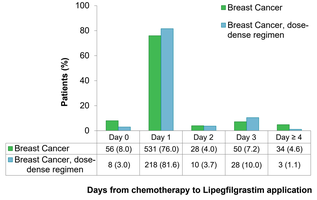

Figure 3: Days from chemotherapy to Lipegfilgrastim application. Day 0 = day of chemotherapy application; n (%). Only patients who received chemotherapy regimens applied once in a cycle were included in this analysis.

Incidence of severe neutropenia and febrile neutropenia

- Severe neutropenia (CTCAE grade 3/4) occurred at least once during the observation period in 29.4 and 33.9% of breast cancer patients and those receiving dose-dense regimens, respectively (Table 4).
- 2.2 and 1.8% breast cancer patients and those receiving dose-dense regimens, respectively, developed at least one episode of febrile neutropenia during the observation period (Table 4).

Table 4: Patients with at least one episode of severe neutropenia (CTCAE grade 3/4) or febrile neutropenia.

	Breast Cancer (n = 741)	Breast Cancer, dose-dense regimens (n = 274)
	n (% [95% CI])	n (% [95% CI])
Severe neutropenia		
Severe Neutropenia (CTC grade 3/4)	218 (29.4 [27.2 - 32.8])	93 (33.9 [28.4 - 39.9])
No severe neutropenia (CTC grade 3/4)	382 (51.6 [47.9 - 55.2])	125 (45.6 [39.6 - 51.7])
Missing	141 (19.0)	56 (20.4)
Febrile neutropenia		
Febrile neutropenia any CTCAE grade*	16 (2.2 [1.2 - 3.5])	5 (1.8 [0.6 - 4.2])
Febrile neutropenia CTCAE grade 3	12 (1.6 [0.8 - 2.8])	3 (1.1 [0.2 - 3.2])
Febrile neutropenia CTCAE grade 4	3 (0.4 [01. - 1.2])	1 (0.4 [0.0 - 2.0])

*For one patient febrile neutropenia with CTCAE grade 2 was documented.

Modifications of chemotherapy

- Most common modifications of chemotherapy were dose reductions, necessary in 17.0 and 15.7% of breast cancer patients and those receiving dose-dense regimens, respectively.
- Chemotherapy dose reductions were reported in 5.5 and 4.2% of cycles, in breast cancer patients and those receiving dose-dense regimens, respectively. In 0.7 and 0.6% of cycles dose was reduced due to chemotherapy-induced neutropenia.

Safety

- For 26.7 and 34.3% of breast cancer patients and those receiving dose-dense regimens, respectively, Lipegfilgrastim-related adverse events were reported.
- The most frequent Lipegfilgrastim-related adverse event was bone pain, which occurred in 11.1 and 18.6% of breast cancer patients and those receiving dose-dense regimens, respectively.
- Lipegfilgrastim-related serious adverse events were reported for 2.6% (n = 19) and 3.3% (n = 9) of breast cancer patients and those receiving dose-dense regimens, respectively.
- The most common Lipegfilgrastim-related serious adverse events in breast cancer / breast cancer dose-dense regimen were peripheral sensory neuropathy (n = 3 / n = 2), platelet count decreased (n = 3 / n = 1), white blood cell decreased (n = 3 / n = 3) and dyspnea (n = 3 / n = 1).

Table 5: Most common adverse events related to Lipegfilgrastim (any CTCAE grade ≥ 2%).

	CTCAE grade 3/4 Breast Cancer / Breast Cancer, dose-dense regimen, n (%)	Any CTCAE grade Breast Cancer / Breast Cancer, dose-dense regimen, n (%)
At least one adverse event related to Lipegfilgrastim	33 (4.5) / 3 (1.1)	198 (26.7) / 94 (34.3)
Blood and lymphatic system disorders		
Anaemia	6 (0.8) / 3 (1.1)	48 (6.5) / 26 (9.5)
General disorders and administration site conditions		
Pain	1 (0.1) / 1 (0.4)	13 (1.8) / 8 (2.9)
Investigations		
Thrombocytopenia	8 (1.1) / 2 (0.7)	32 (4.3) / 15 (5.5)
Leukopenia	13 (1.8) / 10 (3.6)	25 (3.4) / 14 (5.1)
Musculoskeletal and connective tissue disorders		
Arthralgia	1 (0.1) / 1 (0.4)	23 (3.1) / 14 (5.1)
Back pain	- / -	15 (2.0) / 4 (1.5)
Bone pain	6 (0.8) / 4 (1.5)	82 (11.1) / 51 (18.6)
Myalgia	1 (0.1) / -	17 (2.3) / 11 (4.0)

CONCLUSION

- Use of Lipegfilgrastim in patients receiving mainly (neo-)adjuvant chemotherapy for breast cancer in routine clinical practice showed low incidences of febrile neutropenia and severe neutropenia, revealing results comparable with previous publications[2].
- Lipegfilgrastim was well tolerated: The type of reported Lipegfilgrastim-related adverse events were in line with literature[2].
- Lipegfilgrastim was effective even in patients treated with high-risk dose-dense regimens.

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REFERENCES

[1]Aapro MS, et al. Eur J Cancer. 2011;47:8-32
[2]Bondarenko I, et al. BMC Cancer. 2013;13:386-398

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CONFLICTS OF INTEREST

C.M. Kurbacher: Consultancy for TEVA, remunerations and financing of scientific investigations by TEVA

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