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ORIGINAL ARTICLE

Treatment patterns and outcomes in the prophylaxis of chemotherapy-induced (febrile) neutropenia with biosimilar filgrastim (the MONITOR-GCSF study)

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Abstract
Purpose The purpose of this study is to examine the real-world treatment patterns and outcomes of chemotherapy-induced (febrile) neutropenia (chemotherapy-induced (CIN)/febrile neutropenia (FN)) prophylaxis with biosimilar filgrastim (Zarzio®).
Methods MONITOR-GCSF is an international (12 countries), multi-center (140), prospective (max. six cycles), observational, open-label, pharmaco-epidemiologic study of cancer patients (n=1447) treated with myelosuppressive chemotherapy across a total of 6,213 cycles and receiving prophylaxis with Zarzio®. Data were analyzed using both the patient and cycle as unit of analysis.
Results Most (72.3 %) received primary prophylaxis; dosed mainly (53.2 %) at 30 MIU but differentiated by weight, chemotoxicity, and tumor type; and mainly (53.2 %) initiated in the 24–72h post-chemotherapy window but differentiated by prophylaxis type, tumor type, and chemotoxicity and for modal/median duration of 5 days. Relative to European Organisation for Research and Treatment of Cancer (EORTC) guidelines, 56.6 % were correctly prophylacted, 17.4 % under-prophylacted, and 26.0 % over-prophylacted. The following incidence rates were recorded: CIN grade 4 13.2 % of patients and 3.9 % of cycles, FN 5.9 % of patients and 1.4 % of cycles, CIN/FN-related hospitalizations 6.1 % of patients and 1.5 % of cycles, CIN/FN-related chemotherapy disturbances 9.5 % of patients and 2.8 % of cycles, and composite outcomes index 22.3 % of patients and 6.7 % of cycles. Rates varied by type of prophylaxis and tumor, chemotoxicity, initiation day, and prophylaxis duration. There were 1834

Prior dissemination: interim results of the MONITOR-GCSF study were presented at the 2012 (New York, NY, USA) and 2014 (Miami, FL, USA) MASCC congresses. Related abstracts:
Gascón P, Boccadoro M, Bokemeyer C et al. (2012) Support Care Cancer 20(Suppl 1):S206
Aapro M, Ludwig H, Bokemeyer C et al. (2012) Support Care Cancer 20(Suppl 1):S208
Aapro M, Ludwig H, Gascón P (2012) Support Care Cancer 2012;22(Suppl 1):S221

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musculoskeletal events with 24.7 % of patients reporting bone pain of any grade (mostly mild to moderate), and 148 adverse drug reactions, including 4 serious, were recorded in 76 patients.

Conclusions The clinical and safety outcomes are well within the range of historically reported data for originator filgrastim underscoring the clinical effectiveness and safety of biosimilar filgrastim in daily clinical practice.

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

Introduction

Chemotherapy-induced (CIN) and febrile neutropenia (FN) are potentially life-threatening complications of myelosuppressive chemotherapy, may often require hospitalization, and may result in disruptions to the planned chemotherapy regimen [1–5]. Known risk factors for CIN/FN enable clinicians to risk-stratify patients and initiate prophylaxis with granulocyte colony-stimulating factors (GCSF) [1, 3, 6–11].

GCSFs are biological growth factors that stimulate the production of white blood cells by promoting the proliferation, differentiation, and activation of neutrophils in the bone marrow [12]. The efficacy of standard and pegylated agents in FN prophylaxis is well established in terms of decreasing the risk of FN, the severity and duration of FN episodes, and chemotherapy disturbances—with no sustained evidence of superiority of either formulation [9, 10, 13–17].

Following the patent expiration for filgrastim (Neupogen®, Amgen) in Europe in 2006, several biosimilar agents have been approved by the European Medicines Agency, including EP-2006 (Zarzio®, Filgrastim Hexal®; Sandoz/Novartis; hereafter, Zarzio®). A biosimilar or "similar biological medicinal product" is a "copy version of an already authorized biochemical medicinal product with demonstrated similarity in physicochemical characteristics, efficacy and safety, based on a comprehensive comparability exercise" [18 (p. 691)]. The clinical development of Zarzio® has been summarized [19] and reviewed in terms of clinical efficacy and safety [20, 21]. Initial clinical experience suggests an effectiveness and safety profile similar to that of the originator product in core and extrapolated indications [22–25].

The MONITOR-GCSF study examined the real-world patterns, outcomes, and associated determinants of Zarzio® prophylaxis in cancer patients receiving myelosuppressive chemotherapy [26, 27]. Being European in scope, the study was framed within the European Organisation for Research and Treatment of Cancer (EORTC) guidelines for the use of GCSF in CIN/FN prophylaxis [9, 10], which specify that the myelotoxicity and associated FN risk of patients' regimens be assessed at each cycle. Primary prophylaxis is recommended for regimens with an FN risk ≥20 % and for regimens with a risk of 10–20 % if patients present with specific risk factors. GCSF prophylaxis at cycle 1 is not recommended if a regimen's FN risk is <10 %. We report here on the treatment patterns and associated outcomes of CIN/FN prophylaxis with Zarzio® in 1,447 patients from 140 cancer centers in 12 European countries.

Methods

The methodology of MONITOR-GCSF has been described elsewhere [26, 27]. Methodology elements are summarized below.

Design

MONITOR-GCSF was an international, multi-center, prospective, observational, open-label, pharmaco-epidemiologic study of cancer patients treated with myelosuppressive chemotherapy regimens whose treating physicians prescribed CIN/FN prophylaxis with Zarzio® per their best clinical judgment. Patients were recruited from 140 centers in 12 European countries: Austria (3 centers), Belgium (2), Czech Republic (5), France (34), Germany (27), Hungary (8), Italy (23), Poland (14), Romania (7), Spain (11), Switzerland (2), and the UK (4).

Eligible were male or female adults (age ≥18) with 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; and receiving primary or secondary prophylaxis with Zarzio®. The safety sample consisted of patients who received at least one dose of Zarzio®. The evaluable sample was limited to patients for whom at least initiation cycle data and follow-up/outcome data were available.

Data model

At enrollment: demographics, anthropometrics, medical and cancer history, prior cancer treatments, histology, history of (repeated) infections, and CIN/FN history.

At all visits: chemotherapy regimen, including changes; surgery, including changes; performance status; current and recent infections; CIN/FN episodes and associated hospitalizations; antibiotic prophylaxis; blood and urine cultures; Zarzio® prophylaxis; selected concomitant medications; adherence; hematology parameters; clinical events; and adverse drug reactions (ADRs).

At study end: performance status, current and recent infections, CIN/FN episodes and associated hospitalizations, blood and urine cultures, hematology parameters, clinical events, and ADRs.

Other indices

Prophylaxis intensity

The study followed the decision schematic in the 2010 EORTC guidelines for primary prophylaxis with GCSF, which were amended per ad hoc expert consensus to include trajectories for secondary prophylaxis. Patients' were graded accordingly as *under-prophylacted*, *correctly prophylacted*, or *over-prophylacted*.

Patient risk score

This score quantifies the eight risk factors that, according to the EORTC guidelines, may increase FN risk. Each factor was weighted by expert consensus: 3 to *age≥65 years* and *prior FN history*; 1.5 to *advanced disease* and *poor performance and/or nutritional status*; and 0.5 to *no antibiotic prophylaxis*, *female gender*, *hemoglobin <12 g/dL*, and *renal*, *cardiovascular*, *or liver disease*. The sum of the weighted risk factors constituted the patient risk score (PRS) (range 0–11).

Outcomes

We report clinical outcomes using (a) patients and (b) chemotherapy cycles as the unit of analysis. Patient-level data enable analysis of the association of outcomes with prophylaxis type and chemotoxicity. Incidence refers to a given outcome "ever" experienced during the study. As patients enrolled at different cycles and were in the study for varying amounts of time, we also recorded outcomes at the cycle level. This permits analysis of the association with day of initiation and duration of prophylaxis. Cycle-level analysis evaluates the occurrence of an outcome in a given cycle or, in the case of chemotherapy disturbances, in a cycle subsequent to one in which a CIN/FN event was recorded (lag 1).

The outcomes of interest included the following: rate of CIN of any grade (CIN1/4), grades 3/4 combined (CIN3/4), grade 4 (CIN4), and FN; CIN/FN-related hospitalizations; CIN/FN-related chemotherapy disturbance one cycle after a CIN/FN event (lag 1); and a CIN/FN-related composite outcome that included any occurrence of CIN4, FN, CIN/FN-related hospitalizations, and/or CIN/FN-related chemotherapy disturbances.

Specialized statistical issues

The statistical dependence inherent to the structure of the cycle data being "nested" under patients was taken into account using generalized estimating equations. This procedure adjusts standard errors based on the observed within-cluster correlation.

We applied time-to-event modeling methods to estimate the probability of patients developing CIN4 or FN, being hospitalized, or experiencing chemotherapy disturbances due to CIN/FN in later cycles. For patients receiving primary prophylaxis, we estimated the probability of any one of these outcomes occurring in the cycle in which Zarzio® was initiated and the remaining five chemotherapy cycles. For patients receiving secondary prophylaxis in cycle 2, we estimated the probability of any of these outcomes occurring in cycles 2 through 6. The secondary prophylaxis exercise was limited to patients prophylacted in cycle 2 because too few patients were initiated in cycle 3 or later. In both exercises, chemotherapy disturbances were not estimated for the initiation cycle as such disturbances always occur with a cycle lag=1.

Human rights

This study was approved by the ethical review committees of participating centers in accordance with national laws and regulations. Patients provided written informed consent.

Results

Patients

In total, 1,496 patients were enrolled yielding an evaluable sample of 1,447 patients (Fig. 1a). The majority of patients (72.3 %) were enrolled in cycle 1 (Fig. 1b). The sample was predominantly female (61.2 %) (Table 1). Median age was 62 years. Most patients (89.1 %) had an ECOG ≤1 score. Safety-relevant history included musculoskeletal pain (15.5 %), headaches (1.9 %), and bleeding (1.2 %).

Most patients (77.2 %) had a solid tumor, mainly breast (32.2 %) or lung (23.8 %) cancer. The most prevalent hematological malignancy was lymphoma (16.9 %). Proportions of stage 3 versus 4 disease varied across tumor types, with a majority of oncological patients (59.1 %) having stage 4 but equal distribution of either stage in hematological patients. One third of patients (35.8 %) were cancer-treatment-naive; one third (31.8 %) had received at least one line of chemotherapy, while one third (32.6 %) had undergone surgery.

Of the 460 patients with prior chemotherapy, 106 (23.0 %) had experienced ≥1 CIN4 episodes, including 27 (5.9 %) with episodes classified FN. Only 55 (12.0 %) had received GCSF treatment. Thirty-three (7.2 %) required hospitalization, and48 (10.4 %) experienced chemotherapy disturbances.

In the 10–20 % subsample, there were proportionately more patients with the risk factor of *age ≥65* ($p=0.043$), *advanced disease* ($p<0.001$), and *no antibiotic prophylaxis* ($p=0.019$) than in the rest of the sample. The PRS mean (±SD) was 2.85±1.96, with patients receiving secondary prophylaxis having a higher PRS ($p=0.007$). About equal proportions of patients were being treated with regimens with FN risk >20 % (44.3 %) or 10–20 % (45.0 %).

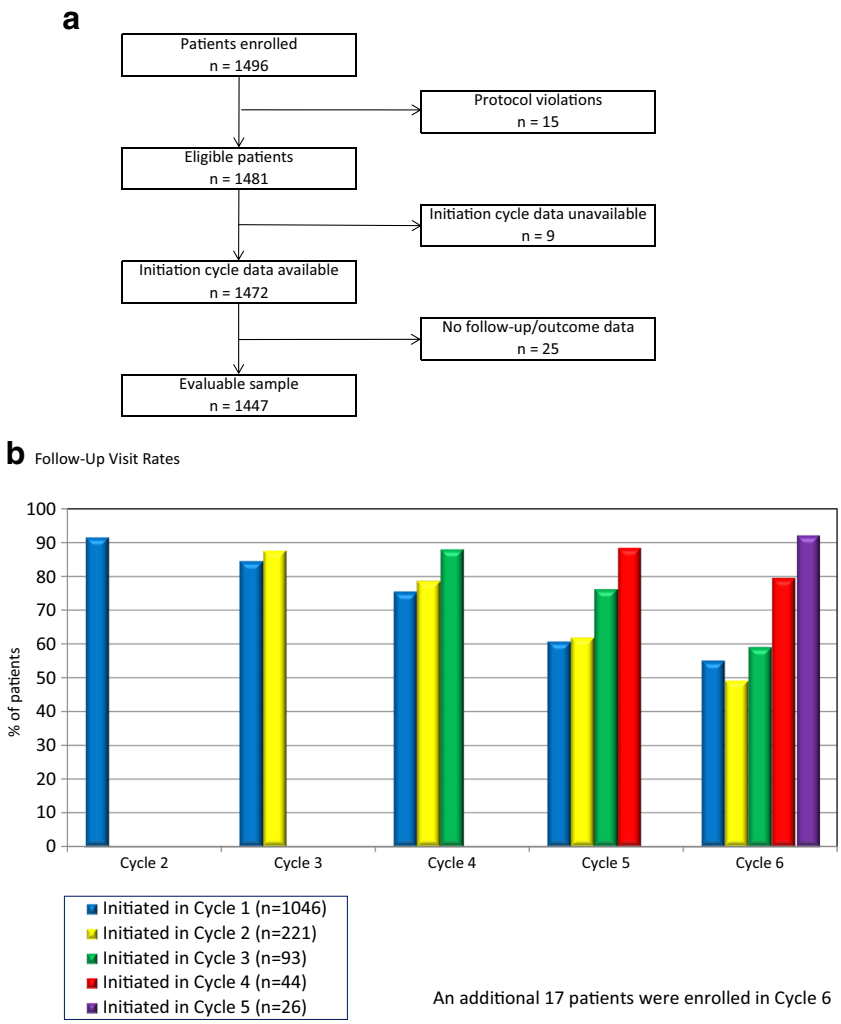

Fig. 1 **a** Subject enrollment and **b** follow-up

Prophylaxis

Zarzio® was initiated as primary prophylaxis in 72.3 % and as secondary prophylaxis in 27.7 % of patients (Table 2). Relative to the EORTC guidelines, 56.6 % of patients were correctly prophylacted, 17.4 % under-prophylacted, and 26.0 % over-prophylacted (Fig. 2). Under-prophylaxis occurred when secondary prophylaxis was given, but primary prophylaxis was recommended by the guidelines, whereas over-prophylaxis occurred when primary prophylaxis was given when not recommended by the guidelines.

Proportionately more patients were administered a dose of 30 MIU ($p<0.001$). This was not a function of type of prophylaxis ($p=$n.s.) but of body weight ($p<0.001$), chemotoxicity ($p=0.007$), and tumor type ($p<0.001$).

In half of patients (53.2 %), Zarzio® was initiated in days 1–3 following chemotherapy (M±SD=3.08±2.98), yet 13.4 % were exposed on the day of, and the remaining 33.4 % ≥4 days following, chemotherapy. Half (52.9 %) of the hematological patients were initiated on days 4–8. Day of GCSF initiation tended to be earlier for patients with solid tumors ($p<0.001$), receiving secondary prophylaxis ($p=0.010$), or on chemotherapy regimens with low or moderate FN risk ($p<0.001$).

The modal duration of prophylaxis was 5 days (45.7 % of patients); 72.7 % received Zarzio® for 4–8 days. Duration was longer with higher chemotoxicity ($p<0.001$) but was independent of prophylaxis or tumor type (both $p=$n.s.).

Clinical outcomes

Patient level

In total, 504 (34.8 %) patients experienced one or more (ever) CIN1/4 episodes (Table 3). Rates were higher among patients receiving secondary prophylaxis ($p<0.001$) but were independent of chemotherapy regimen. The CIN3/4 and CIN4 rates were 22.9 and 13.2 %, respectively, and were independent of prophylaxis type (both $p=$n.s.) but rose with chemotoxicity (both $p<0.03$). The FN incidence was 5.9 %, was independent of prophylaxis type but was associated with chemotoxicity ($p<0.001$).

Table 1 Demographics, clinical status, and cancer and CIN/FN history at enrollment

Demographics				
	Gender (*n*, %)	Male	561	38.8 %
		Female	886	61.2 %
	Ethnicity (*n*, %)	Caucasian	1042	99.0 %
		Other	10	1.0 %
		Not reported[a]	395	
	Age (*M*±SD, median)		61.3±11.8	62
	Country	Austria	27	1.9 %
		Belgium	3	0.2 %
		Czech Republic	50	3.4 %
		France	395	27.3 %
		Germany	145	10.0 %
		Hungary	143	9.9 %
		Italy	175	12.1 %
		Poland	286	19.8 %
		Romania	64	4.4 %
		Spain	116	8.0 %
		Switzerland	11	0.8 %
		UK	32	2.2 %
Biometrics				
	Height (cm) (*M*±SD, median)		165.6±8.5	165
	Weight (kg) (*M*±SD, median)		72.1±15.0	70
	BMI (*M*±SD, median)		26.3±5.0	25.7
ECOG performance status (*n*, %)		0	553	40.9 %
		1	652	48.2 %
		2	121	8.9 %
		3	26	1.9 %
		4	1	0.1 %
Comorbidities (*n*, %)				
	Hypertension		458	31.7 %
	Coronary disease		93	6.4 %
	Cardiac arrhythmia		71	4.9 %
	Peripheral vascular disease		67	4.6 %
	Cardiac failure		28	1.9 %
	Other cardiovascular		47	3.2 %
	Anemia		138	9.5 %
	Type 2 diabetes		122	8.4 %
	Type 1 diabetes		17	1.2 %
	COPD		86	5.9 %
	Other respiratory		66	4.6 %
	Allergies		90	6.2 %
	Hepatitis		22	1.5 %
	Gastro-intestinal disease		64	4.4 %
	Renal disease		43	3.0 %
	Neurological disease		43	3.0 %
	Cerebrovascular disease		27	1.9 %
Relevant medical history (*n*, %)				
	Bone pain		116	8.0 %
	Joint pain		78	5.4 %
	Muscle pain		31	2.1 %
	Headache		28	1.9 %
	Epistaxis		8	0.6 %

Table 1 (continued)

	Gastro-intestinal bleeding		7	0.5 %		
	Skin hemorrhage		1	0.1 %		
Tumor type (*n*, %)[b]	All patients			Stage 3	Stage 4	
	Solid	1117	77.2 %	454	40.9 %	655	59.1 %
	Breast	466	32.2 %	267	57.9 %	194	42.1 %
	Lung	345	23.8 %	101	29.5 %	241	70.5 %
	Ovarian	140	9.7 %	63	45.0 %	77	55.0 %
	Prostate	102	7.1 %	7	6.9 %	95	93.1 %
	Bladder	64	4.4 %	16	25.0 %	48	75.0 %
	Hematological	330	22.8 %	156	50.8 %	151	49.2 %
	Lymphoma	245	16.9 %	103	43.3 %	135	56.7 %
	Multiple myeloma	85	5.9 %	53	76.8 %	16	23.2 %
Prior cancer treatments (*n*,%)[c]						
	None	518	35.8 %			
	Surgery	472	32.6 %			
	Chemotherapy	460	31.8 %			
	Of these:					
	Adjuvant	196	42.6 %			
	In metastatic setting	206	44.8 %			
	Of these: prior lines of chemo[b]					
	1	103	51.8 %			
	2	54	27.1 %			
	≥3	42	21.1 %			
	Radiation therapy	274	18.9 %			
	Hormonal therapy	198	13.7 %			
	Targeted therapy	45	3.1 %			
	Bone marrow transplant	12	0.8 %			
	Other (incl. CAM)	25	1.7 %			
History of repeated infections (*n*, %)		35	2.4 %			
	Of these:					
	Chronic	8	22.9 %			
	Recurrent acute	27	77.1 %			
	Of these: number of episodes in past 3 months[b]					
	1	15	46.9 %			
	2	7	21.9 %			
	≥3	3	9.5 %			
CIN/FN in prior line of chemo (*n*, %)			% Prior chemo			
	Prior CIN grade four episode(s)	106	23.0 %			
	Of these: number of episodes[b]		% Episodes			
	1	79	79.8 %			
	2	5	5.0 %			
	≥3	15	15.2 %			
			% Prior chemo	% Prior CIN4		
	Prior FN episode(s)	27	5.9 %	25.5 %		
	CIN/FN-related hospitalization	33	7.2 %	31.1 %		
	CIN/FN-related chemotherapy disturbances[c]					
	Any disturbance	48	10.4 %	45.3 %		
	Chemotherapy delay	41	8.9 %	38.7 %		
	Chemotherapy dose reduction	12	2.6 %	11.3 %		
	Chemotherapy cancellation	5	1.1 %	4.7 %		
	Prior GCSF therapy	55	12.0 %	51.9 %		

Table 1 (continued)

Chemotherapy during study (*n*, %)					
Chemotherapy cycle at entry into study					
1	1046	72.3%			
2	221	15.3%			
3	93	6.4%			
4	44	3.0%			
5	26	1.8%			
6	17	1.2%			
Myelotoxicity-associated FN risk					
<10 %	154	10.7%			
10–20 %	650	45.0%			
>20 %	640	44.3%			
FN risk factors (*n*, %)	All patients		10–20% FN risk		*p*
High risk					
Age ≥65years	598	41.3%	290	44.6%	0.043
Increased risk					
Advanced disease[d]	187	13.7%	127	20.8%	<0.001
History of FN	27	1.9%	13	2.0%	n.s.
No antibiotic prophylaxis	1261	87.8%	590	91.3%	0.019
Other factors					
Poor performance and/or nutritional status	178	13.1%	82	13.3%	n.s.
Female gender	886	61.2%	376	57.8%	n.s.
Hemoglobin <12g/dL	482	39.6%	243	45.9%	n.s.
Renal, cardiovascular, or liver disease	304	23.1%	156	26.9%	n.s.
Patient risk score (PRS)	*M*±SD	Median			*p*
All patients	2.85±1.96	2.5			
By type of prophylaxis					0.007
Primary	2.73±1.92	2.5			
Secondary	3.14±2.01	3.0			
Concurrent cancer treatments during study (*n*, %)[c]					
Surgery	100	6.9%			
Radiation therapy	102	7.1%			
Hormonal therapy	85	5.9%			
Targeted treatment	89	6.2%			
Bone marrow transplant	31	2.1%			
Other (incl. CAM)	98	6.8%			

BMI body mass index, *CAM* complementary and alternative medicine, *CIN* chemotherapy-induced neutropenia, *COPD* chronic obstructive pulmonary disease, *ECOG* Eastern Cooperative Oncology Group, *FN* febrile neutropenia, *GCSF* granulocyte colony-stimulating factor

[a] French regulations do not permit recording of ethnicity in clinical studies

[b] Frequencies as reported

[c] Not mutually exclusive. Patient may have had more than one

[d] Stage 3 (stage 3 or 4 if multiple myeloma) and prior chemo in metastatic setting

Eighty-eight patients (6.1 %) were hospitalized. Hospitalization was independent of prophylaxis type and chemotoxicity (both p=n.s.). The chemotherapy regimen of 138 patients (9.5 %) was disturbed, and this more so among secondary prophylaxis patients (both $p<0.001$). Chemotherapy disturbances were independent of chemotoxicity.

Three hundred twenty-three patients (22.3 %) scored positive on the CIN/FN-related composite outcome. This was independent of prophylaxis type (p=n.s.), but associated with chemotoxicity ($p=0.043$).

Table 4 summarizes, for patients who received primary prophylaxis, the number who experienced each event; the associated cumulative probabilities derived from time-to-event analyses as patients progressed through chemotherapy cycles; and, as an index of variability, the difference in probabilities between the highest and lowest estimates in a series. Similar data are presented for patients on secondary prophylaxis, but analysis was limited to patients initiated on Zarzio® in cycle 2, as statistically too few patients received secondary prophylaxis at later time points. The frequencies indicate the number of patients who experienced one of the four outcomes while the associated probabilities were derived from the time-to-event modeling calculations.

Among patients receiving primary prophylaxis, the most infrequently expected event over up to six cycles of chemotherapy was hospitalization in cycle 1 with a modeled occurrence of 2 % of patients. The most frequently observed

Table 2 Zarzio® prophylaxis patterns

						P value
Type of prophylaxis	Primary (%)	Secondary (%)				<0.001
	72.3 %	27.7 %				
Dose						
	All patients					<0.001
	30 MIU/day		53.2 %			
	48 MIU/day		46.0 %			
	Other		0.8 %			
	By type of prophylaxis		Primary	Secondary		n.s.
	30 MIU/day		53.7 %	53.2 %		
	48 MIU/day		46.3 %	46.8 %		
	By patient weight		≤65 kg	>65 kg		<0.001
	30 MIU/day		66.1 %	45.9 %		
	48 MIU/day		33.9 %	54.1 %		
	By chemotoxicity		<10 %	10–20 %	>20 %	0.007
	30 MIU/day		65.4 %	54.3 %	50.7 %	
	48 MIU/day		34.6 %	45.7 %	49.3 %	
	By tumor type		Oncology	Hematology		<0.001
	30 MIU/day		49.8 %	66.7 %		
	48 MIU/day		50.2 %	33.3 %		
Day of initiation[a]						
		All	Oncology	Hematology		<0.001
	0	13.4 %	16.0 %	4.2 %		
	1	30.7 %	33.6 %	20.4 %		
	2	13.4 %	14.9 %	8.0 %		
	3	9.1 %	9.8 %	6.9 %		
	4	4.6 %	4.1 %	6.2 %		
	5	6.8 %	6.7 %	7.2 %		
	6	6.7 %	3.4 %	18.6 %		
	7	7.2 %	5.8 %	12.2 %		
	8	3.9 %	2.5 %	8.7 %		
	9	1.0 %	1.0 %	0.9 %		
	10	0.8 %	0.6 %	1.5 %		
	11	0.6 %	0.5 %	1.1 %		
	≥12	1.8 %	1.1 %	4.1 %		
			Mean	SD	Median	*p*
	All patients		3.08	2.98	2	
	By type of prophylaxis					0.010
	Primary		3.19	3.00	2	
	Secondary		2.63	2.87	1	
	By chemotoxicity					<0.001
	<10 %		2.31	2.85	1	
	10–20 %		2.95	3.00	2	
	≥20 %		3.34	2.96	2	
	By tumor type					<0.001
	Oncology		2.60	2.70	2	
	Hematology		4.76	3.30	5	

Table 2 (continued)

Duration of prophylaxis (days)					
	1	3.6%			
	2	5.7%			
	3	12.3%			
	4	7.1%			
	5	45.7%			
	6	6.5%			
	7	11.5%			
	8	1.9%			
	9	0.9%			
	10	2.0%			
	11	0.2%			
	12	0.3%			
	13	0.1%			
	14	1.8%			
	≥15	0.4%			
			Mean	SD	Median	*p* value
	All patients		5.11	2.32	5	
	By type of prophylaxis					n.s.
	Primary		5.10	2.21	5	
	Secondary		5.17	2.68	5	
	By chemotoxicity					<0.001
	<10%		4.59	2.41	5	
	10–20%		4.98	2.23	5	
	≥20%		5.33	2.35	5	
	By tumor type					n.s.
	Oncology		5.14	2.24	5	
	Hematology		5.03	2.56	5	

[a] Zarzio® initiation expressed in days after chemotherapy (0=same day; 1=1 day after, 2=2 days after, etc.)

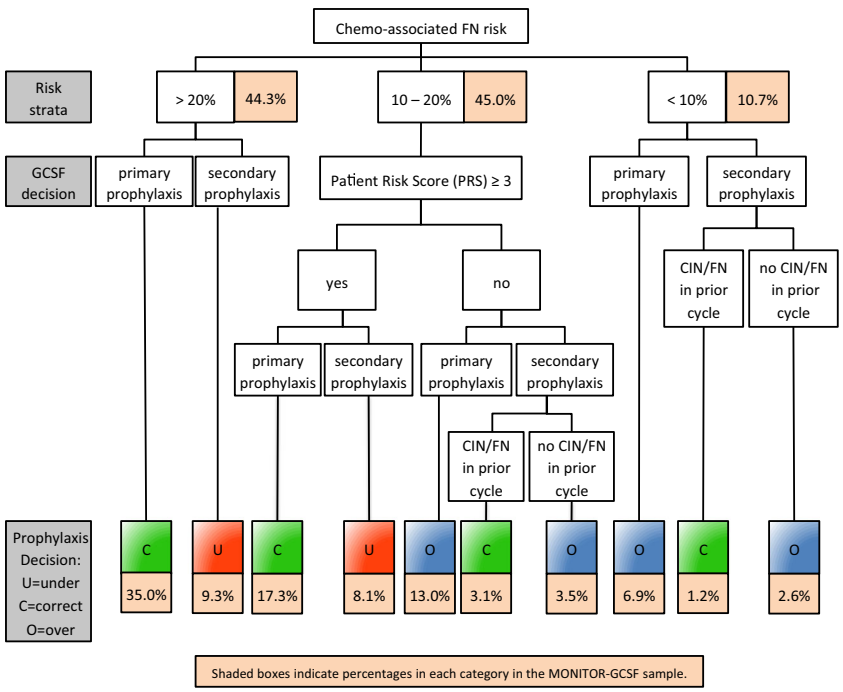

Fig. 2 Treatment decision relative to EORTC guidelines

Table 3 Clinical outcomes at the patient and cycle levels

Unit of analysis: patient			By prophylaxis			By chemotoxicity			
	All patients (*n*, %)		Primary (%)	Secondary (%)	*p*	<10 % (%)	10–20 % (%)	>20 % (%)	*p* value
Neutropenia episodes									
CIN grades 1 through 4	504	34.8 %	32.1	41.9	0.001	29.9	36.0	34.8	n.s.
CIN grades 3 or 4	332	22.9 %	22.5	24.2	n.s.	14.9	22.9	25.0	0.029
CIN grade 4	191	13.2 %	13.8	11.7	n.s.	7.8	11.9	15.9	0.010
FN	86	5.9 %	6.7	4.0	n.s.	3.9	3.5	8.9	<0.001
CIN/FN-related hospitalizations	88	6.1 %	6.1	6.0	n.s.	3.9	5.4	7.3	n.s.
CIN/FN-related chemotherapy disturbances[a]									
Any chemotherapy disturbance	138	9.5 %	7.5	15.0	<0.001	8.4	10.8	8.6	n.s.
Chemotherapy dose reduction	45	3.1 %	2.9	3.7	n.s.	3.9	3.2	2.8	n.s.
Chemotherapy delay	113	7.8 %	5.8	13.0	<0.001	7.1	8.9	6.9	n.s.
Chemotherapy cancellation	3	0.2 %	0.1	0.5	n.s.	0.0	0.0	0.5	n.s.
CIN/FN-related composite outcome[b]	323	22.3 %	21.5	24.4	n.s.	16.9	20.9	25.2	0.043

Unit of analysis: cycle			By day of initiation of prophylaxis				By duration of prophylaxis			
	All cycles (*n*, %)		Day of chemo (%)	24–72 h (%)	>72 h (%)s	*p*	1–3 days (%)	4–5 days (%)	≥6 days	*p* value
Neutropenia episodes										
CIN grades 1 through 4	1083	14.3 %	13.0	13.4	20.0	<0.001	15.7	13.4	20.0	<0.001
CIN grades 3 or 4	602	8.0 %	6.7	6.3	13.4	<0.001	9.1	7.6	10.3	0.008
CIN grade 4	294	3.9 %	3.1	2.8	7.3	<0.001	3.6	3.9	5.5	0.015
FN	105	1.4 %	1.0	1.2	2.1	0.029	1.2	1.2	2.2	0.015
CIN/FN-related hospitalizations	111	1.5 %	1.9	1.1	1.8	n.s.	1.2	1.4	1.8	n.s.
CIN/FN-related chemotherapy disturbances[a]										
Any chemotherapy disturbance	174	2.8 %	3.5	2.9	1.9	n.s.	2.0	2.1	4.7	<0.001
Chemotherapy dose reduction	46	0.7 %	1.1	0.6	0.9	n.s.	0.6	0.8	1.0	n.s.
Chemotherapy delay	142	2.3 %	3.8	2.4	1.2	<0.001	2.0	1.5	3.9	<0.001
Chemotherapy cancellation	3	0.1 %	0.0	<0.1	0.1	n.s.	0.0	0.1	0.0	n.s.
CIN/FN-related composite outcome[b]	507	6.7 %	5.8	5.4	9.1	<0.001	6.0	5.8	9.3	<0.001

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

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

outcome was a CIN4 episode at 16 % over six cycles. Among patients on secondary prophylaxis, the most infrequently expected event over up to six cycles of chemotherapy was an FN episode in the initiation cycle (cycle 2) at 4 % of patients, while the most frequent event modeled, just as in primary prophylaxis, was CIN4 over six cycles at 16 %.

Cycle level

CIN1/4, CIN3/4, CIN4, and FN episodes were recorded in, respectively, 14.3, 8.0, 3.9, and 1.4 % of cycles (Table 3). These rates were higher for prophylaxis initiated >72 h following chemotherapy (all $p<0.03$) and for prophylaxis of ≥6-day duration (all $p<0.02$).

CIN/FN-related hospitalizations occurred in 1.5 % of cycles but was independent of initiation or duration of prophylaxis (both p=n.s.). In total, 174 (2.8 %) chemotherapy cycles were disturbed, which was independent of day of initiation (p=n.s.) but higher for prophylaxis lasting ≥6 days ($p<0.001$). Chemotherapy delay was the most frequent disturbance (2.3 %) and was associated with prophylaxis initiation ($p<0.001$) and duration ($p=0.001$).

In total, 507 cycles (6.7 %) were positive on the CIN/FN-related composite outcome. The rate was higher for cycles in which prophylaxis was initiated >72 h ($p<0.001$) or lasted ≥6 days ($p<0.001$).

Safety

In the safety sample (1,496 patients with 6,392 cycles), 4271events were observed in 777 (53.7 %) patients (Table 5). Bone pain was the most prevalent (24.7 %) and was mostly mild to moderate. Five hundred twenty patients (35.9 %) experienced more than one event. Sixty-one patients died, mainly due to cancer (67.2 %). There were 148 ADRs reported (2.3 % of cycles) in 76 (5.1 %) patients. Most ADRs were mild or moderate (83.8 %) and

Table 4 Observed outcomes over the course chemotherapy cycles for patients receiving primary (Zarzio® initiated in cycle 1) and secondary (Zarzio® initiated in cycle 2 only) prophylaxis and associated probabilities

Primary prophylaxis	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		ΔP (event)[c]
	n[a]	P (event)[b]	n[a]	P (event)[b]	n[a]	P (event)[b]	n[a]	P (event)[b]	n[a]	P (event)[b]	n[a]	P (event)[b]	
Patients with													
CIN4	74	0.07	31	0.10	12	0.12	11	0.13	7	0.14	9	0.16	0.09
FN	31	0.03	14	0.04	11	0.06	5	0.06	3	0.07	6	0.08	0.05
Hospitalization	22	0.02	10	0.03	9	0.04	4	0.05	5	0.05	3	0.06	0.04
Chemotherapy disturbance			36	0.04	17	0.06	10	0.07	7	0.08	7	0.09	0.05
Secondary prophylaxis			Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		ΔP (event)[c]
			n[a]	P (event)[b]	n[a]	P (event)[b]	n[a]	P (event)[b]	n[a]	P (event)[b]	n[a]	P (event)[b]	
Patients with													
CIN4			18	0.08	6	0.11	2	0.12	2	0.14	2	0.16	0.07
FN			9	0.04	2	0.05	0	0.05	1	0.06	0	0.06	0.02
Hospitalization			10	0.05	1	0.05	1	0.06	1	0.06	0	0.06	0.02
Chemotherapy disturbance					6	0.03	5	0.06	8	0.12	2	0.13	0.10

[a] n is the count of patients experiencing the event at each cycle

[b] P (event) is the cumulative probability of having the event by a given cycle

[c] ΔP (event) is the change in probability of event from initiation cycle to cycle 6 (except for chemotherapy disturbance which has a one-cycle lag; see "Methods" section

resolved completely (95.9 %). The most frequent were bone pain (23.0 %), arthralgia (14.2 %), myalgia (7.4 %), diarrhea (6.8 %), back pain (4.7 %), and rash (4.7 %). Four serious ADRs (2.7 % of ADRs in 4 or 0.3 % of patients) were reported, these being bone pain, drug hypersensitivity, vulval abscess, and loss of consciousness. There were no neutropenia-related and no Zarzio®-related deaths.

Discussion

In this European study of patients with stage 3 or 4 cancer, treated with chemotherapy regimens with varying degrees of FN risk and receiving primary or secondary prophylaxis with Zarzio®, the rates of CIN4 and FN episodes, associated hospitalizations and chemotherapy disturbances, adverse events, and ADRs were statistically within the range of rates reported historically [16, 28, 29]. This documents the effectiveness and safety of Zarzio® in daily practice and extends the efficacy and safety data from its clinical development program [19–21]. These effectiveness and safety findings should address prescribers' concerns about biosimilars [30]. More importantly, this study revealed the impact of significant variability in prophylaxis patterns, often divergent from the EORTC guidelines for GCSFs. More than a decade of clinical experience with filgrastim has translated into practice patterns that differ from the normative filgrastim regimen in randomized controlled trials; attempt to balance chemotoxicity-associated CIN/FN risk, risk factors, patient safety, and clinician experience; and aim to achieve therapeutic efficiency.

Zarzio® was used mainly for 5 days of primary prophylaxis at a dose of 30 MIU, which tended to be increased to 48 MIU in function of weight, chemotoxicity, and tumor type. Almost six out of ten oncology patients were initiated in the EORTC-recommended time window of 24–72 h post-chemotherapy compared to one third of hematology patients. The latter tended to be started on prophylaxis between days 5 and 8. Patients on a regimen with<10 % risk or on secondary prophylaxis tended to be prophylacted sooner. The modal and median durations of prophylaxis were 5 days, considerably shorter than the 10–11 days in trials, consistent with early findings from claim databases [31], and thus reflective of well-established CIN/FN prophylaxis patterns. Over a quarter of patients received secondary prophylaxis, which is essential in patients with a neutropenic event in a previous cycle. Yet, this relatively high proportion, coupled with the 17.4 % under-prophylaxis data, suggests that, still, too many patients received secondary prophylaxis when primary prophylaxis was indicated. The low rate of antibiotic prophylaxis is likely due to the limited number of hematological malignancy patients, who have been shown to benefit from such prophylaxis [32].

Significant proportions of patients were under- (17.4 %) or over-prophylacted (26.0 %). Under-prophylaxis concerned patients on high FN risk chemotherapy or patients on moderate FN risk regimens but with FN risk factors. This is inconsistent with established evidence, further compounded by the increasingly shorter duration of prophylaxis. The over-prophylaxis involved patients on low-chemotoxicity regimens or patients on moderate-risk regimens but without risk factors. This may signal a real-world trend for clinicians to "over-

Table 5 Tolerability and safety

			Patients[a]	% Patients	Events[b]	% Events
Clinical events (not mutually exclusive)						
	Musculoskeletal					
		Bone pain	357	24.7 %	862	11.4 %
		Muscle pain	210	14.5 %	519	6.9 %
		Joint pain	200	13.8 %	453	6.0 %
	Hematological					
		Thrombocytopenia	230	15.9 %	548	7.2 %
		Epistaxis	29	2.0 %	41	0.5 %
		Skin hemorrhage	8	0.6 %	15	0.2 %
		Gastro-intestinal bleeding	9	0.6 %	10	0.1 %
		Other bleeding	30	2.1 %	35	0.5 %
	Elevated laboratory values					
		Serum LDH	222	15.3 %	456	6.0 %
		Serum GGT	178	12.3 %	363	4.8 %
		Serum ALP	168	11.6 %	357	4.7 %
		Blood uric acid	88	6.1 %	151	2.0 %
	Neurological					
		Headache	100	6.9 %	184	2.4 %
		Confusion/altered mental status	43	3.0 %	62	0.8 %
		Other neurological symptoms	102	7.1 %	189	2.5 %
	Splenomegaly		13	0.9 %	26	0.3 %
			Patients[c]	% Patients		
Death			61	4.1 %		
	Of which:					
		Cancer-related	41	67.2 %		
		Cancer-unrelated	14	22.9 %		
		Unknown	6	9.9 %		
Adverse drug reactions (ADR)			Patients[c]	% Patients	Events[d]	% Events
	Incidence of ADRs		76	5.1 %	148	2.3 %
		Of which classified as serious	4	0.3 %	4	<0.1 %
					Events[e]	% Events[e]
	ADR intensity					
		Mild			66	44.6 %
		Moderate			58	39.2 %
		Severe			8	5.4 %
		Not reported			16	10.8 %
	Treatment					
		None			89	60.1 %
		Medical			50	33.8 %
		Non-medical			6	4.1 %
		Not reported			3	2.0 %
	Outcome					
		Resolved completely			142	95.9 %
		Resolved with sequelae			1	0.7 %
		On-going			1	0.7 %
		Not reported			4	2.7 %

Table 5 (continued)

Impact on Zarzio® treatment			
	No impact	100	67.6 %
	Dose reduction	12	8.1 %
	Interruption	8	5.4 %
	Discontinuation	26	17.6 %
	Not reported	2	1.3 %

[a] Counts of patients in the evaluable sample (n=1447) ever reporting a given event across all cycles

[b] Counts of events reported across all cycles (including "study end" observation) in the evaluable sample (n=7580)

[c] Counts of patients in the safety sample (n=1496) ever reporting a given safety event across all cycles

[d] Counts of events reported across all cycles in the safety sample (n=6392)

[e] Counts within 148 ADR events occurring in safety sample across all cycles

protect" and reflect a change in practice that heretofore has not been described in real-world studies. If confirmed in future studies, the over-prophylaxis pattern may result in modifications of existing prophylaxis paradigms. The under-prophylaxis patterns are a reminder that, despite risk stratification and evidence-based guidelines, a significant proportion of patients may receive inadequate CIN/FIN prophylaxis.

One in seven patients received their first dose of Zarzio® on the day of chemotherapy. While the evidence is limited, derived mainly from non-controlled studies of pegfilgrastim, and often contradictory in findings, NCCN guidelines now cautiously acknowledge that "same-day administration may be considered in certain circumstances" [15]. The cycle-level analyses showed that same-day initiation was not associated with higher CIN rates.

In both the patient-level and cycle-level analyses, type and duration of prophylaxis, day of initiation, and FN risk were found to impact the CIN1/4, CIN3/4, CIN4, and FN rates; CIN/FN-related hospitalizations and chemotherapy disruptions; and the composite outcome. This is consistent with prior evidence [4, 5, 16, 24].

Seemingly paradoxical, higher rates of CIN, FN, and CIN/FN-related outcomes were found in cycles in which Zarzio® was administered for ≥6 days. However, duration was longer in patients on regimens with FN risk >20 % and presenting with additional risk factors. This may reflect clinician vigilance about chemotoxicity and risk factors and a goal of optimizing outcomes. Noteworthy, rates for chemotherapy disturbances, in general, and for chemotherapy delays specifically were at least twice as high in patients on secondary prophylaxis, thus exposing these patients to the risk of impaired tumor control.

The rates of musculoskeletal, hematological, elevated laboratory values, neurological, and splenomegaly events were consistent with the known safety profile for GCSFs. Likewise, ADR rates were consistent with known rates.

The use of biosimilar filgrastim offers significant cost savings over standard filgrastim (Neupogen®) or pegfilgrastim (Neulasta®). In fact, an economic analysis for the European Union (EU) G5 countries comparing 1 to 14 days of prophylaxis with Zarzio® versus 1 to 14 days with Neupogen® or a singular injection with Neulasta® showed, that under all scenarios, Zarzio® was the most cost-efficient approach to prophylaxis [33]. Further, savings achieved with conversion to biosimilars can be applied, in a budget-neutral way, to purchase additional curative anticancer therapy, and this expands patient access to such treatments as rituximab for diffuse large B cell non-Hodgkin's lymphoma and trastuzumab for metastatic HER2-positive breast cancer. For the EU G5 countries, it has been estimated that, depending on regimen, such expanded access to rituximab can be achieved by converting between 4 and 14 patients from Neupogen® and between 2 and 24 patients from Neulasta® to Zarzio®. Likewise, expanded access to trastuzumab would require converting between 4 and 14 patients from Neupogen® and between 2 and 24 patients from Neulasta® [34].

Our study has limitations. It was not a population-based study, was limited to centers using Zarzio®, and included only patients prophylacted with this biosimilar. The investigators selected patients, and this may be a source of selection bias. Despite strict inclusion and exclusion criteria, most patients had no or minimal impairment in performance status, and about a quarter had experienced a CIN or FN episode in a prior chemotherapy line or cycle. It is possible that investigators showed preference for less-impaired patients with better prognosis or patients with a prior CIN/FN history and therefore candidates for prophylaxis—some of whom may have been over-prophylacted relative to the EORTC guidelines. The design did not permit calculation of the relative dose intensity (RDI) of chemotherapy regimens, which has been shown to be associated with all-cause mortality [4]. Further analysis is needed to identify determinants of the CIN/FN

incidence, hospitalization, and chemotherapy disturbance rates and to compare specific subgroups such as oncological vs. hematological patients; elderly vs. non-elderly patients; under-, correctly, and over-prophylacted patients; and patients with same-day vs. 24–72-h vs. >72-h initiation of prophylaxis.

Conclusion

The clinical and safety outcomes of prophylaxis with biosimilar filgrastim are within the range of historically reported data for originator filgrastim. This underscores not only the clinical effectiveness and safety of biosimilar filgrastim prophylaxis in daily clinical practice, but also the need to improve primary prophylaxis rates in patients with chemotherapy-related and patient-related risk factors for FN.

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Conflict of interest P.G., M.A., H.L., C.B., and M.B. received compensation from Sandoz Biopharmaceuticals for their participation in the work reported here. M.T. is an employee of Sandoz Biopharmaceuticals. K.D., K.M., and I.A. 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.

References

1. Lalami Y, Paesmans M, Muanza F et al (2006) Can we predict the duration of chemotherapy-induced neutropenia in febrile neutropenic patients, focusing on regimen-specific risk factors? A retrospective analysis. Ann Oncol 17:507–514
2. Lalami Y, Paesmans M, Aoun M et al (2004) A prospective randomized evaluation of G-CSF or G-CSF plus oral antibiotics in chemotherapy-treated patients at high risk of developing febrile neutropenia. Support Care Cancer 12:725–730
3. Lyman GH, Lyman CH, Agboola O (2005) Risk models for predicting chemotherapy-induced neutropenia. Oncologist 10: 427–437
4. Lyman GH, Dale DC, Culakova E et al (2013) The impact of the granulocyte colony-stimulating factor on chemotherapy dose intensity and cancer survival: a systematic review and meta-analysis of randomized controlled trials. Ann Oncol 24:2475–2484
5. Lyman GH, Abella E, Pettengell R (2014) Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: a systematic review. Crit Rev Oncol Hematol 90:190–199
6. Kuderer N, Dale D, Crawford J et al (2007) Impact of primary prophylaxis with granulocyte colony-stimulating factor or febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. J Clin Oncol 25:3158–3167
7. Crawford J, Dale D, Lyman GH (2003) Chemotherapy-induced neutropenia. Cancer 100:228–237
8. Komorokji R, Lyman G (2004) The colony-stimulating factors: use to prevent and treat neutropenia and its complications. Exp Opin Biol Ther 4:1897–1910
9. Aapro M, Cameron D, Pettengell R et al (2006) EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapyinduced febrile neutropenia in adult patients with lymphomas and solid tumours. Eur J Cancer 42:2433–2453
10. Aapro MS, Bohlius J, Cameron DA et al (2011) 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. Eur J Cancer 47:8–32
11. Gridelli C, Aapro M, Barni S et al (2007) Role of colony stimulating factors (CSFs) in solid tumours: results of an expert panel. Crit Rev Oncol Hematol 63:53–64
12. Raposo CG, Marin AP, Barón MG (2006) Colony-stimulating factors: clinical evidence for treatment and prophylaxis of chemotherapy-induced febrile neutropenia. Clin Transl Oncol 8:729–734
13. Wingard JR, Elmongy M (2009) Strategies for minimizing complications of neutropenia: Prophylactic myeloid growth factors or antibiotics. Crit Rev Oncol Hematol 72:144–154
14. Morrison V, Wong M, Hershman D et al (2007) Observational study of the prevalence of febrile neutropenia in patients who received filgrastim or pegfilgrastim associated with 3–4 week chemotherapy regimens in community oncology practices. J Manag Care Pharm 13:337–348
15. 15 National Comprehensive Center Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Myeloid growth factors version 2.2014. Available at http://www.nccn.org/professionals/physician_gls/pdf/myeloid_growth.pdf. Accessed 2 Oct 2014
16. Klastersky J, Awada A (2011) Prevention of febrile neutropenia in chemotherapytreated cancer patients: Pegylated versus standard myeloid colony stimulating factors. Do we have a choice? Crit Rev Oncol Hematol 78:17–23
17. Klastersky J, Awada A, Paesmans M, Aoun M (2011) Febrile neutropenia: a critical review of the initial management. Crit Rev Oncol Hematol 78:185–194
18. Weise M, Bielsky MC, De Smet K et al (2011) Biosimilars – why terminology matters. Nat Biotechnol 29:690–693
19. Gascón P, Fuhr U, Sörgel F et al (2010) Development of a new G-CSF product based on biosimilarity assessment. Ann Oncol 21: 1419–1429
20. Abraham I, Tharmarajah S, MacDonald K (2013) Clinical safety of biosimilar recombinant human granulocyte colony stimulating factors. Exp Opin Drug Saf 12:235–246
21. Tharmarajah S, Mohammed A, Bagalagel A et al (2014) Clinical efficacy and safety of Zarzio (EP2006), a biosimilar recombinant human granulocyte colony stimulating factor. Biogeosciences 4:1–9
22. Verpoort K, Möhler TM (2012) A non-interventional study of biosimilar granulocyte colony-stimulating factor as prophylaxis for chemotherapy-induced neutropenia in a community oncology centre. Ther Adv Med Oncol 4:289–293
23. Salesi N, Di Cocco B, Veltri E (2012) Biosimilar medicines in oncology: singlecenter experience with biosimilar G-CSF. Fut Oncol 8:625–630
24. Gascón P, Tesch H, Verpoort K et al (2013) Clinical experience with Zarzio® in Europe: what have we learned? Support Care Cancer 21: 2925–2932
25. Bonig H, Becker PS, Schwebig A, Turner M (2015) Biosimilar granulocyte-colonystimulating factor for healthy donor stem cell mobilization: need we be afraid? Transfusion 55:430–439

26. Gascón P, Aapro M, Ludwig H et al (2011) Background and methodology of MONITOR-GCSF, a pharmaco-epidemiological study of the multi-level determinants, predictors, and clinical outcomes of febrile neutropenia prophylaxis with biosimilar granulocyte-colony stimulating factor filgrastim. Crit Rev Oncol Hematol 77:184–197
27. Gascón P, Aapro M, Ludwig H et al (2011) Update on the MONITOR-GCSF study of biosimilar filgrastim to reduce the incidence of chemotherapy-induced febrile neutropenia in cancer patients: Protocol amendments. Crit Rev Oncol Hematol 77:198–200
28. Kuderer N, Dale D, Crawford J et al (2007) Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. J Clin Oncol 25:3158–67
29. 29 European Medicines Agency. Zarzio. Annex I. Summary of product characteristics. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000917/WC500046525.pdf. Accessed 22 Nov 2014
30. Aapro MS (2012) What do prescribes think of biosimilars? Targ Oncol 7(Suppl 1):S51–S55
31. Weycker D, Hackett J, Edelsberg JS et al (2006) Are shorter courses of filgrastim prophylaxis associated with increased risk of hospitalization? Ann Pharmacother 40:402–407
32. Gafter-Gvili A, Fraser A, Paul M et al (2012) Antibiotic prophylaxis for bacterial infections in afebrile neutropenic patients following chemotherapy. Cochrane Database Syst Rev 201, CD004386
33. Aapro M, Cornes P, Abraham I (2011) Comparative cost-efficiency across the European G5 countries of various regimens of filgrastim, biosimilar filgrastim, and pegfilgrastim to reduce the incidence of chemotherapy-induced febrile neutropenia. J Oncol Pharm Pract 18:171–179
34. Sun D, Andayani TM, Altyar A et al (2015) Potential cost savings from chemotherapyinduced febrile neutropenia prophylaxis with biosimilar filgrastim and expanded access to targeted antineoplastic treatment across the European G5 countries: a simulation study. Clin Ther 37:842–857