

Over- and under-prophylaxis for chemotherapy-induced (febrile) neutropenia relative to evidence-based guidelines is associated with differences in outcomes: findings from the MONITOR-GCSF study

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Abstract

Purpose In the MONITOR-GCSF study of chemotherapy-induced (febrile) neutropenia with biosimilar filgrastim, 56.6% of patients were prophylaxed according to amended EORTC guidelines, but 17.4% were prophylaxed below and 26.0% above guideline recommendations.

Methods MONITOR-GCSF is a prospective, observational study of 1447 evaluable patients from 140 cancers centers in 12 European countries treated with myelosuppressive chemotherapy for up to 6 cycles receiving biosimilar GCSF prophylaxis. Patients were classified as under-, correctly-, or over-prophylaxed with GCSF relative to guideline recommendations

based on their chemotherapy risk, individual risk factors, and type of GCSF prophylaxis (primary versus secondary).

Results Differences between under- (17.4%), correctly- (56.6%), or over-prophylaxed (26.0%) groups were found in terms of patient risk factors (age, performance status, history of FN, comorbid conditions) as well as prophylaxis patterns (type of prophylaxis, day of GCSF initiation, and GCSF duration). Rates of chemotherapy-induced neutropenia (CIN) (all grades), FN, and CIN-related hospitalizations were consistently lower in over-prophylaxed patients relative to under- and correctly-prophylaxed patients. No differences were observed between under- and correctly-prophylaxed patients except for CIN/FN-related chemotherapy disturbances. No GCSF safety differences were found between groups (except for headaches).

Conclusions The real-world evidence provided by the MONITOR-GCSF study indicates that providing GCSF support may yield better CIN, FN, and CIN/FN-related hospitalization outcomes if patients are prophylaxed at levels above guideline recommendations. Patients who are under-prophylaxed are at higher risk for disturbances to their chemotherapy regimens. Our findings support the guideline recommendation that CIN/FN risk be assessed at the beginning of each chemotherapy cycle.

Keywords Chemotherapy-induced neutropenia · Febrile neutropenia · Granulocyte colony stimulating factor · Filgrastim · EP2006 · Biosimilar · Prophylaxis

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Introduction

Evidence-based guidelines for the prophylaxis of chemotherapy-induced (CIN) and febrile neutropenia (FN) of the European

Organization for Research and Treatment of Cancer (EORTC) [1] and the National Comprehensive Cancer Network (NCCN) [2] recommend that clinical decision-making be based on the relative myelotoxicity of patients' chemotherapy therapy regimens and the presence of potential risk factors. Prophylaxis with granulocyte colony-stimulating factors (GCSF) is indicated for patients treated with chemotherapy with an FN risk $\geq 20\%$ and for patients receiving chemotherapy with an FN risk of 10–20% if they also present with risk factors. No prophylaxis is recommended for patients given chemotherapy with an FN risk $< 10\%$.

The MONITOR-GCSF study was a pan-European multi-center longitudinal prospective study of practice patterns and outcomes associated with CIN/FN prophylaxis with biosimilar filgrastim (EP2006, Zarzio®/ Zarzio®, Hexal AG/ Sandoz International GmbH) that includes 1447 evaluable patients from 140 cancers centers in 12 European countries treated with myelosuppressive chemotherapy across a total of 6213 cycles [3, 4]. This study used the EORTC guidelines [1] as a framework, specifically the algorithm of evaluating the myelotoxicity of the chemotherapy regimen and the associated FN risk ($< 10\%$, 10–20%, $\geq 20\%$) as well as the presence of conditions with high risk (age ≥ 65 years) and increased FN risk (advanced disease, history of FN, no antibiotic prophylaxis), as well as other factors associated with FN (poor performance and/or nutritional status, female gender, hemoglobin < 12 g/dL, renal, cardiovascular, or liver disease). This algorithm was amended by expert consensus to recommend secondary prophylaxis in patients who experienced a CIN or FN episode in a prior cycle and receiving low-risk ($< 10\%$) or medium-risk (10–20%) chemotherapy (Fig. 1). The amended algorithm also specified that secondary prophylaxis was not indicated for patients receiving chemotherapy regimens with $\geq 20\%$ myelotoxicity or with 10–20% myelotoxicity but in the presence of patient risk factors (as primary prophylaxis should have been administered) or for patients treated with regimens with $< 10\%$ or 10–20% myelotoxicity but no CIN/FN in a prior cycle.

We used this amended algorithm to classify patients according to prophylaxis intensity level. As reported earlier, of 1444 classifiable patients, 817 (56.6%) were correctly-prophylacted, 251 (17.4%) were under-prophylacted, and 376 (26.0%) were over-prophylacted (Fig. 1) [5]. Modeling analyses revealed that under-prophylaxis was an independent predictor of patients experiencing an FN episode or a CIN/FN-related hospitalization [6]. In contrast, over-prophylaxis was associated with a lowered risk for a CIN grade 4 or FN episode or a CIN/FN-related hospitalization.

To further explore the impact of prophylaxis intensity below or above guideline-recommended levels, we performed analyses stratified by prophylaxis intensity (under/correctly/over-prophylacted) that compare patients' in terms of demographics and clinical status at the start of chemotherapy, Zarzio® prophylaxis patterns, and clinical and safety

outcomes. In keeping with our prior reports [5, 6], we distinguish between results using patients and results using cycles as the unit of analysis. The patient-level evaluations focus on outcomes “ever” experienced anytime during the whole period of chemotherapy and inform about patient outcomes across this line of chemotherapy. The cycle-level analyses target outcomes recorded during a particular cycle and from 1 cycle to the next, and inform about outcomes as patients progress through the cycles of chemotherapy.

Methods

The background and methodology of MONITOR-GCSF [3, 4] as well as the study sample's demographics and clinical status at baseline, Zarzio® prophylaxis, and outcomes [5] have been described elsewhere. We summarize below elements relevant to the present analyses.

Design

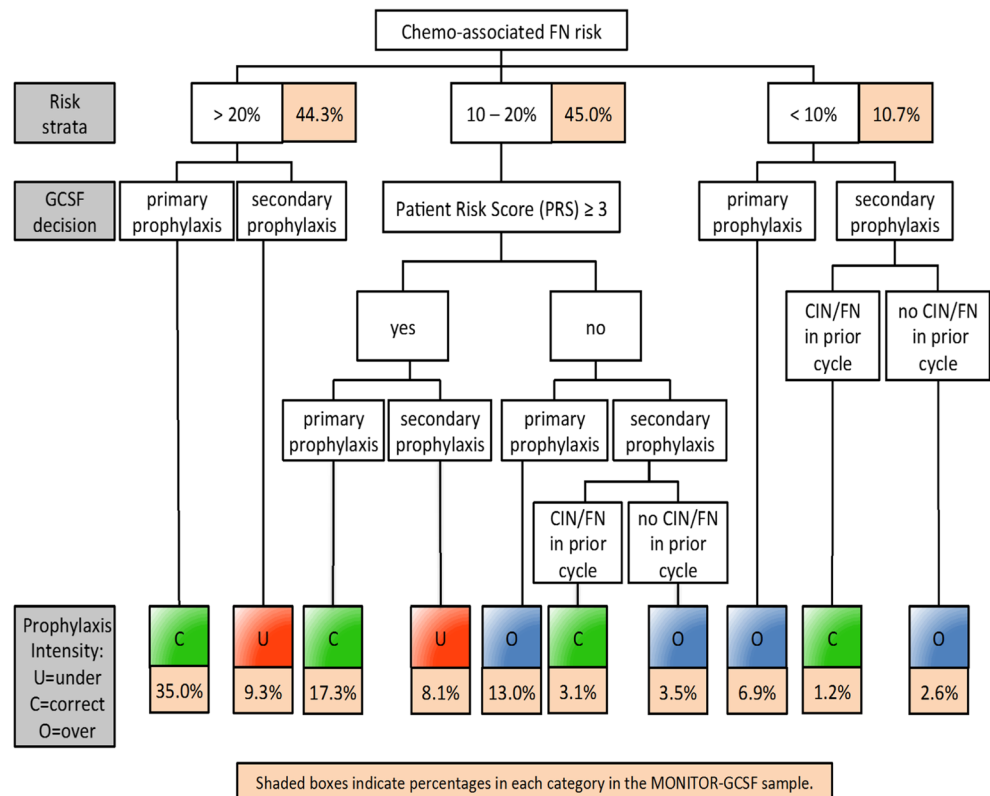
MONITOR-GCSF is a prospective, real-world, observational study of cancer patients receiving myelosuppressive chemotherapy, whose treating physicians prescribed CIN/FN prophylaxis with biosimilar filgrastim (EP2006, Zarzio®) per their best clinical judgment. Eligible were adults (age ≥ 18) with stages 3 or 4 breast, ovarian, bladder, or lung cancer; metastatic prostate cancer; and stages 3 or 4 diffuse large B-cell lymphoma or multiple myeloma. Patients were followed up for a maximum of six chemotherapy cycles. Patients were classified as to prophylaxis intensity according the schematic in Fig. 1.

Outcomes

The following outcomes were recorded at both the patient- and cycle-levels: occurrence of an episode of CIN of any grade (CIN1/4), specified further as CIN grades 3 or 4 (CIN3/4), CIN grade 4 (CIN4), or an FN episode; CIN/FN-related hospitalization or chemotherapy disturbance (dose reduction, delay in administration of chemotherapy, cancelation of administration 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 patient risk factors associated with CIN/FN specified in the EORTC guidelines [1] and was developed by consensus by four of the authors (C.B., P.G., M.A., H.L). Weights of three were assigned to *age ≥ 65* and *history of prior FN*; 1.5 to *advanced disease* and *poor performance and/or nutritional status*; and 0.5 to *no antibiotic prophylaxis, female*

Fig. 1 Treatment decision relative to EORTC guidelines

gender, hemoglobin <12 g/dL, and renal, cardiovascular or liver disease. A PRS ≥ 3 was used to consider a patient as being at elevated risk for CIN/FN (Fig. 1).

Cycle data were “nested” under patients and patients under centers, violating the assumption of statistical independence. Hence we applied generalized estimating equations (GEE) [7], which adjust standard errors based on within-cluster correlations, to estimate adjusted odds ratios (OR) and 95% confidence intervals (95%CI). We calculated ORs for each outcome for each prophylaxis intensity cohort separately to determine the odds of each outcome for each cohort, as well as in pairwise combinations, to contrast the relative odds of one prophylaxis intensity level against another level. Chemotherapy disturbances were estimated for the cycle after (lag = 1) the CIN/FN event occurred.

Results

Patients

Of the 1444 patients who could be classified as to prophylaxis intensity, 817 (56.6%) were correctly-prophylaxed, 251 (17.4%) were under-prophylaxed, and 376 (26.0%) were over-prophylaxed (Fig. 1; Table 1). The three cohorts were similar in terms of gender and history of repeated infections (both $p = \text{n.s.}$). They

differed in terms of average age ($p < 0.001$), with under-prophylaxed patients older and over-prophylaxed patients younger than correctly-prophylaxed patients. The cohorts also varied in performance status ($p = 0.011$), with proportionately more over-prophylaxed patients having ECOG 0/1 scores and more under-prophylaxed patients having ECOG 1/2 scores relative to correctly-prophylaxed patients. When comparing the cohorts on the EORTC risk factors, no differences were observed in the proportions of female patients and those without antibiotic prophylaxis (both $p = \text{n.s.}$). However, there were proportionately more under-prophylaxed patients age ≥ 65 ($p < 0.001$), with a history of FN ($p = 0.029$), Hb <12 g/dL ($p < 0.001$), and renal, cardiovascular, or liver disease ($p < 0.001$). Both under- and over-prophylaxed patients had proportionately more patients with advanced disease ($p = 0.009$) but fewer with poor performance and/or nutritional status ($p = 0.005$) compared to correctly-prophylaxed patients. Mean PRS was highest among under-prophylaxed and lowest among over-prophylaxed patients ($p < 0.001$).

The over-prophylaxed cohort included significantly more patients with solid and fewer with hematological malignancies compared to the under- and correctly-prophylaxed cohorts ($p = 0.009$), who did not differ from each other ($p = \text{n.s.}$). Both the under- and over-prophylaxed cohorts had proportionately more patients previously treated with chemotherapy

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

	Under 251 (17.4%)	Correct 817 (56.6%)	Over 376 (26.0%)	<i>p</i>
Demographics and clinical status				
Gender				n.s.
Male	45.0%	37.2%	37.8%	
Female	55.0%	62.8%	62.2%	
Age (M ± SD, Mdn)	65.2 ± 11.0, 67	61.8 ± 12.5, 63	57.7 ± 9.5, 58	<0.001
ECOG performance status				
0	31.5%	40.7%	47.4%	
1	57.8%	46.1%	46.5%	
2	9.9%	10.9%	4.2%	0.011
3	0.9%	2.4%	1.7%	
4	0.0%	0.0%	0.3%	
History of repeated infections	4.3%	2.3%	2.0%	n.s.
FN risk factors (EORTC)				
High risk				
Age ≥ 65 years	61.4%	46.1%	17.3%	<0.001
Increased risk				
Advanced disease ^a	15.3%	11.2%	18.2%	0.009
History of FN	6.5%	0.8%	1.8%	0.029
No antibiotic prophylaxis	90.0%	85.4%	91.6%	n.s.
Other factors				
Poor performance and/or nutritional status	11.8%	16.2%	8.5%	0.005
Female gender	55.0%	62.8%	62.2%	n.s.
Hemoglobin <12 g/dL	60.0%	34.4%	39.4%	<0.001
Renal, cardiovascular, or liver disease	31.6%	24.7%	13.5%	<0.001
Patient risk score (M ± SD, Mdn)	3.8 ± 2.0, 4	2.9 ± 2.0, 3	2.0 ± 1.6, 1.5	<0.001
Cancer				
Tumor type				0.009
Solid	72.5%	73.7%	88.0%	
Hematological	27.5%	26.3%	12.0%	
Prior treatments				
Chemotherapy	37.1%	26.9%	39.1%	0.004
Of these adjuvant in metastatic setting	41.8%	48.2%	50.4%	n.s.
Of these prior lines of chemo	48.1%	47.7%	56.1%	n.s.
1	42.1%	48.9%	60.3%	
2	31.6%	27.3%	24.7%	n.s.
≥3	26.3%	23.9%	15.1%	
Radiation therapy	19.5%	16.9%	23.1%	n.s.
Chemotoxicity				
<10%	0.0%	2.1%	36.4%	<0.001
10–20%	46.6%	36.0%	63.6%	
≥20%	53.4%	61.9%	0.0%	

^a Stage 4 (stage 3 if multiple myeloma) and prior chemotherapy in metastatic setting *n.s.* not significant

(*p* = 0.004); however, there were no differences between cohorts as to whether this was in the adjuvant or meta-static setting, nor the number of prior lines of chemotherapy (all *p* = *n.s.*). Cohorts had similar rates of prior radiation therapy

(*p* = *n.s.*). There was an association between prophylaxis intensity and chemotoxicity. All over-prophylacted patients were treated with regimens with <10% (36.4%) and 10–20% FN risk (63.6%), whereas all under-prophylacted patients

received chemotherapy with 10–20% (46.6%) and $\geq 20\%$ (53.4%) FN risk. 61.9% of correctly-prophylaxed patients were administered regimens with $\geq 20\%$ FN risk ($p < 0.001$).

Prophylaxis patterns

All under-prophylaxed patients received secondary prophylaxis only, almost all (92.4%) of correctly-prophylaxed patients had primary prophylaxis, whereas 76.6% of over-prophylaxed patients were given primary and 23.4% secondary prophylaxis ($p < 0.001$) (Table 2). The median day of Zarzio® initiation was the second day after chemotherapy; however, the mean initiation day for over-prophylaxed patients was 2.70 days post-chemotherapy, compared to 2.99 for under- and 3.26 for correctly-prophylaxed patients ($p = 0.001$). Further, 19.5% of over-prophylaxed patients were initiated on the day of chemotherapy completion, compared to 12.1 and 11.2% of, respectively, under- and correctly-prophylaxed patients. Despite a similar median prophylaxis duration of 5 days across all three cohorts, mean duration was shortest for over-prophylaxed and longest for under-prophylaxed patients ($p < 0.001$). Cohorts did not differ in terms of proportions of patients given 30 MIU/day versus 40 MIU/day of Zarzio®.

Outcomes

Consistently, whether in the patient- or the cycle-level analyses, the three cohorts differed overall in the observed rates of CIN1/4, CIN3/4, CIN4, and FN, CIN/FN-related hospitalizations, and the composite outcome score (all $p \leq 0.001$) (Table 3). The proportions of patients experiencing CIN/FN-related chemotherapy disturbances were not statistically different across cohorts ($p = \text{n.s.}$); however, the proportion of cycles with chemotherapy disturbances was highest among under-prophylaxed patients ($p = 0.032$).

Pairwise contrast analyses at the patient-level showed that, generally, the likelihood of CIN and FN episodes anytime during chemotherapy did not differ between under- and correctly-prophylaxed patients (all $p = \text{n.s.}$) (Table 4). However, over-prophylaxed patients were less likely to experience CIN/FN than correctly-prophylaxed patients *ever* during chemotherapy (all $p < 0.001$) or in any given cycle ($p < 0.001$ for all CIN, $p = 0.004$ for FN). Compared to over-prophylaxed patients, under-prophylaxed patients had a greater likelihood of CIN and FN anytime during chemotherapy ($p = 0.044$ to $p < 0.001$).

Pairwise contrast analyses at the cycle-level revealed that the likelihood of CIN/FN in a given cycle did not differ between under- and correctly-prophylaxed patients (all $p = \text{n.s.}$) (Table 4). Over-prophylaxed patients were less likely to experience CIN/FN than correctly-prophylaxed patients in any given cycle ($p < 0.001$ for all CIN, $p = 0.004$ for FN). Under-

prophylaxed patients had a greater likelihood of CIN and FN in any given cycle compared to over-prophylaxed patients ($p = 0.025$ to $p < 0.001$).

Safety

With the exception of proportionately fewer under-prophylaxed patients experiencing headaches ($p = 0.027$), differences between cohorts in the rates of patients reporting clinical events of interest during the course of chemotherapy were not statistically significant (all $p = \text{n.s.}$) (Table 5). Reported rates of adverse drug reactions over 6142 cycles were statistically similar across the three cohorts ($p = \text{n.s.}$).

Discussion

By the time of the approval of Zarzio® by the European Medicines Agency in 2008 and the launch of the MONITOR-GCSF study in 2010, two decades of evidence with reference filgrastim had accumulated. Much of this was summarized in, for example, the original [8] and updated EORTC guidelines [1] and in systematic reviews and meta-analyses [9–16]. In the process, it became apparent that the normative, trial-based prophylaxis pattern of treating with standard GCSFs through the nadir of the absolute neutrophil count (ANC) was being replaced with shorter regimens varying across tumor types in the average number of injections [17].

The relative maturity of the clinical experience with standard GCSFs in routine clinical practice was documented in our earlier report on treatment patterns and outcomes in the MONITOR-GCSF study [5]. The median duration of prophylaxis was 5 days, and there were no differences in mean duration between patients receiving primary and those receiving secondary prophylaxis and when comparing oncological versus hematological patients. However, mean durations were progressively longer as the relative FN risk of patients' chemotherapy regimens rose from $< 10\%$ ($M = 4.59$ days) to 10–20% ($M = 4.98$) and $\geq 20\%$ ($M = 5.33$) ($p < 0.001$). Also noted were differences in prophylaxis intensity relative to the amended EORTC guidelines used in the MONITOR-GCSF study. Slightly over half of patients (56.6%) were prophylaxed relative to the guidelines, about one in six patients received less prophylaxis than recommended, and about a quarter were administered more prophylaxis than advised by the guidelines. These deviations from evidence-based guidelines in daily clinical practice suggest either questionable clinical practice or may provide new real-world data to integrate into guidelines as the evidence migrates from initial RCT-based findings to incorporating real-world data from a mature clinical experience base in GCSF support and CIN/FN prophylaxis.

Table 2 Zarzio® prophylaxis patterns

Type of prophylaxis	Under	Correct	Over	<i>p</i>
Primary	0.0%	92.4%	76.6%	<0.001
Secondary	100.0%	7.6%	23.4%	
Dose	Under	Correct	Over	n.s.
30 MIU/day	51.4%	53.4%	55.1%	
48 MIU/day	48.6%	46.6%	44.9%	
Day of initiation ^a	Under	Correct	Over	<0.001
0 (during chemo)	12.1%	11.2%	19.5%	
1–3 (according to guidelines)	59.3%	55.2%	56.8%	
4 or more (late)	28.6%	33.5%	23.7%	
	Mean	SD	Median	
By prophylaxis decision				0.001
Under	2.99	3.01	2	
Correct	3.26	2.99	2	
Over	2.70	2.92	2	
Duration of prophylaxis at baseline (days)				
	Under	Correct	Over	
1	3.3%	2.6%	5.3%	
2	5.3%	3.4%	10.5%	
3	17.9%	12.1%	15.5%	
4	3.7%	7.7%	4.7%	
5	41.5%	46.8%	42.8%	
6	5.3%	7.4%	6.4%	
7	11.0%	11.5%	9.1%	
8	3.3%	1.9%	2.2%	
9	0.8%	1.5%	0.6%	
10	2.0%	2.2%	0.8%	
11	1.2%	0.4%	0.3%	
12	1.2%	0.4%	0.0%	
13	0.0%	0.3%	0.3%	
14	2.9%	1.6%	1.4%	
≥15	0.8%	0.2%	0.3%	
	Mean	SD	Median	
By prophylaxis decision				<0.001
under	5.44	2.70	5	
correct	5.20	2.20	5	
over	4.72	2.33	5	
Duration (all visits)	Under	Correct	Over	0.001
1–3 days	23.7%	18.0%	29.1%	
4–5 days	47.1%	55.0%	50.7%	
6 + days	29.2%	27.0%	20.2%	

^a Zarzio® initiation expressed in days after chemotherapy

0 same day, 1 1 day after, 2 2 days after, etc. n.s. not significant

The analyses stratified by prophylaxis intensity reported here revealed that, compared to correctly-prophylaxed patients, under-prophylaxed patients were at no greater risk for experiencing CIN (all grades) and FN episodes, nor for CIN/FN-related hospitalizations, over the course of their chemotherapy regimen; though they were at increased risk for disturbances to this regimen. Relative to over-prophylaxed

patients, under-prophylaxed patients were at significantly higher risk for adverse outcomes over the period of chemotherapy, including a twofold increased risk for disruptions to their chemotherapy regimen and a threefold greater likelihood of CIN/FN-related hospitalizations. The apparent incremental protective effect of over-prophylaxis was also evident from comparisons to correctly-prophylaxed patients. The odds of

Table 3 Clinical outcomes at the patient and cycle levels by prophylaxis decision

	Under		Correct		Over		<i>p</i>
	%	95% CI	%	95% CI	%	95% CI	
Unit of analysis, patient							
Neutropenia episodes							
CIN grades 1 through 4	41.0%	(32.7%–49.9%)	39.9%	(32.8%–47.4%)	19.7%	(14.4%–26.3%)	<0.001
CIN grades 3 or 4	24.3%	(18.3%–31.6%)	27.4%	(21.3%–34.5%)	12.5%	(8.5%–18.1%)	<0.001
CIN grade 4	12.0%	(8.2%–17.2%)	16.8%	(12.4%–22.3%)	6.4%	(3.9%–10.3%)	<0.001
FN	5.2%	(2.6%–10.0%)	8.0%	(6.1%–10.3%)	2.1%	(1.1%–4.1%)	<0.001
CIN/FN-related hospitalizations	8.0%	(4.8%–12.9%)	7.1%	(5.0%–10.0%)	2.7%	(1.4%–4.9%)	0.001
CIN/FN-related chemotherapy disturbances ^a	14.7%	(10.4%–20.5%)	8.8%	(6.4%–12.1%)	7.7%	(4.9%–11.9%)	n.s.
CIN/FN-related composite outcome ^b	24.7%	(18.5%–32.2%)	26.0%	(21.2%–31.4%)	13.0%	(9.4%–17.8%)	<0.001
Unit of analysis, cycle							
Neutropenia episodes							
CIN grades 1 through 4	17.9%	(14.7%–21.7%)	16.0%	(14.3%–17.9%)	8.3%	(6.4%–10.7%)	<0.001
CIN grades 3 or 4	9.5%	(7.2%–12.4%)	9.4%	(8.2%–10.9%)	3.8%	(2.8%–5.3%)	<0.001
CIN grade 4	4.0%	(2.8%–5.8%)	4.8%	(4.0%–5.8%)	1.7%	(1.1%–2.7%)	<0.001
FN	1.6%	(0.9%–2.9%)	1.7%	(1.3%–2.2%)	0.5%	(0.2%–1.1%)	<0.001
CIN/FN-related hospitalizations	2.5%	(1.6%–4.1%)	1.6%	(1.2%–2.2%)	0.6%	(0.3%–1.1%)	<0.001
CIN/FN-related chemotherapy disturbances ^a	4.2%	(3.1%–5.7%)	2.4%	(1.9%–3.0%)	2.3%	(1.6%–3.4%)	0.032
CIN/FN-related composite outcome ^b	8.6%	(6.7%–11.0%)	7.5%	(6.5%–8.6%)	3.9%	(2.9%–5.3%)	<0.001

^a Type of chemotherapy disturbances are not mutually exclusive. Any patient may have experienced more than one type. Measured with 1 cycle lag

^b Includes any occurrence of CIN grade 4, FN, CIN/FN-related hospitalization, and/or CIN/FN-related chemotherapy disturbance. *CI* confidence interval *n.s.* not significant

CIN or FN episodes during the course of chemotherapy were significantly lowered, as were the odds for hospitalization. This protective effect did not extend to preventing disruptions to the chemotherapy regimen. As a caution, note that these and similar results about prophylaxis intensity and CIN/FN outcomes were obtained from association-based analyses.

The relative robustness of these findings at the patient-level were confirmed in the cycle-level analyses. The likelihood of CIN and FN episodes and CIN/FN-related hospitalizations during a given cycle was not statistically different in under-prophylacted patients when compared to correctly-prophylacted patients, but was statistically different relative to over-prophylacted patients. The likelihood of chemotherapy regimens being changed in a subsequent cycle was greater for under-prophylacted patients compared to other patients, but not for correctly-prophylacted patients. The relative robustness of both the patient- and cycle-level findings was underscored in the analyses of the composite outcome, which was an index of the “worst case scenario” of experiencing CIN grade 4, FN, CIN/FN-related hospitalizations, and/or CIN/FN-related chemotherapy disturbances ever during the course of chemotherapy or from 1 cycle to the next.

The patient- and cycle-level analyses of prophylaxis intensity draw attention to some well-established CIN/FN risk factors that are ignored in some cases leading to under-prophylaxis or are emphasized in other cases leading to

prophylaxis patterns “above” the guideline recommendation. These include age 65 years or older, ECOG performance score, tumor type, prior chemotherapy, and prior history of FN.

Note in this regard that the cycle-level analyses affirmed that CIN/FN outcomes may be a function of the cycle of chemotherapy, not just of the chemotherapy regimen in general. The results from these analyses enable clinicians to evaluate the risk of a CIN/FN episode at the start of each cycle, not just at the start of chemotherapy. This is consistent with the guideline recommendations to re-evaluate the risk of CIN/FN at the beginning of each cycle and to take the necessary precautions to prevent adverse CIN/FN outcomes.

The findings that, generally, under- and correctly-prophylacted patients were at similar risk of adverse CIN/FN outcomes (except for chemotherapy disturbances) may seem counter-intuitive as one would expect that the former would have worse outcomes than the latter. Certainly, under-prophylaxis is not indicated in general, in fact, the finding confirms the general need for prophylaxis. Clinicians’ decision-making may play a role here, as they may choose to deviate from guideline recommendations, rely on clinical experience, determine CIN/FN prophylaxis on a case-by-case basis, and, as a result, under-prophylact some patients treated with less myelotoxic regimens, better clinical and performance status, and fewer if any risk factors. In fact,

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

	Under- versus correctly-prophylacted			Over-versus correctly-prophylacted			Under-versus over-prophylacted		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Unit of analysis, patient									
Neutropenia episodes									
CIN grades 1 through 4	1.048	0.720–1.527	n.s.	0.369	0.261–0.522	<0.001	2.840	1.859–4.339	<0.001
CIN grades 3 or 4	0.850	0.571–1.266	n.s.	0.378	0.261–0.547	<0.001	2.247	1.378–3.665	0.001
CIN grade 4	0.674	0.420–1.081	n.s.	0.338	0.206–0.555	<0.001	1.991	1.111–3.569	0.021
FN	0.632	0.301–1.326	n.s.	0.252	0.121–0.524	<0.001	2.513	1.025–6.157	0.044
CIN/FN-related hospitalizations	1.133	0.640–2.007	n.s.	0.358	0.195–0.657	<0.001	3.169	1.555–6.457	0.002
CIN/FN-related chemotherapy disturbances ^a	1.789	1.141–2.806	0.011	0.865	0.553–1.353	n.s.	2.069	1.150–3.723	0.015
CIN/FN-related composite outcome ^b	0.936	0.627–1.398	n.s.	0.428	0.293–0.624	<0.001	2.189	1.375–3.486	0.001
Unit of analysis, cycle									
Neutropenia episodes									
CIN grades 1 through 4	1.147	0.875–1.503	n.s.	0.475	0.348–0.648	<0.001	2.415	1.674–3.484	<0.001
CIN grades 3 or 4	1.006	0.718–1.411	n.s.	0.381	0.262–0.555	<0.001	2.638	1.679–4.146	<0.001
CIN grade 4	0.834	0.541–1.285	n.s.	0.348	0.213–0.569	<0.001	2.395	1.323–4.333	0.004
FN	0.926	0.482–1.779	n.s.	0.301	0.132–0.686	0.004	3.081	1.150–8.254	0.025
CIN/FN-related hospitalizations	1.588	0.895–2.818	n.s.	0.354	0.174–0.718	0.004	4.489	2.008–10.033	<0.001
CIN/FN-related chemotherapy disturbances ^a	1.824	1.216–2.734	0.004	0.991	0.634–1.550	n.s.	1.840	1.124–3.012	0.015
CIN/FN-related composite outcome ^b	1.169	0.855–1.599	n.s.	0.504	0.357–0.713	<0.001	2.318	1.532–3.505	<0.001

^aType of chemotherapy disturbances are not mutually exclusive. Any patient may have experienced more than one type. Measured with 1 cycle lag

^bIncludes any occurrence of CIN grade 4, FN, CIN/FN related hospitalization, and/or CIN/FIN-related chemotherapy disturbances *n.s.* not significant

proportionately more under-prophylacted patients were male, over the age of 65, with ECOG scores of 1 or 2, and generally

in poorer health compared to correctly-prophylacted patients. Despite these differences, the prophylaxis patterns of both

Table 5 Safety outcomes by prophylaxis decision

	Under	Correct	Over	<i>p</i>
Clinical Events (patient level, <i>n</i> = 1447)				
Bone pain	23.6%	28.5%	25.0%	n.s.
Thrombocytopenia	19.4%	17.4%	17.7%	n.s.
Serum LDH increase	16.6%	20.2%	14.4%	n.s.
Muscle pain	12.1%	16.8%	16.1%	n.s.
Joint pain	11.6%	15.9%	15.6%	n.s.
Serum GGT increase	12.8%	14.9%	15.4%	n.s.
Serum ALP increase	11.9%	13.3%	15.3%	n.s.
Other neurological symptoms	8.7%	7.5%	7.4%	n.s.
Headache	3.4%	8.9%	7.3%	0.027
Blood uric acid increase	9.3%	7.7%	5.0%	n.s.
Confusion/altered mental status	3.5%	2.6%	4.6%	n.s.
Epistaxis	1.8%	2.2%	2.5%	n.s.
Bleeding other than GI, skin hemorrhage	2.6%	2.0%	2.8%	n.s.
Splenomegaly	1.3%	1.2%	0.3%	n.s.
GI bleeding	0.4%	0.9%	0.3%	n.s.
Skin hemorrhage	0.4%	0.8%	0.3%	n.s.
Adverse drug reactions (cycle-level, <i>n</i> = 6142)	2.3%	1.8%	1.5%	n.s.

ALP alkaline phosphatase, GGT gamma glutamyl transpeptidase, GI gastro intestinal, LDH lactate dehydrogenase *n.s.* not significant

cohorts were similar in terms of Zarzio® dose, day of prophylaxis initiation, duration of prophylaxis, except that all under-prophylaxed patients were on secondary, and virtually all correctly-prophylaxed patients were on primary prophylaxis.

Our findings point at the relative benefit of prophylacting at a higher intensity than recommended in the guidelines. This does not mean that over-prophylaxis is indicated across-the-board, but may merit consideration for selected patients. Proportionally, over-prophylaxed patients tended to be younger; with no or minimal impairment in performance status; with only a few presenting with comorbid renal, cardiovascular, or liver; with lower Patient Risk Scores; with mainly solid tumors in more advanced stages of disease; having received a prior line of chemotherapy; and currently being treated with regimens with <10% or 10–20% FN risk. For instance, one-third of patients ($n = 466$, 32.2%) in the study had stages III or IV breast cancer. Of the 408 breast cancer patients who had an ECOG score of 0 or 1, 28.4% were over-prophylaxed, slightly higher than (and contributing to) the full sample rate of 26.0%. However, the over-prophylaxis rate was 37.3% in stage IV breast cancer patients with ECOG score of 0 or 1, and 36.3% in stage III patients with an ECOG score of 0.

Over-prophylaxis may indicate a “playing-it-sure-and-safe” approach among clinicians, by focusing on subgroups of patients with a more balanced profile of risk factors in which a more intense prophylaxis approach is believed to lead to better outcomes. In contrast to the perhaps more benign (relatively speaking, that is) profile of over-prophylaxed patients, under-prophylaxed patients were generally the opposite: proportionately older, more impaired in performance, with more of them presenting with major comorbid disease, with more of them being treated for a hematological malignancy, with ≥ 2 prior lines of chemotherapy, and currently receiving myelotoxic chemotherapy regimens with 10–20% or $\geq 20\%$ FN risk. Of concern, this may reflect a trend in routine clinical practice to ignore the interaction of patient risk factors with the myelotoxicity of their chemotherapy regimens, leading to inadequate CIN/FN prophylaxis. Worse, it might reflect a trend to under-prophylact patients with a poor prognosis.

Whether there is an association between prophylaxis intensity and the occurrence of CIN/FN-related chemotherapy disturbances remains unclear, at least partially. Whether at the chemotherapy regimen level or the chemotherapy cycle level, under-prophylaxis was associated with an elevated risk of either dose reductions and delayed or canceled chemotherapy sessions.

The safety analyses revealed no differences in the rates of clinical events between the three prophylaxis intensity cohorts. The exception was headache, which was reported with greater frequency in correctly- and over-prophylaxed

patients. This might be related to the fact that under-prophylaxed patients received secondary prophylaxis and therefore had less drug exposure. Likewise, the rates of adverse drug reactions observed across cycles were similar across the three cohorts. The safety profile corresponds to what is known about standard filgrastim in general and biosimilar filgrastim in particular [18].

The analyses reported here warrant some caution in addition to limitations identified in our prior reports on the MONITOR-GCSF study [5, 6]. We classified patients into three levels of prophylaxis intensity, and further gradations might be possible. However, this may render comparative analyses more unwieldy if not overwhelming and yield differentiations that may not be clinically meaningful. Future analyses should also attempt to identify alternate methods for classifying patients into prophylaxis intensity categories that go beyond the amended EORTC assessment algorithm and take into account on-treatment data and markers. Our analyses were associative and the MONITOR-GCSF study was not designed to compare the effect of different levels of prophylaxis intensity to each other and an untreated control group. Such a comparison may not show a difference in outcome, and randomized controlled trials are necessary to evaluate the impact of differential prophylaxis on CIN/FN outcomes. We had the benefit of a large sample size. While lending statistical power to the study, it may also yield statistically significant results that may not necessarily be clinically meaningful.

The conclusion that clinicians’ prophylaxis decisions may have been driven in part by patient-specific factors implies that, methodologically, there may have been a patient selection bias. However, by the same token and perhaps more relevant from a real-world evidence point of view, this may reflect routine clinical practice. This underscores the external validity of our findings.

Conclusion

The real-world evidence provided by the MONITOR-GCSF study indicates that providing GCSF support may yield better CIN, FN, and CIN/FN-related hospitalization outcomes if patients are prophylaxed at levels above guideline recommendations. In contrast, patients who received inadequate GCSF prophylaxis are at markedly higher risk for poor outcomes. Our analyses show that guidelines may not be followed due to clinicians’ expectation of therapeutic benefit and clinical outcome, and provide real-world evidence to be integrated into future guidelines for GCSF prophylaxis in patients with solid tumors and hematological malignancies.

Compliance with ethical standards

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