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ORIGINAL ARTICLE

Outcomes of chemotherapy-induced (febrile) neutropenia prophylaxis with biosimilar filgrastim (Zarzio®) initiated "same-day" (< 24 h), "per-guidelines" (24–72 h), and "late" (> 72 h): findings from the MONITOR-GCSF study

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Abstract

Purpose Granulocyte colony-stimulating factors (G-CSFs) are indicated for prophylaxis or management of chemotherapy-induced neutropenia (CIN) and febrile neutropenia (FN). Guidelines recommend G-CSF 24–72 h following chemotherapy; however, some evidence suggests that G-CSF initiated < 24 h may benefit some patients.

Methods MONITOR-GCSF was a prospective, observational, multicenter, pan-European study of 1447 chemotherapy-treated patients receiving daily biosimilar (standard) filgrastim (Zarzio®/Zarxio®, filgrastim-sndz, Hexal AG, Sandoz Inc.). In this analysis, cycles were classified as *same-day*, *per-guidelines*, or *late* if G-CSF support was initiated < 24 h, 24–72 h, and > 72 h after chemotherapy. Outcomes included occurrence of CIN of any grade (CIN1/4), grade 3 or 4 (CIN3/4), grade 4 (CIN4), or FN: CIN/FN-related hospitalization or CIN/FN-related chemotherapy disturbance.

Results A total of 5930 chemotherapy cycles from 1423 evaluable patients from MONITOR-GCSF had data for day of G-CSF initiation: 795 cycles (13.4%) classified as *same-day*, 3320 (56.0%) as *per-guidelines*, and 1815 (30.6%) as *late*. Groups did not differ as to CIN1/4 and FN episodes, or CIN/FN-related hospitalizations or chemotherapy disturbances. Patients in the *same-day* and *per-guidelines* groups had statistically similar odds of not experiencing any outcomes of interest in any given cycle. Patients in the *late* group had worse odds of experiencing CIN1/4, CIN3/4, and CIN4 episodes in any given cycle. Proportions of patients reporting clinical events of interest were generally similar.

Conclusions This real-world evidence indicates that CIN/FN prophylaxis initiated with biosimilar filgrastim within 24–72 h post-chemotherapy is effective and safe. Filgrastim administration on the day of chemotherapy may be appropriate in some patients.

Keywords Biosimilar · Filgrastim · Granulocyte colony-stimulating factors · Chemotherapy-induced neutropenia · Febrile neutropenia

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Introduction

Granulocyte colony-stimulating factors (G-CSFs) are biological growth factors that stimulate production of white blood cells and are indicated for use in the prophylaxis or management of chemotherapy-induced neutropenia (CIN) and febrile neutropenia (FN) [1, 2]. It is recommended to administer G-CSFs between 24 and 72 h following the administration of chemotherapy. Administering G-CSFs early within 24 h of chemotherapy increases the risk that the cytotoxicity of the

regimen will impair myeloblasts to differentiate into promyelocytes and neutrophils, thus compromising neutrophil recovery. However, observational [3–10] and randomized studies [11] have supported prophylaxis with single-dose pegfilgrastim (Neulasta®, Amgen) initiated within the first 24 h (same-day). This option has found support among clinicians in the USA [12], especially in outpatient practice for patients living at some distance from their treatment center.

Other than one study conducted in Greece [8], all studies were performed in the USA; all involved pegfilgrastim, and none evaluated outcomes associated with *late* (> 72 h) initiation. The MONITOR-GCSF study [13] was a prospective, observational, multicenter (140), pan-European (12 countries) study of 1447 chemotherapy-treated patients (6213 cycles) receiving primary (72.3%) or secondary prophylaxis (27.7%) with daily biosimilar (standard) filgrastim (EP2006, Zarzio®/Zarxio®, Hexal AG) [14]. Unadjusted crude rates indicated that about one in seven patients was prophylacted on the day of chemotherapy (< 24 h; same-day), about half (53.2%) within the 24–72-h time window (per-guidelines), and about one third (33.4%) after 72 h (late) [14]. In addition, relative to amended EORTC guidelines [1], 56.6% of patients were prophylacted in accordance with guidelines, but 17.4% were under-prophylacted and 26.0% were over-prophylacted [14].

To further explore relevance of prophylaxis initiation, we performed analyses stratified by initiation cohorts (same-day/per-guidelines/late) and compared patients in terms of demographics and clinical status at start of chemotherapy, prophylaxis patterns, and clinical and safety outcomes. Consistent with our prior reports [14–17], we analyzed data using both patients and cycles as the units of analysis. The patient-level analyses target outcomes "ever" experienced by patients across the line of chemotherapy. The cycle-level analyses assess outcomes recorded during a particular cycle and, for chemotherapy disturbances, from one cycle to the next.

Methods

Previous publications have presented the background and methodology of MONITOR-GCSF [13, 18]; demographics and clinical status of subjects at baseline, Zarzio® prophylaxis patterns, and observed outcomes [14]; and the determinants of these outcomes [14, 15]. Here, we summarize elements relevant to the present analyses.

Design

MONITOR-GCSF was a prospective real-world observational study of cancer patients receiving myelosuppressive chemotherapy, whose treating physicians prescribed CIN/FN prophylaxis with Zarzio®. Eligible were adults (age ≥ 18 years) with stage III or IV breast, ovarian, bladder, or lung cancer; metastatic prostate cancer; and stage III or IV diffuse large B cell lymphoma, or multiple myeloma. Patients were followed for up to six chemotherapy cycles.

Cycles were classified as *same-day*, *per-guidelines*, or *late* if G-CSF support was initiated, respectively, < 24 h, 24–72 h, and > 72 h after chemotherapy. Before performing the analyses reported here, the crude rates for day of initiation reported by Gascón et al. [14] were adjusted per expert consensus (authors HL, PG, CB, MA, MB) to be *per-guidelines* for 168 cycles initiated after 72 h from 68 patients on regimens (e.g., etoposide) deemed appropriate for G-CSF initiation on any day of the cycle.

Outcomes

The following outcomes were evaluated at both the patient- and cycle-level: episodes of CIN of any grade (CIN1/4), grade 3 or 4 (CIN3/4), grade 4 (CIN4), or FN; CIN/FN-related hospitalization or CIN/FN-related chemotherapy disturbance (dose reduction, delay in administration, cancelation of chemotherapy); and a (worst-case) composite index of any of these outcomes occurring.

Specialized statistical issues

The patient risk score (PRS) is the weighted sum (range 0–11) of each of the eight CIN/FN patient risk factors in the European Organization for Research and Treatment of Cancer (EORTC) guidelines [1], developed by consensus by four of the authors (HL, PG, CB, MA). Weights of three were assigned to *age ≥ 65 years* and *history of prior FN*; weights of 1.5 to *advanced disease* and *poor performance and/or nutritional status*; and weights of 0.5 to *no antibiotic prophylaxis, female gender, hemoglobin < 12 g/dL,* and *renal, cardiovascular or liver disease*. A PRS ≥ 3 classified a patient as being at elevated risk for CIN/FN.

Cycle data were "nested" under patients and patients under centers, violating the assumption of statistical independence. Therefore, we applied generalized estimating equations (GEE) [19] to estimate adjusted odds ratios (OR) and 95% confidence intervals. GEE adjusts standard errors based on within-cluster correlations.

We calculated ORs for each outcome for each cohort (same-day; per-guidelines; late) and calculated ORs in pairwise combinations to contrast the relative odds of one prophylaxis initiation approach against another. Chemotherapy disturbances were estimated for the cycle after the CIN/FN event occurred (lag = 1).

Post hoc analysis

Cycles initiated *late* were examined to identify the role, if any, that fever, infection, or low neutrophil count may have had on timing of G-CSF initiation and to see if these factors differed between the *same-day*, *per-guidelines*, and *late* cohorts.

With newer treatment regimens for multiple myeloma often mandating weekly, twice-weekly, and/or daily treatment for 3 weeks (or a combination of these), G-CSF prophylaxis no longer follows the common chemotherapy regimen of a fixed number of cycles administered at 3- or 4-week intervals. Therefore, we conducted a post hoc sensitivity analysis to determine whether the inclusion of the multiple myeloma cohort influenced clinical and safety-related outcomes.

Results

A total of 5930 chemotherapy cycles from 1423 evaluable patients in the MONITOR-GCSF study had data for day of G-CSF initiation: 795 cycles (13.4%) classified as *same-day*, 3320 (56.0%) as *per-guidelines*, and 1815 (30.6%) as *late*. These data serve as the evaluable sample for all cycle-level analyses. There were 1274 patients who had (1) data for day of G-CSF initiation at their enrollment cycle and (2) consistent day of initiation from cycle to cycle throughout the study. These 1274 patients comprise the evaluable sample for all patient-level analyses, including 172 patients (13.5%) classified as *same-day*, 718 (56.4%) as *per-guidelines*, and 384 (30.1%) as *late* (Table 1).

Patient characteristics

The three cohorts (same-day, per-guidelines, and late) were similar in terms of gender, age, Eastern Cooperative Oncology Group (ECOG) score, history of repeated infections, advanced disease status, FN history, poor performance/nutritional status, anemia, renal, cardiovascular or liver disease, and PRS (Table 1; all p = n.s.). Proportionally, more patients initiated *late* received antibiotic prophylaxis ($p < 0.001$). Of the 172 patients in the *same-day* group, 92.4% had a solid tumor vs. 61.5% of the 384 patients in the *late* group ($p < 0.001$). There were no differences between groups in the proportions of patients with prior chemotherapy or radiotherapy. Patients in the *same-day* group were distributed roughly in thirds across the three chemotoxicity groups, whereas 51.6% of patients in the *per-guidelines* group were treated with regimens with 10–20% toxicity, and more than half (54.4%) in the *late* group were exposed to treatments with ≥ 20% FN risk ($p = 0.002$).

Prophylaxis patterns

In the majority of cycles (56.0%), G-CSF was initiated *per-guidelines* within the 24–72-h window with 13.4% initiated *same-day* and 30.6% *late*. Of the 1815 cycles in which G-CSF was initiated *late* (> 72 h after chemotherapy), 12.8% were initiated 4 days after chemotherapy, 20.5% on day 5, 20.9% on day 6, 22.5% on day 7, 11.9% on day 8, and 11.4% on day 9 or later.

The proportions of patients receiving primary vs. secondary prophylaxis were distributed almost equally across the three cohorts (p = n.s.) (Table 2). More *per-guidelines* patients were dosed at 48 MIU/day, whereas more patients in the *same-day*, and especially in the *late* cohort, were dosed at 30 MIU/day ($p < 0.001$). The median duration of prophylaxis was 5 days for all three groups, but *same-day* patients tended to have shorter durations—especially relative to *per-guidelines* patients ($p < 0.001$). Over one third (36.9%) of *same-day* patients received between one and three daily injections, whereas durations were longer for the other groups ($p < 0.001$).

Expanding upon a previous analysis [17], we classified patients per the intensity of their G-CSF prophylaxis into being under-, correctly-, or over-prophylacted. In the *same-day* cohort, most patients were either correctly prophylacted (46.8%) or over-prophylacted (39.2%), whereas only 14.0% were under-prophylacted (Fig. 1). Similarly, in the *per-guidelines* group, most patients were either correctly prophylacted (54.8%) or over-prophylacted (26.3%), with 18.9% being under-prophylacted. Of the *late* patients, most (64.1%) were correctly prophylacted, an additional 19.3% over-prophylacted, and the remaining 16.6% under-prophylacted.

Outcomes

Rates

Consistently, in both the patient- and the cycle-level analyses, the three cohorts differed in observed CIN rates, especially CIN3/4 and CIN4, with higher rates in the *late* cohort (p ranging < 0.001 to 0.01). The cohorts did not differ in FN rates in either patient- or cycle-level analyses (Table 3).

At the patient-level, the three groups did not differ significantly in their rates of CIN/FN-related hospitalizations, chemotherapy disturbances, and the composite "worst-case" index "ever" occurring over the period of chemotherapy (all p = n.s.). At the cycle-level, the likelihood of CIN/FN-related chemotherapy disturbances in a given cycle was the highest in the *same-day* group, followed by the *per-guidelines*, and the *late* group, which had the lowest rate ($p = 0.017$). The composite index (i.e., the probability of any negative outcome to occur in

Table 1 Patient demographics, clinical status, and cancer and CIN/FN history

	Day of Zarzio® initiation			
	Same-day(< 24 h)	Per-guidelines(24–72 h)	Late(> 72 h)	*P*
Sample[a], *n* (%)	172 (13.5)	718 (56.4)	384 (30.1)	
Demographics and clinical status				
Gender, %				n.s.
Male	47.7	34.4	43.5	
Female	52.3	65.6	56.5	
Age (years), mean ± SD, median	63.7 ± 10.1, 63	60.5 ± 11.7, 61	62.0 ± 12.7, 63	n.s.
ECOG performance status, %				
0	44.6	41.7	42.0	n.s.
1	45.8	48.2	44.0	
2	6.6	8.4	11.5	
3	3.0	1.5	2.5	
4	0.0	0.2	0.0	
History of repeated infections, %	3.1	1.6	2.2	n.s.
FN risk factors (EORTC)				
High risk, %				
Age ≥ 65 years	45.9	38.3	46.6	n.s.
Increased risk, %				
Advanced disease[b]	16.0	13.6	14.6	n.s.
History of FN	3.1	1.4	2.8	n.s.
No antibiotic prophylaxis	95.9	92.3	76.1	< 0.001
Other factors, %				
Poor performance and/or nutritional status	12.7	11.8	16.0	n.s.
Female gender	52.3	65.6	56.5	n.s.
Hemoglobin < 12 g/dL	48.3	37.6	38.8	n.s.
Renal, cardiovascular, or liver disease	26.4	22.8	22.0	n.s.
Patient risk score, mean ± SD, median	3.1 ± 1.9, 3	2.8 ± 1.9, 2	3.0 ± 2.1, 3	n.s.
Cancer				
Tumor type, %				< 0.001
Solid	92.4	83.0	61.5	
Hematological	7.6	17.0	38.5	
Prior treatments, %				
Chemotherapy	36.1	30.9	32.0	n.s.
of these:				
adjuvant	57.1	46.5	45.6	n.s.
in metastatic setting	50.9	51.0	51.3	n.s.
of these: prior lines of chemo				
1	38.5	54.1	50.9	n.s.
2	42.3	26.5	26.3	
≥ 3	19.2	19.4	22.8	
Radiation therapy	22.1	20.8	15.4	n.s.
Chemotoxicity, %				0.002
<10%	28.7	6.3%	8.6	
10–20%	39.7	51.6%	37.0	
≥20%	31.6	42.1%	54.4	

CIN chemotherapy-induced neutropenia, *ECOG* Eastern Cooperative Oncology Group, *EORTC* European Organization for Research and Treatment of Cancer, *FN* febrile neutropenia, *SD* standard deviation

[a] Sample ($N = 1274$) includes MONITOR-GCSF patients whose day of initiation was consistent across all cycles

[b] Stage IV (stage III if multiple myeloma) and prior chemotherapy in metastatic setting

a particular cycle) was highest in the *late* group, followed by the *same-day* group, and the *per-guidelines* group ($p = 0.003$).

Pairwise contrast analyses: patient level

Patients in the *same-day* and *per-guidelines* groups had statistically similar odds of not experiencing any of the outcomes of interest at any time during their chemotherapy treatment (all p = n.s.) (Table 4). When these two groups were compared pair-wise to the *late* group, patients in the latter group had worse odds of experiencing CIN3/4 ($p = 0.001$ and $p = 0.018$) and CIN4 episodes ($p = 0.006$ and $p = 0.047$) compared to *per-guidelines* and *same-day* patients, respectively. Groups did not differ on rates of CIN1/4, FN episodes, CIN/FN-related hospitalizations or chemotherapy disturbances, or the composite index (all p = n.s.).

Table 2 Zarzio® prophylaxis patterns

	Day of Zarzio® initiation			
	Same-day(< 24 h)	Per-guidelines(24–72 h)	Late(> 72 h)	*p*
Type of prophylaxis, %				
Primary	66.3	69.8	78.4	n.s.
Secondary	33.7	30.2	21.6	
Dose, %				
30 MIU/day	55.7	45.7	66.6	< 0.001
48 MIU/day	44.3	54.3	33.4	
Prophylaxis intensity[a], %				
Under-prophylacted	14.0	18.9	16.6	0.001
Correctly prophylacted	46.8	54.8	64.1	
Over-prophylacted	39.2	26.3	19.3	
Duration of prophylaxis (days), %				
1	4.5	4.2	2.0	
2	20.5	3.7	2.7	
3	11.9	12.0	12.8	
4	10.6	5.7	8.1	
5	28.9	45.1	54.2	
6	5.1	5.8	8.4	
7	10.8	13.8	7.6	
8	3.5	1.7	1.7	
9	0.6	0.9	1.0	
10	1.3	2.9	0.9	
11	0.3	0.2	0.1	
12	0.5	0.5	0.0	
13	0.0	0.2	0.1	
14	0.9	2.9	0.1	
≥ 15	0.6	0.4	0.3	
	Mean	SD	Median	
Duration of prophylaxis (days) by day of initiation cohort				< 0.001
Same-day (< 24 h)	4.5	2.5	5	
Per-guidelines (24–72 h)	5.4	2.5	5	
Late (> 72 h)	4.9	1.7	5	
Duration category, %				
1–3 days	36.9	19.9	17.5	< 0.001
4–5 days	39.5	50.8	62.3	
6+ days	23.6	29.3	20.2	

EORTC European Organization for Research and Treatment of Cancer, *MIU* milliinternational units, *SD* standard deviation

[a] Prophylaxis intensity: under-prophylacted = secondary when primary was indicated per EORTC guidelines; correctly = either primary or secondary but as recommended per EORTC guidelines; over = either primary or secondary when not indicated per EORTC guidelines

In a sensitivity analysis of day of initiation and rates of CIN/FN and related outcomes, we plotted patient-level outcomes by day of initiation. Across all three day-of-initiation cohorts, rates were lower over-prophylacted patients (Fig. 2a) but higher in those prophylacted *late* (Fig. 2b).

Pairwise contrast analyses: cycle level

Pairwise contrast analyses at the cycle-level revealed that patients in the *same-day* and *per-guidelines* groups had statistically similar odds of not experiencing any of the outcomes of

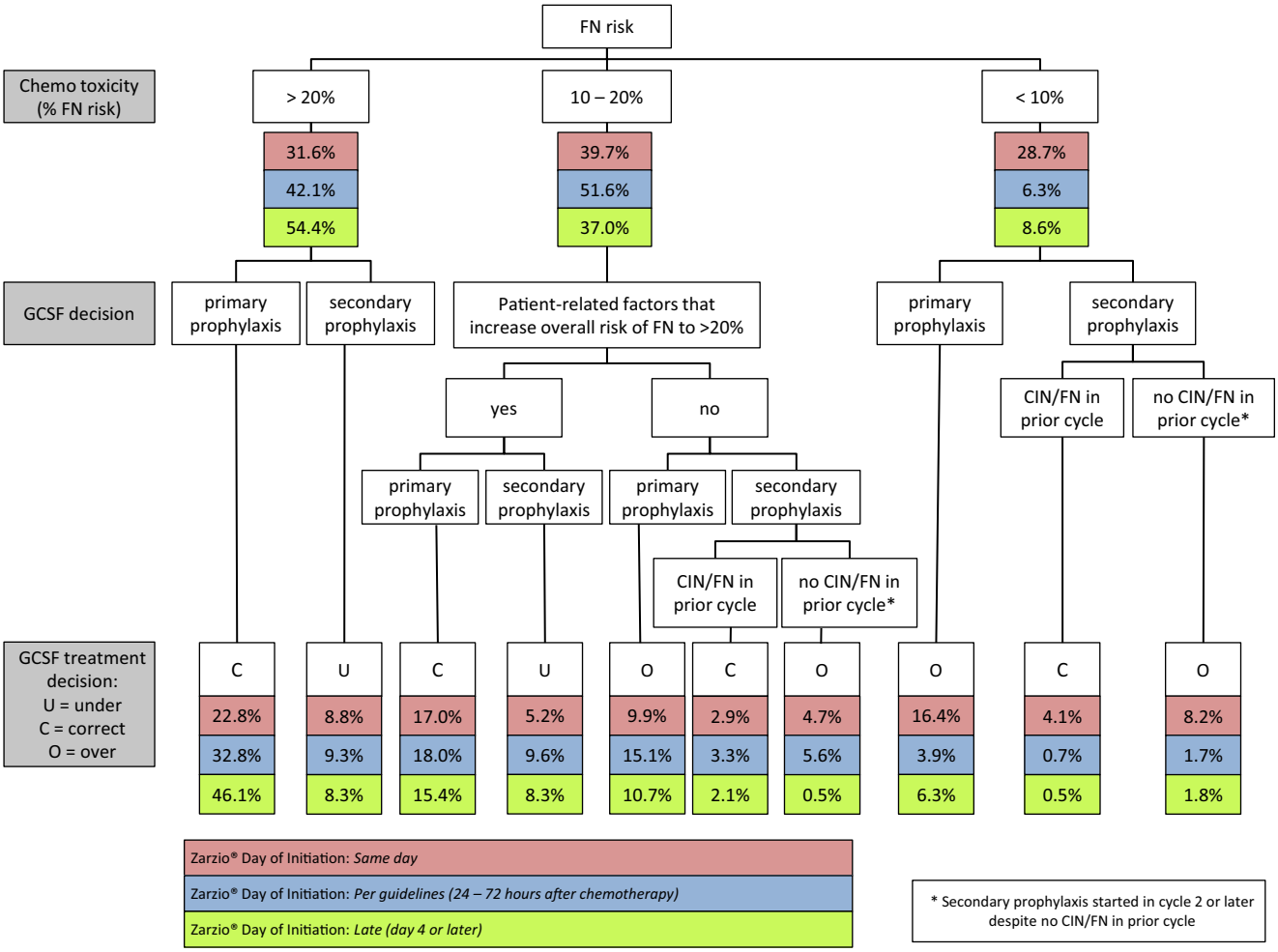

Fig. 1 Treatment decision relative to EORTC guidelines by cohort. CIN chemotherapy-induced neutropenia, EORTC European Organization for Research and Treatment of Cancer, FN febrile neutropenia, G-CSF Granulocyte colony stimulation factor

interest in any given cycle (all p = n.s.). Patients in the *late* group had worse odds of experiencing CIN1/4 ($p < 0.001$ and $p = 0.002$), CIN3/4 (both $p < 0.001$), and CIN4 episodes (both $p < 0.001$) in any given cycle compared to *per-guidelines* and *same-day* patients, respectively. Compared to *per-guidelines* patients, *late* patients had worse odds of an FN episode ($p = 0.039$) or scoring positive on the composite index ($p = 0.001$). In contrast, *same-day* patients had worse odds of experiencing a chemotherapy disturbance in a subsequent cycle compared to *late* patients ($p = 0.005$).

Safety

Other than bone pain ($p < 0.001$) and increase in serum lactate dehydrogenase (LDH) ($p = 0.016$), no significant differences in rates of clinical events of interest between cohorts were observed (all p = n.s.). For bone pain, proportions were lowest in the *same-day* group (13.0%), followed by the *per-guidelines* group (25.0%), and highest in the *late* group (33.5%). A similar pattern was found for LDH with 8.5% in the *same-day*, 16.2% in the *per-guidelines*, and 23.4% in the *late* groups. Reported rates of adverse drug reactions over 5930 cycles were statistically similar across the three cohorts (p = n.s.).

Post hoc analysis

Late cycles

Of the 1815 cycles initiated late, 35 (1.9%) were initiated late due to fever, infection, or neutropenia. However, in *late* cycles, patients with fever did not have higher rates of any of the CIN/FN-related outcomes than patients with fever who were treated *same-day* or *per-guidelines* (all p = n.s.); the same was true for infection, fever and/or infection, and absolute neutrophil count < 2000/μl (all p = n.s.).

Multiple myeloma cohort

Post hoc sensitivity analyses revealed no statistically significant differences in the rates of CIN/FN and related outcomes

Table 3 Clinical outcomes at the patient and cycle levels by day of initiation

	Same-day(< 24 h)		Per-guidelines(24–72 h)		Late(> 72 h)		*p*
	%	95% CI	%	95% CI	%	95% CI	
Unit of analysis: patient[a]							
Neutropenia episodes							
CIN grades 1–4	27.9	18.8–39.3	29.8	24.0–36.4	40.6	29.1–53.3	n.s.
CIN grades 3 or 4	16.9	9.9–27.3	16.3	12.1–21.7	33.3	23.3–45.1	0.005
CIN grade 4	7.6	3.0–18.1	9.1	6.0–13.4	19.8	13.1–28.8	0.010
FN	2.9	1.4–6.1	5.7	4.1–8.0	6.8	4.3–10.4	n.s.
CIN/FN-related hospitalizations	7.6	2.7–19.6	5.4	3.7–7.9	6.3	4.1–9.5	n.s.
CIN/FN-related chemotherapy disturbances[b]	12.8	6.2–24.6	9.1	6.5–12.6	6.5	3.9–10.8	n.s.
CIN/FN-related composite outcome[c]	18.0	10.8–28.4	18.4	14.2–23.4	25.8	18.7–34.4	n.s.
	Same-day (< 24 h)		Per-guidelines (24–72 h)		Late (> 72 h)		*p*
	%	95%CI	%	95%CI	%	95%CI	
Unit of analysis: cycle[d]							
Neutropenia episodes							
CIN grades 1–4	13.0	10.1–16.4	13.4	11.7–15.4	20.0	17.2–23.2	< 0.001
CIN grades 3 or 4	6.7	4.8–9.2	6.3	5.1–7.6	13.4	11.3–15.9	< 0.001
CIN grade 4	3.1	2.0–4.9	2.8	2.1–3.7	7.3	5.8–9.1	< 0.001
FN	1.0	0.5–2.2	1.2	0.9–1.7	2.1	1.4–3.0	n.s.
CIN/FN-related hospitalizations	1.9	1.1–3.2	1.1	0.81.6	1.8	1.1–3.0	n.s.
CIN/FN-related chemotherapy disturbances[b]	4.2	2.8–6.1	2.8	2.3–3.6	1.9	1.42.8	0.017
CIN/FN-related composite outcome[c]	7.7	5.610.4	6.1	5.1–7.2	9.5	7.9–11.5	0.003

Valid % used

CI confidence interval, *CIN* chemotherapy-induced neutropenia, *FN* febrile neutropenia

[a] Includes patients ($n = 1274$) whose day of initiation was consistent across all cycles

[b] Type of chemotherapy disturbances are not mutually exclusive. Any patient may have experienced more than one type. Measured with 1-cycle lag

[c] Includes any occurrence of CIN grade 4, FN, CIN/FN-related hospitalization, and/or CIN/FIN-related chemotherapy disturbance

[d] Includes cycles ($n = 5930$) of all patients with valid day of initiation data ($n = 1423$) including patients whose day of initiation varied from cycle to cycle

(i.e., hospitalization, chemo disturbance, and composite) between subjects with multiple myeloma and all other subjects (data not shown). Likewise, no significant influence of the multiple myeloma cohort was found in the pairwise contrast ORs for CIN/FN and related outcomes. Similarly, safety outcomes were found to be unaffected by inclusion of patients with multiple myeloma (all p = n.s.).

Discussion

While single-dose pegfilgrastim might be the prevailing method of prophylaxis in many countries, daily administration of standard filgrastim remains common in Europe and is being re-emphasized by US private payers. The findings reported here provide novel evidence about prophylaxis initiation outside the recommended 24–72-h *per-guidelines* time window, the effectiveness and safety of (generally shorter) durations of prophylaxis with daily-injected biosimilar filgrastim, and the patients in whom deviation from guideline-recommended prophylaxis patterns was observed.

First, at the patient level, CIN risk in patients whose prophylaxis was initiated on the *same-day* as chemotherapy was similar to those initiated *per-guidelines* 24–72-h post-chemotherapy, whereas *late* initiation was associated with a higher risk of CIN grades 3 and 4. The three groups did not differ in their relative risk of FN episodes, hospitalizations, or chemotherapy disturbances.

Table 4 Pairwise contrast odds ratios for clinical outcomes as a function of day of initiation at the patient and cycle levels

	Same-day vs. per-guidelines			Per-guidelines vs. late			Same-day vs. late		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Unit of analysis: patient[a]									
Neutropenia episodes									
CIN grades 1–4	0.912	0.535–1.555	n.s.	0.621	0.359–1.073	n.s.	0.566	0.284–1.126	n.s.
CIN grades 3 or 4	1.042	0.548–1.980	n.s.	0.389	0.219–0.693	0.001	0.406	0.192–0.859	0.018
CIN grade 4	0.821	0.276–2.441	n.s.	0.403	0.212–0.767	0.006	0.331	0.111–0.985	0.047
FN	0.494	0.225–1.087	n.s.	0.834	0.455–1.529	n.s.	0.412	0.167–1.017	n.s.
CIN/FN-related hospitalizations	1.424	0.453–4.471	n.s.	0.862	0.485–1.529	n.s.	1.226	0.406–3.708	n.s.
CIN/FN-related chemotherapy disturbances[b]	1.473	0.620–3.504	n.s.	1.429	0.794–2.574	n.s.	2.106	0.859–5.164	n.s.
CIN/FN-related composite outcome[c]	0.976	0.505–1.886	n.s.	0.649	0.394–1.066	n.s.	0.633	0.314–1.278	n.s.
Unit of analysis: cycle[d]									
Neutropenia episodes									
CIN grades 1–4	0.961	0.699–1.320	n.s.	0.618	0.487–0.786	< 0.001	0.594	0.426–0.829	0.002
CIN grades 3 or 4	1.070	0.718–1.594	n.s.	0.431	0.324–0.572	< 0.001	0.461	0.310–0.684	< 0.001
CIN grade 4	1.135	0.673–1.914	n.s.	0.365	0.253–0.527	< 0.001	0.414	0.248–0.693	< 0.001
FN	0.830	0.363–1.901	n.s.	0.584	0.351–0.972	0.039	0.485	0.203–1.161	n.s.
CIN/FN-related hospitalizations	1.702	0.894–3.241	n.s.	0.607	0.331–1.111	n.s.	1.032	0.499–2.137	n.s.
CIN/FN-related chemotherapy disturbances[b]	1.486	0.930–2.376	n.s.	1.482	0.969–2.267	n.s.	2.203	1.276–3.802	0.005
CIN/FN-related composite outcome[c]	1.290	0.887–1.876	n.s.	0.612	0.462–0.809	0.001	0.789	0.533–1.167	n.s.

CI confidence interval, *CIN* chemotherapy-induced neutropenia, *FN* febrile neutropenia, *OR* odds ratio

[a] Includes patients ($n = 1274$) whose day of initiation was consistent across all cycles

[b] Type of chemotherapy disturbances are not mutually exclusive. Any patient may have experienced more than one type. Measured with 1-cycle lag

[c] Includes any occurrence of CIN grade 4, FN, CIN/FN-related hospitalization, and/or CIN/FIN-related chemotherapy disturbance

[d] Includes cycles ($n = 5930$) of all patients with valid day of initiation data ($n = 1423$) including patients whose day of initiation varied from cycle to cycle

Second, our cycle-level findings provide real-world support for the guideline recommendation that CIN/FN risk be reevaluated at the start of each chemotherapy cycle. *Late*-initiated patients were at higher risk of experiencing a CIN episode of any grade in a given cycle than patients prophylacted *per-guidelines* or *same-day*. Similarly, these patients were at higher risk for in-cycle FN than those initiated *per-guidelines*. Hospitalization due to CIN/FN was similar across the three groups. There was an increased risk of CIN/FN-related disruptions to chemotherapy for *same-day* patients compared to *late* patients, and this risk nearly attained statistical significance when compared to *per-guidelines* patients.

Third, the three groups of patients were similar in demographics, FN risk factors (except for antibiotic prophylaxis), and prior cancer treatments (if any). However, the ratio of patients with solid vs. hematological tumors was highest in the *same-day* group (92.4% vs. 7.6%) and lowest in the *late* group (61.5% vs. 38.5%). Further, only 31.6% of *same-day* patients were treated with chemotherapy regimens with ≥ 20 FN risk, compared to 42.1% of patients initiated *per-guidelines* and 54.4% of patients prophylacted *late*.

Fourth, there were marked differences between the three groups in terms of prophylaxis patterns. Though similar proportions received primary vs. secondary prophylaxis, patients prophylacted *same-day* tended to receive the 30 MIU/kg Zarzio® dose and were disproportionally over-prophylacted relative to amended EORTC guidelines than those initiated *per-guidelines* or *late* [17]. In addition, they were prophylacted mainly between 1 and 5 days' duration. Patients in the *late* group also tended to be given the lower Zarzio® dose, but were more likely to be correctly- than over-prophylacted, relative to guidelines. Similar to the *same-day* patients, duration tended to be shorter and seldom exceeded 5 days. Yet, in our modeling of predictors of CIN/FN and related outcomes [15], Zarzio® initiated *per-guidelines* (vs. same-day or late) had an odds-lowering effect in one patient-level model (composite outcome) and two cycle-level models (CIN4 and composite).

The analyses reported here extend our prior conclusion that approximately two decades of clinical experience with filgrastim has led physicians to prescribe shorter durations of prophylaxis [14, 15]. They may do so to compensate for the trend to (over-)prophylact patients [17] receiving chemotherapy with low (< 10%) and moderate (10–20%) FN risk, especially elderly patients [16]. This may suggest a clinical practice of risk management rather than strictly following

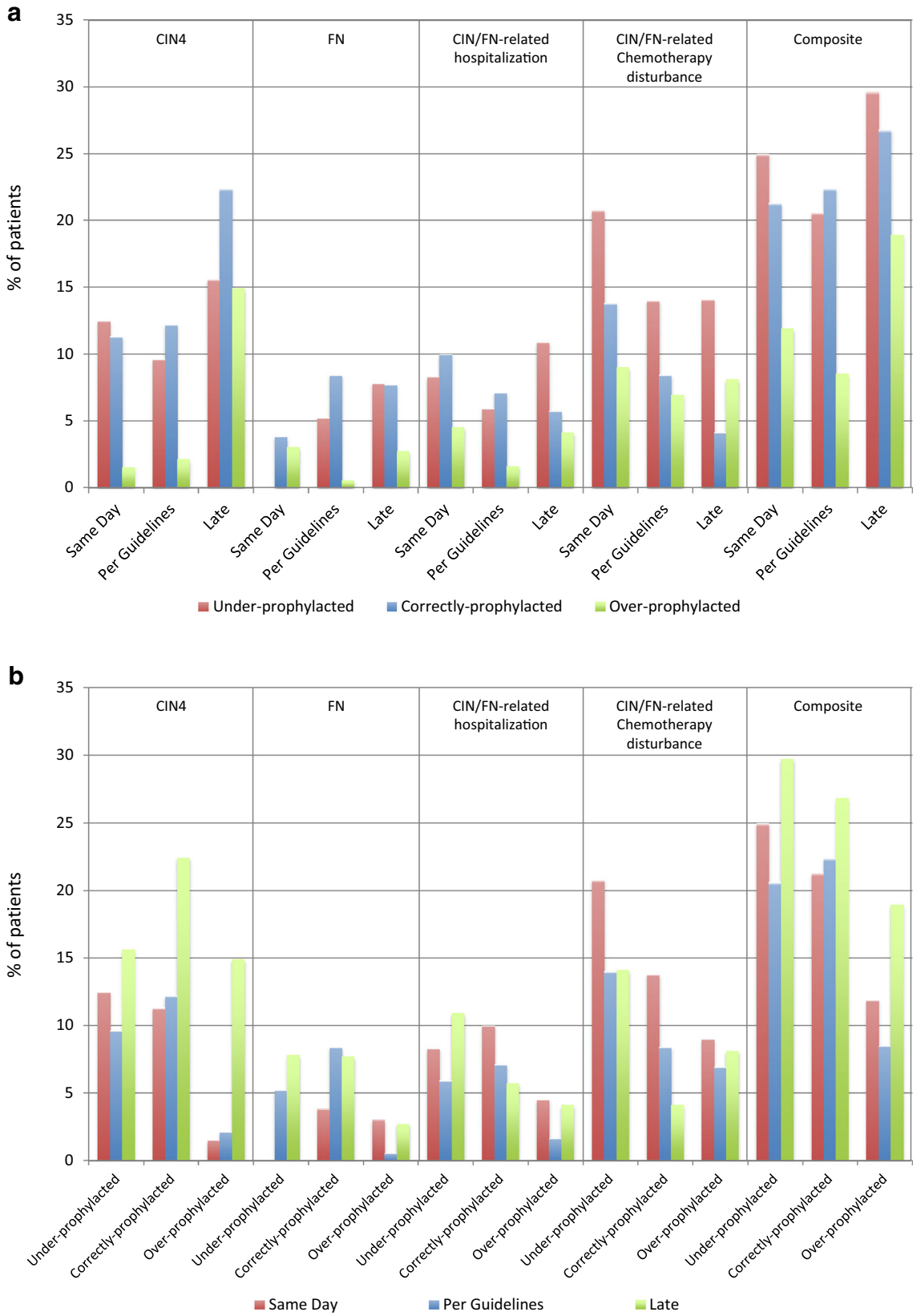

Fig. 2 Patient-level outcomes by **a** day of initiation and prophylaxis decision and **b** prophylaxis decision and day of initiation. CIN chemotherapy-induced neutropenia, FN febrile neutropenia

guidelines, in which clinical judgment, patient risk factors, and patient preferences and barriers are considered [12]. It may explain why approximately one out of seven patients was prophylacted on the day of chemotherapy.

That physicians may have exercised caution is evident from the profile of the *same-day* patients treated mainly with lower-risk chemotherapy regimens: correctly but especially over-prophylacted, perhaps to hedge against the cytotoxic effect of chemotherapy interfering with myeloblast differentiation; with standard (30 MIU/kg) dose Zarzio®; and for durations as short as 1–3 days. In summary, relatively "safe" patients are likely to achieve outcomes similar to those prophylacted *per-guidelines*. One outstanding issue, to be investigated in future studies, is the observation that *same-day* patients may be at greater risk for disruptions to their chemotherapy.

On the other hand, the profile of *late*-initiated patients is less homogeneous. This group, which had a higher likelihood of experiencing CIN episodes "ever" during chemotherapy, and in any given cycle, included proportionally more hematological patients (38.5% vs. 7.6% same-day and 17.0% *per-guidelines*). There is clinical evidence of later initiation in the hematological setting; in fact, we re-assigned to the *per-guidelines* group 168 cycles from 68 patients initiated after 72 h on chemotherapy regimens deemed appropriate for G-CSF initiation on any day of the cycle. Yet, in sub-analyses comparing patients with solid tumors vs. hematological malignancies [unpublished data], the latter group tended to be older (median 64 years, with 49.7% ≥ 65 years), with poorer performance status (66.2% with ECOG 1–2), and being treated with highly myelotoxic chemotherapy (71.4%). However, the concern that patients with multiple myeloma may have influenced the overall rates of CIN/FN outcomes by day of initiation was not supported by the post hoc analysis, as there was no association between multiple myeloma and clinical outcomes. Of note, increased LDH and bone pain were most frequent in the *late* initiation group, which had the greatest proportion of myeloma patients and who may present with these complications in periods of insufficiently controlled disease.

The differences in CIN rates between *late* and other patients cannot be attributed solely to hematological disease, as 61.5% of patients in this group had a solid tumor. One reason may be that clinicians took the risk of *late* initiation per clinical experience, or initiated prophylaxis *late*, when a drop in absolute neutrophil count was observed. Regardless, note that *late* patients were only more likely to experience CIN episodes, not FN episodes, or CIN/FN-related hospitalizations, or chemotherapy disturbances.

To our knowledge, ours is the first analysis of *same-day* initiation of prophylaxis with standard filgrastim. G-CSF support with daily filgrastim is common if not prevailing in many countries. In addition, private payers in the USA have recently begun to disallow prophylaxis with pegfilgrastim, authorizing instead up to 7 days of standard filgrastim. Our findings are consistent with studies on *same-day* prophylaxis with pegfilgrastim. In observational studies, Whitworth et al. found no differences in the rate of CIN, FN, dose modifications, and chemotherapy delays in the setting of gynecological malignancies [4]. Also in this setting, Billingsley et al. reported higher nominal rates of CIN, FN, and dose modifications associated with *same-day* pegfilgrastim administration; however, none of these were statistically significant [10]. None of the patients with non-small cell lung cancer (NSCLC) receiving pegfilgrastim on the same day as chemotherapy in the non-comparative study by Lokich experienced leukopenia necessitating dose interruption or FN [3]. In a non-comparative study of patients with ovarian or primary peritoneal cancer, Schuman et al. observed no episodes of FN or hospitalizations [7]. In the non-Hodgkin's lymphoma setting, Lokich compared 21 cycles with *same-day* pegfilgrastim administration to 22 cycles without prophylaxis [6]. Though nominally higher CIN4 (4/21 vs. 2/22) and FN rates (1/21 vs. 0/22) were reported in the *same-day* cycles, these differences were not statistically significant. In contrast, Cheng et al. reported a significantly higher incidence of FN across all cycles among *same-day* pegfilgrastim non-Hodgkin's lymphoma (NHL) patients, but a non-significant difference after the first cycle [5]. Comparing breast cancer patients treated with dose-dense adjuvant chemotherapy receiving *same-day* pegfilgrastim vs. standard filgrastim on days 2–10, Skarlos et al. observed significantly higher FN rates in the *same-day* pegfilgrastim group, but no differences in severe neutropenia, chemotherapy dose reductions, treatment delays, or treatment discontinuations [8]. Burris et al. summarized four multicenter, double-blind, randomized phase II non-inferiority studies of *same-day* vs. next-day pegfilgrastim prophylaxis in breast cancer, NHL, NSCLC, and ovarian cancer [11]. Increased rates of CIN4, FN, and hospitalization were reported in some studies but not in others, suggesting possible trends that may warrant further study.

Clinically, caution remains warranted when initiating prophylaxis on the day of chemotherapy. *Same-day* prophylaxis cannot be recommended in general; certainly not while phase III randomized controlled trials have not been concluded, and we do not better understand the finding of a higher risk for chemotherapy disturbances. Our findings point at a subgroup of relatively "safe" cancer patients treated mainly with chemotherapy regimens with low or moderate FN risk; correctly but especially over-prophylacted relative to prevailing guidelines, and managed with standard (30 MIU/kg) dose Zarzio® for relatively short durations. Conversely, our findings do not support initiating prophylaxis after the 24–72-h time window, at least not in patients on 2- to 4-weekly chemotherapy regimens. Note also that no unknown safety signals were detected in this study.

In addition to the limitations of the MONITOR-GCSF study identified in our prior analyses [14–17], this present analysis is limited by being from an observational study. A randomized controlled trial is indicated that compares, at a minimum, *same-day* with 24–72-h initiation, but ideally also > 72-h initiation. Such a trial should have balanced treatment arms and highly specific biological and clinical endpoints. It should also include differentiated analyses of chemotherapy disturbances, including the calculation of relative dose intensity, and the impact on tumor control and disease progression. Further, the 24-h and 72-h cut-offs are driven largely by trial evidence. As early as 1997, Crawford and colleagues showed that starting filgrastim on day 4 or day 6 had little impact, but that starting on day 8 had a significant negative impact on hematological recovery [20]. In the *late* cohort, there was a small number of cycles where initiation was delayed due to fever, infection, or low neutrophil count, which could have confounded the outcomes observed. However, the rates on these three variables were not different from those in the *same-day* and *per-guidelines* cohorts.

Conclusion

Real-world evidence from the MONITOR-GCSF study indicates that CIN/FN prophylaxis initiated with Sandoz biosimilar filgrastim within the 24–72-h time window post-chemotherapy is effective and safe. Filgrastim administration on the day of chemotherapy may be appropriate in a select subgroup of patients; this should be per clinicians' best judgment and considering patient preferences and barriers, but may be associated with disruptions of the chemotherapy regimen. Filgrastim given > 72 h post-chemotherapy is not indicated in patients on 2- to 4-weekly chemotherapy regimens. The risk of CIN/FN should be assessed at both the start of chemotherapy and before each cycle. The Sandoz biosimilar filgrastim is an effective and safe agent for primary and secondary prophylaxis of CIN, FN, and associated adverse outcomes.

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Compliance with ethical standards

Conflict of interest CB, PG, MA, HL, and MB received compensation from Sandoz Biopharmaceuticals for their participation in the work reported here. AK is an employee of Hexal AG. KD, IA, and KM are affiliated with Matrix45. By company policy, they cannot hold equity in sponsor organizations and cannot receive direct personal benefits, financial or other, from sponsor organizations. Matrix45 provides similar services to other biopharmaceutical companies without exclusivity constraints.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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