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Predictive modeling of the outcomes of chemotherapy-induced (febrile) neutropenia prophylaxis with biosimilar filgrastim (MONITOR-GCSF study)

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Background: Risk models of chemotherapy-induced (CIN) and febrile neutropenia (FN) have to date focused on determinants measured at the start of chemotherapy. We extended this static approach with a dynamic approach of CIN/FN risk modeling at the start of each cycle.

Design: We applied predictive modeling using multivariate logistic regression to identify determinants of CIN/FN episodes and related hospitalizations and chemotherapy disturbances (CIN/FN consequences) in analyses at the patient ('ever' during the whole period of chemotherapy) and cycle-level (during a given chemotherapy cycle). Statistical dependence of cycle data being 'nested' under patients was managed using generalized estimation equations. Predictive performance of each model was evaluated using bootstrapped *c* concordance statistics.

Results: Static patient-level risk models of 'ever' experiencing CIN/FN adverse events and consequences during a planned chemotherapy regimen included predictors related to history, risk factors, and prophylaxis initiation and intensity. Dynamic cycle-level risk models of experiencing CIN/FN adverse events and consequences in an upcoming cycle included predictors related to history, risk factors, and prophylaxis initiation and intensity; as well as prophylaxis duration, CIN/FN in prior cycle, and treatment center characteristics.

Conclusion(s): These 'real-world evidence' models provide clinicians with the ability to anticipate CIN/FN adverse events and their consequences at the start of a chemotherapy line (static models); and, innovatively, to assess risk of CIN/FN adverse events and their consequences at the start of each cycle (dynamic models). This enables individualized patient treatment and is consistent with the EORTC recommendation to re-appraise CIN/FN risk at the start of each cycle. Prophylaxis intensity (under-, correctly-, or over-prophylacted relative to current EORTC guidelines) is a major determinant. Under-prophylaxis is clinically unsafe. Over-prophylaxis of patients administered chemotherapy with intermediate or low myelotoxicity levels may be beneficial, both in patients with and without risk factors, and must be validated in future studies.

Key words: chemotherapy-induced neutropenia, febrile neutropenia, granulocyte colony-stimulating factor, filgrastim, biosimilar, modeling

introduction

Granulocyte colony-stimulating factors (GCSF) are biological agents that stimulate production of white blood cells and are indicated in the prophylaxis of chemotherapy-induced (CIN) and febrile neutropenia (FN) [1–3]. Short- and long-acting/pegylated formulations of filgrastim have been shown to be efficacious in reducing the incidence of FN episodes, the severity and duration of these episodes, and the risk for chemotherapy dose reduction, discontinuation, or delay—with no sustained evidence of superiority of either formulation [1, 3–8]. Risk factors for CIN/FN have been identified [2, 5, 9–12], yet predominantly as static variables present at the beginning of a study, not as dynamic variables that may change as patients proceed through several cycles of chemotherapy.

Since the loss of exclusivity of reference filgrastim (Neupogen®, Amgen) in Europe, the European Medicines Agency has approved

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several biosimilar agents, including Zarzio® (EP2006, Sandoz), which was also approved as a biosimilar by the US Food and Drug Administration in March 2015. The MONITOR-GCSF study evaluated the 'real-world' treatment patterns, outcomes, and associated determinants of Zarzio® prophylaxis in patients with stage 3 or 4 solid or hematological malignancies receiving myelosuppressive chemotherapy and at risk for CIN/FN [13–15] using the 2010 updated European Organisation for Research and Treatment of Cancer (EORTC) guidelines for the use of GCSF in the prophylaxis of CIN/FN as framework [2].

We reported recently on the real-world treatment patterns and associated outcomes of Zarzio® prophylaxis observed in the 1447 patients from 140 cancer centers in Europe enrolled in MONITOR-GCSF [15]. Tumor types included were: stage 3 or 4 breast, ovarian, bladder, or lung cancer; metastatic prostate cancer; stage 3 or 4 diffuse large B-cell lymphoma or multiple myeloma (note that acute leukemias were excluded). The following incidence rates were observed at the patient-level and indicate the rate that patients '*ever*' experienced a given outcome over the course of chemotherapy: 13.2% for CIN grade 4 (CIN4), 5.9% for FN, 6.1% for CIN/FN-related hospitalizations, 9.5% for any chemotherapy disturbance (dose reduction, discontinuation, or delay), and 22.3% for a CIN/FN-related composite index score of any occurrence of these four outcomes. Rates were also calculated at the cycle-level, indicating the incidence that these outcomes were recorded in a given cycle (after correcting for statistical dependence): 3.9% for CIN4, 1.4% for FN, 1.5% for CIN/FN-related hospitalizations, 2.8% for any CIN/FN-related chemotherapy disturbances, and 6.7% for the composite score.

In follow-up, we report here on the predictive modeling of determinants of these outcomes in the real-world setting. Hence, we departed from actual observations of clinicians' prophylaxis patterns and associated patient outcomes [15] to derive predictive models of the determinants of these outcomes. We assumed that the determinants driving outcomes reflect the clinical factors that clinicians considered in their prophylaxis decisions.

We distinguish between static models using patients and dynamic models using chemotherapy cycles as the unit of analysis. The patient-level analysis focuses on outcomes '*ever*' experienced by a patient anytime during the whole period of chemotherapy. It informs about the determinants of patient outcomes across this line of chemotherapy. The cycle-level analysis targets outcomes observed during a given cycle and from one cycle to the next. It informs about the determinants of outcomes as patients progress through the cycles of their chemotherapy regimen.

patients and methods

design

The background and methodology of MONITOR-GCSF have been described elsewhere [13, 14]. Summarized, MONITOR-GCSF was a pan-European (12 countries), multi-center (140), prospective, observational study of cancer patients treated with myelosuppressive chemotherapy regimens whose treating physician prescribed CIN/FN prophylaxis with Zarzio® per best clinical judgment. Patients were entered at initiation of prophylaxis and followed for up to six chemotherapy cycles in a hybrid prospective and retrospective design based on their time of entry into the study.

indices and variables in modeling

Several indices were constructed (see supplementary material, available at *Annals of Oncology* online). *Prophylaxis intensity* graded patients as *under-prophylacted*, *correctly prophylacted*, or *over-prophylacted* relative to the amended EORTC guidelines (Figure 1). The *Patient risk score* (PRS) quantified eight patient risk factors that predispose patients for FN as specified in the EORTC guidelines. The *GCSF initiation score* (GIS) was based on the day of Zarzio® initiation after the last administration of chemotherapy. *Knowledge about FN risk factors* was a questionnaire administered to physician-investigators. The *Composite outcome score* reflected the occurrence of any of the individual outcomes of interest. The variables used in the modeling included patient data at enrollment and at each cycle, as well as aggregated and '*ever during study*'; center data; and physician-investigator data (see supplementary material, available at *Annals of Oncology* online).

The outcomes modeled included the occurrence of CIN4 episodes, FN episodes, CIN/FN-related hospitalizations, any CIN/FN-related chemotherapy disturbances (dose reduction, delay in administration of chemotherapy, cancellation of administration of chemotherapy), and the composite outcome of any of these four outcomes having occurred both at the patient-level ('ever' during the chemotherapy period) and the cycle-level (during a given cycle).

predictive modeling

Multivariate logistic regression modeling was applied to identify patient, center, and physician variables predictive of the outcomes in five patient-level and five cycle-level analyses. Statistical dependence associated with cycle data being 'nested' under patients was managed using generalized estimation equations, a procedure adapting standard errors based on observed within-cluster correlations. Adjusted odds ratios (OR) and 95% confidence intervals (95% CI) quantified the direction and strength of the relationship between predictors and outcomes. The predictive performance of each model was evaluated by means of the *c*-statistic of concordance [16–18]. To further estimate the stability of the *c*-statistic, we used a bootstrapping method involving 2000 iterations to construct a 95% CI around each *c*-statistic [19].

results

patients, centers, and investigators

A comprehensive description of the sample of 1447 patients is provided by Gascón et al. [15]. The demographic and clinical data of interest to the models reported here are summarized in supplementary Table S1, available at *Annals of Oncology* online, as are the FN risk factors at enrollment. Characteristics of the 140 participating centers and physician-investigators are included in supplementary Table S2, available at *Annals of Oncology* online. Zarzio® treatment patterns are described in supplementary Table S3, available at *Annals of Oncology* online.

predictive risk modeling: patient-level

The risk of a patient '*ever*' experiencing a CIN4 episode during the study increased if this patient had a history of CIN4 at enrollment or was prescribed concomitant antibiotic prophylaxis at the initiation of Zarzio® prophylaxis; but was mitigated if the patient was over-prophylacted rather than correctly prophylacted (Table 1). The likelihood of an FN episode was higher among patients with Eastern Cooperative Oncology Group

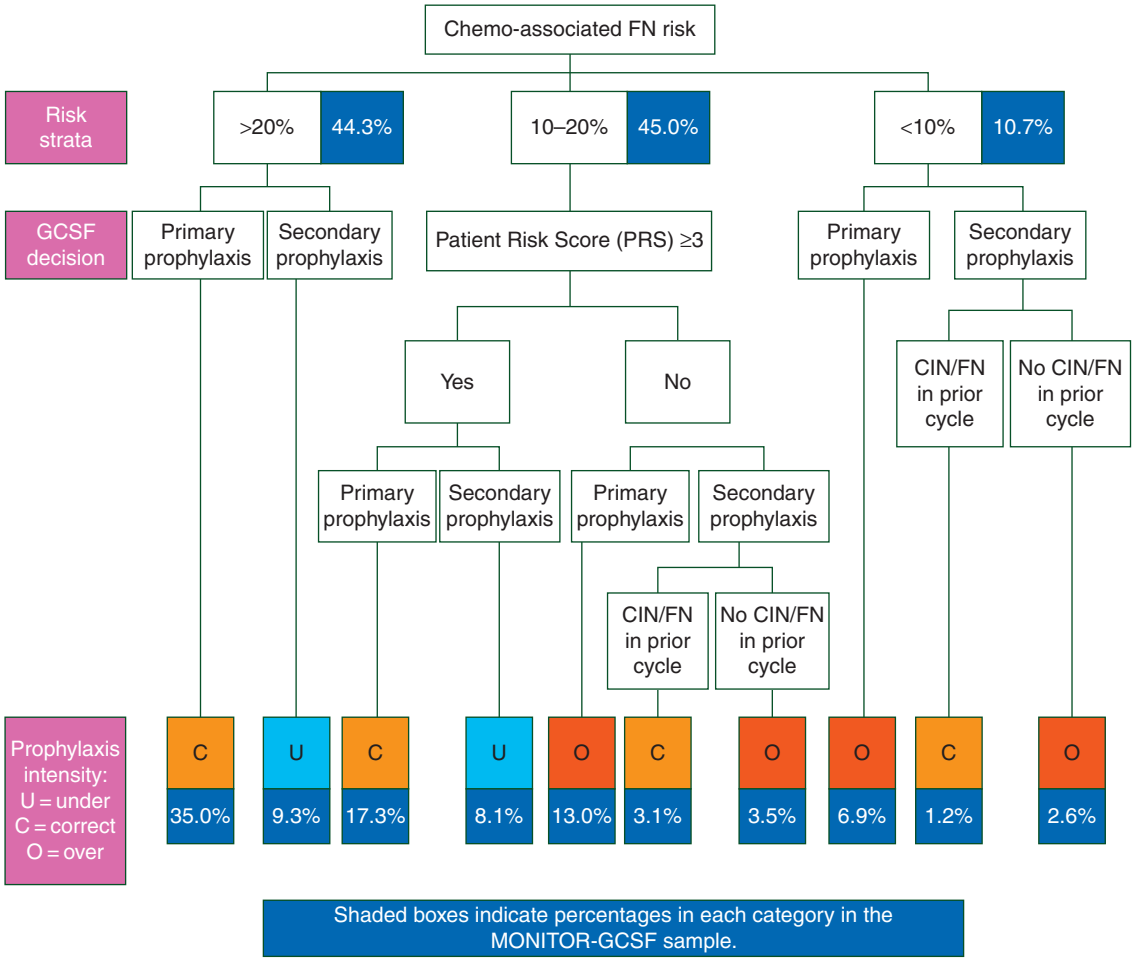

Figure 1. Treatment decision relative to EORTC guidelines.

(ECOG) status ≥2 anytime during the study, patients receiving antibiotic prophylaxis, and under-prophylacted versus over-prophylacted patients. In contrast, being over-prophylacted decreased the odds of an FN episode. Counter-intuitively, patient age was associated with lower FN odds; however, fewer elderly patients received chemotherapy regimens with high (>20%) risk of FN (35.6% in patients ≥65 years versus 50.5% in younger patients; $P = 0.0004$). Hospitalization risk was higher for patients with ECOG ≥2 during the study and in under-prophylacted patients; but lower in over-prophylacted patients. Chemotherapy disturbances (dose reductions, delay in or cancellation of administration of chemotherapy) were more likely among female patients and patients with prior history of CIN4. Predictors of a positive composite score included female gender, prior history of CIN4 or repeated infections, and being under-prophylacted. Being over-prophylacted and a GIS score of 1 mitigated the risk on the composite score. The *c*-statistics for these five models ranged from 0.60 to 0.72.

predictive risk modeling: cycle-level

The likelihood of a CIN4 episode occurring during a given cycle increased if there was CIN1/4 in the previous cycle and with concomitant in-cycle antibiotic prophylaxis; but was mitigated by a GIS score of 1 (Table 2). In-cycle CIN4 risk was higher in patients with prior history of CIN4 at enrollment but lower if the patient was initially over-prophylacted rather than correctly prophylacted. In-cycle FN risk increased if CIN1/4 occurred in the preceding cycle, with each ECOG point above 0, with concomitant in-cycle antibiotic prophylaxis, and with being under- rather than over-prophylacted. Perhaps paradoxically, a history of anemia at enrollment was associated with a decrease in the likelihood of an in-cycle FN episode. The probability of in-cycle hospitalization rose if CIN1/4 occurred in the preceding cycle, in patients with impaired performance status in-cycle, antibiotic prophylaxis in-cycle, or if patients were initially under-prophylacted (Table 2). Over-prophylaxis mitigated hospitalization risk. In-cycle chemotherapy disturbances were more likely in patients with CIN1/4 in the previous cycle but less likely among patients with hematological malignancies. The likelihood also decreased for each cancer patient seen in the center in the year preceding the start of the study; but increased as a function of each chemotherapy-treated cancer patient seen in the preceding year. Cycles were more likely to be disturbed in academic and academic-affiliated centers. A composite outcome score of 1 was more likely if a patient evidenced impaired performance status during the cycle, had a history of CIN4 at enrollment,

Table 1. Predictive modeling of outcomes using the patient as unit of analysis

	Outcomes																	
	CIN grade 4 episode				FN episode				CIN/FN-related hospitalization				CIN/FN-related chemotherapy disturbance				Composite outcome			
	$n = 191$ patients (13.2%)				$n = 86$ patients (5.9%)				$n = 88$ patients (6.1%)				$n = 138$ patients (9.5%)				$n = 323$ patients (22.3%)			
	OR	95% CI		*P* value	OR	95% CI		*P* value	OR	95% CI		*P* value	OR	95% CI		*P* value	OR	95% CI		*P* value
Patient-level predictors																				
Patient age (per 1 year)[a]					0.975	0.958	0.991	0.003												
Female gender													1.965	1.218	3.172	0.006	1.621	1.152	2.281	0.006
History of CIN4 at enrollment	2.925	1.592	5.374	0.001									2.594	1.469	4.581	0.001	1.898	1.209	2.979	0.005
History of repeated infections at enrollment																	2.680	1.200	5.984	0.016
ECOG ≥2 during study					2.398	1.610	3.570	<0.001	2.473	1.550	3.946	<0.001								
Concomitant antibiotic prophylaxis[b]	2.572	1.331	4.969	0.005	2.562	1.450	4.527	0.001												
Over- versus correctly prophylacted	0.328	0.193	0.557	<0.001	0.232	0.108	0.499	0.000	0.382	0.210	0.695	0.002					0.438	0.291	0.660	<0.001
Under- versus over-prophylacted					3.261	1.315	8.084	0.011	3.108	1.560	6.192	0.001					2.053	1.295	3.256	0.002
GIS at enrollment (1 versus 0)																	0.558	0.332	0.939	0.028
Predictive performance of model	*c*	95% CI			*c*	95% CI			*c*	95% CI			*c*	95% CI			*c*	95% CI		
	0.67	0.62	0.71		0.72	0.66	0.76		0.66	0.60	0.71		0.60	0.55	0.65		0.65	0.61	0.69	

No center-level predictors retained.
Cycle-level predictors are not applicable here.
[a]Counter-intuitive finding as FN probability is known to increase with age. Therefore, patient age should be considered a proxy for physician vigilance.
[b]Counter-intuitive finding as CIN4 and FN probability are known to decrease with antibiotic prophylaxis. Therefore, antibiotic prophylaxis should be considered a proxy for physician vigilance.

experienced CIN1/4 in the previous cycle, was female, or if in-cycle antibiotic prophylaxis was administered; yet less likely if the GIS was 1. A composite score of 1 was also less likely with either 1–3 days or 4–5 days duration, rather than 6 or more days of Zarzio® prophylaxis. The *c*-statistics for these five models ranged from 0.73 to 0.81.

discussion

A recent review by Lyman et al. [4] of 10 prospective and 21 retrospective studies of risk factors for FN distinguished between patient-related, treatment-related, and disease-related risk factors. The review confirmed the risk factors used in evidence-based guidelines, suggested methods for measuring certain risk factors, and identified several additional but not always confirmed risk factors. Evident from the review is that studies to date evaluated risk factors predominantly as static variables present at the beginning of the study period, not as dynamic variables that may change as patients undergo several cycles of chemotherapy.

Our study adds to this body of research by confirming, within the framework of the current EORTC guidelines, the direction and strength by which several variables intensify or attenuate the likelihood of patients experiencing CIN4 and FN episodes and related hospitalizations and chemotherapy disruptions '*ever*' over the course of a line of chemotherapy. Our study extends this research by identifying patient-, cycle-, and center-related predictors of the likelihood of adverse CIN/FN events to occur in a new cycle as patients progress through their chemotherapy. This supports the EORTC guidelines recommendation to assess CIN/FN risk at the start of each cycle. Unique to our study is that we evaluated these determinants within an implied (causal) chain: CIN4 episodes possibly evolving into FN episodes and either or both potentially leading to hospitalization with or without ensuing disruptions to the planned chemotherapy regimen.

To our knowledge, our study is the first to integrate the *static* approach of examining variables assessed at the beginning of a line of chemotherapy with a *dynamic* approach of investigating which and how determinants of outcome may emerge, disappear, or change in intensity across the cycles of a chemotherapy regimen. The patient-level analyses confirm to clinicians the need for assessing risk factors, determinants, and predictors before the first cycle of chemotherapy. The cycle-level analyses substantiate the need for clinicians to reassess risk at the beginning of each cycle, as recommended explicitly in the EORTC guidelines.

Several predictors were retained in two or more models. In the patient-level analyses, recurrent predictors with negative impact included female gender, history of CIN4 at enrollment, ECOG ≥2 any time during the study, under-prophylaxis, and concomitant antibiotic therapy. Over-prophylaxis mitigated the likelihood of negative outcomes. In the cycle-level analyses, recurrent predictors of in-cycle negative outcomes included a CIN episode of any grade in the preceding cycle, impaired performance status, under-prophylaxis, and concomitant antibiotic prophylaxis. Mitigating the probability of negative outcomes were prophylaxis initiated within the recommended 24–72 h time window and over-prophylaxis. That several of these predictors were identified in both the patient-level and cycle-level analyses underscores their consistency in the incidence of

Table 2. Predictive modeling of outcomes using chemotherapy cycle as unit of analysis

	Outcomes																			
	CIN grade 4 episode				FN episode				CIN/FN-related hospitalization				CIN/FN-related chemotherapy disturbance				Composite outcome			
	n = 294 cycles (3.9%)				*n* = 105 cycles (1.4%)				*n* = 111 cycles (1.5%)				*n* = 174 cycles (2.8%)				*n* = 507 cycles (6.7%)			
	OR	95% CI		*P* value	OR	95% CI		*P* value	OR	95% CI		*P* value	OR	95% CI		*P* value	OR	95% CI		*P* value
Cycle-level predictors																				
GIS (1 versus 0)	0.544	0.365	0.812	0.003													0.590	0.424	0.821	0.002
Zarzio duration: 4–5 days versus 6 or more																	0.644	0.489	0.859	0.003
Zarzio duration: 1–3 days versus 6 or more																	0.579	0.398	0.842	0.004
ECOG score (per 1 point)					1.673	1.284	2.179	<0.001	1.814	1.397	2.355	<0.001					1.369	1.140	1.643	0.001
Concomitant antibiotic prophylaxis	4.795	3.242	7.092	<0.001	4.704	2.777	7.968	<0.001	3.296	1.791	6.0652	<0.001					3.499	2.456	4.985	<0.001
CIN1/4 in previous cycle	4.083	3.242	7.092	<0.001	2.190	1.342	3.574	0.002	2.205	1.380	3.524	0.001	8.931	5.426	14.699	<0.001	4.064	3.096	5.336	<0.001
Patient-level predictors																				
Female gender																	1.545	1.175	2.033	0.002
Hematological cancer (versus oncologic)													0.336	0.152	0.740	0.007				
History of anemia at enrollment					0.215	0.067	0.687	0.010												
History of CIN grade 4 at enrollment	2.460	1.542	3.925	<0.001													1.596	1.088	2.340	0.017
Under- versus correctly prophylacted									1.863	1.054	3.293	0.032								
Over- versus correctly prophylacted	0.452	0.267	0.766	0.003					0.385	0.168	0.879	0.024								
Under- versus over-prophylacted					3.501	1.169	10.487	0.025	4.843	1.964	11.942	0.001								
Center-level predictors																				
Cancer patients seen in 2009 (per 1 patient)													0.999	0.999	1.000	0.006				
Chemotherapy-treated cancer patients in 2009 (per 1 patient)													1.001	1.000	1.001	<0.001				
Center type: academic versus non-academic													2.456	1.127	5.353	0.024				
Center type: academic-affiliated versus non-academic													3.344	1.342	8.331	0.010				
Predictive performance of model	*c*	95% CI			*c*	95% CI			*c*	95% CI			*c*	95% CI			*C*	95% CI		
	0.77	0.73	0.81		0.77	0.71	0.82		0.73	0.67	0.79		0.81	0.74	0.87		0.74	0.70	0.77	

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outcomes. The strength of the models is emphasized additionally by the magnitude, in the 2.0–4.0 range, of most of the adjusted OR. This enhances the models' value to clinicians.

Several findings merit additional consideration. First, concomitant antibiotic prophylaxis was associated with increased risk of negative outcome—when, clinically, one might expect an attenuating effect: 12.2% of patients were prescribed antibiotic prophylaxis at enrollment and concomitant antibiotic prophylaxis was recorded in 9.8% of cycles. These rates may be due to the lower proportion of patients with hematological malignancies in our study—when such patients especially benefit from prophylaxis [20]. It may also reflect the limited evidence base on antibiotic prophylaxis in the hematological setting; the fact that the EORTC guidelines focus on solid tumors and do not detail indications for prophylaxis in the hematological setting; and that the use of antibiotics in this setting is often protocol-driven. Further, physicians may have anticipated a higher CIN/FN risk in certain patients, may have limited antibiotic prophylaxis to patients at risk for or with evidence of bacterial infections, and may have practiced conservative antibiotic use to minimize resistance [2, 6]. Antibiotic prophylaxis may also be a proxy of the severity of illness of patients and hence their vulnerability to (opportunistic) infections. Secondly, age and history of anemia are known risk factors for CIN/FN [2] but were not retained in our models. Neither increased the odds of an adverse outcome in any of the patient- or cycle-level models. If anything, age mitigated the likelihood of an FN episode during the study, and history of anemia mitigated FN episode risk at the cycle-level. In our study, age and history of anemia may have served as proxies for clinician vigilance. Physicians may have enrolled older patients who they believed might respond and react to treatment like younger patients because of fitness or a perceived biological age being lower than their chronological age. Thirdly, patients treated at academic and academic-affiliated hospitals were at greater risk for chemotherapy disturbances. This probably does not reflect a quality of care issue but instead that such hospitals treat more patients with far advanced disease and in the metastatic setting, and potentially administer more lines of chemotherapy. Positively, higher cancer patient volume reduced the likelihood of chemotherapy disturbances, pointing at the effect of center experience. Fourthly, perhaps surprisingly, the FN risk of a patient's chemotherapy regimen was not retained as a predictor in any of the models. Most likely this is due to the distribution of the FN risk of patients' chemotherapy regimens. As we reported earlier, 45.0% of patients were being treated with a regimen with 10%–20% FN risk, 44.3% with >20% risk, and the remaining 10.7% at <10% FN risk [15].

A clinically challenging question concerns the effect of prophylaxis intensity. The models categorically indicate that under-prophylaxis is unsafe and unwarranted clinical practice—especially when not providing appropriate prophylaxis to patients with a history of CIN/FN. However, over-prophylaxis consistently and firmly reduced the likelihood of several negative outcomes in both the patient- and cycle-level analyses. Future studies should examine whether, and under what conditions, GCSF support in regimens with myelotoxicity of <10% or 10%–20% in the absence of risk factors is indicated. This may challenge evidence-based guidelines to be expanded with real-world evidence, especially in the case of GCSFs where a long history of clinical experience has accumulated.

In keeping with the real-world evidence focus of the MONITOR-GCSF study, our intent was to develop models of determinants of outcomes under non-controlled, routine clinical practice conditions and thus under greater conditions of heterogeneity in patients, providers, and settings than typically seen in controlled trials. Hence, patients enrolled in the study were those who per their treating physician's best clinical judgment were in need of GCSF support. This decision to administer GCSF may or may not have been in compliance with guidelines or protocols. Several models included guideline-related or guideline-specified determinants, which confirm that clinicians followed guidelines at least to some extent. The findings underscore, though, that clinicians will deviate from and override guidelines if they believe this is in the best interest of their patients.

Our study has limitations in addition to those identified in our preceding report [15]. The study was framed within the context of the EORTC guidelines. Future studies should adopt the perspective on patient-related, treatment-related, and disease-related risk factors of the Lyman et al. review [4] as well as our approach to evaluating CIN/FN risk and incidence at the start of chemotherapy and again at each cycle. Future studies should include relative dose intensity (RDI) as an outcome. Additionally, linking RDI to tumor/disease control would create a (causal) chain demonstrating how GCSF support affects CIN4 and FN incidence under varying conditions of myelotoxicity; how this translates into hospitalization and/or chemotherapy disturbances; how the latter affects RDI; and how reduced RDI affects tumor control and survival [21–23]. The PRS and GIS metrics need to be further validated. The predictive models must be verified in different samples of cancer patients receiving GCSF support. We did not analyze data at the granularity of each chemotherapy regimen because there were too many regimens and variations thereof, and the primary interest was in the relative myelotoxicity and associated FN risk. Finally, both a strength and a limitation, this was an observational study not designed to understand how and why clinicians chose to provide GCSF support, and why, in the process, they decided to deviate from guidelines.

conclusion

Our 'real-world' models of predictors of patients experiencing an adverse neutropenic event '*ever*' or within a specific cycle give cancer clinicians the ability to anticipate such clinical developments. A *static* approach of evaluating a patient's risk at the start of chemotherapy enables clinicians to anticipate CIN/FN complications over the course of chemotherapy. A *dynamic* approach of re-assessing the likelihood of adverse CIN/FN events at each cycle supports clinicians in assessing risk at the start of each cycle and thus individualize patient treatment. The dynamic approach is consistent with the EORTC recommendation to re-appraise CIN/FN risk at the start of each cycle. In this, the role of prophylaxis intensity relative to the EORTC guidelines is evident. Under-prophylaxis is clinically unsafe and unwarranted. Over-prophylaxis of patients receiving intermediate or low myelotoxic chemotherapy may be beneficial, both in patients with and without risk factors. Our findings, having been obtained as part of a study on biosimilar filgrastim, should alleviate clinician concerns about biosimilar agents [24].

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disclosure

MA, HL, CB, PG, and MB received compensation from Hexal AG/Sandoz International GmbH for their participation in the work reported here. AK and MG are employees of Hexal AG. KD, KMD, and IA 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.

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