EUROPEAN JOURNAL OF CANCER 46 (2010) 2389–2398

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Trends in G-CSF use in 990 patients after EORTC and ASCO guidelines

C. Falandry [a,*], M. Campone [b], G. Cartron [c], D. Guerin [d], G. Freyer [a]

[a] Medical Oncology Unit, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre Bénite, Université Lyon 1, Lyon, France
[b] Institut Régional du Cancer Nantes Atlantique, CLCC René Gauducheau, Centre de Recherche en Cancérologie, INSERM 892, Nantes, Saint Herblain, France
[c] Hematology Department, CHU Montpellier, UMR-CNRS5235, Université Montpellier, Montpellier, France
[d] A+A Healthcare Marketing Research, Lyon, France

ARTICLE INFO

Article history:
Received 6 February 2010
Received in revised form 26 April 2010
Accepted 29 April 2010
Available online 8 June 2010

Keywords:
Granulocyte colony-stimulating factor
Guideline
Decision making
Criteria

ABSTRACT

Background: Although international guidelines have standardised conditions for G-CSF administration, real practice seems to vary.

Patients and methods: A large survey was undertaken in France following a three-step method. Data concerning 990 patients in seven main indications were collected prospectively and analysed for their compliance with international guidelines.

Results: G-CSF prescription rate varied from 81% in non-Hodgkin lymphoma (NHL), 55% in ovarian, 44% in breast and 21% in colorectal cancer. The main criteria for G-CSF administration were a chemotherapy regimen with a high risk of neutropaenia (65%) and associated risk factors (51%). Public hospital practitioners prescribed G-CSF more frequently as primary prophylaxis, whereas prescriptions of recently graduated practitioners (⩽5 years) and former ones (⩾16 years) were often proposed as secondary prophylaxis or as G-CSF therapy, i.e. during ongoing neutropaenia. In prophylactic settings, administration schedules were highly variable depending on molecules, with a first day of administration between days 1 and 3 after chemotherapy in 66%, but before the end of the chemotherapy infusion in 13% of the cases. Concerning lenograstim (38% of prescriptions) and filgrastim (20%), the mean treatment duration was 5.5 days, significantly shorter than in 1999 (7.8 days).

Conclusion: G-CSF prescription was mainly in compliance with international guidelines. However, some too early administrations during chemotherapy are at risk of increased myelosuppression and should be more clearly disadvised in next international guidelines.

1. Introduction

Chemotherapy-induced neutropaenia is a major risk factor for febrile neutropaenia and infection-related morbidity and mortality. It leads also to dose reductions and to delayed chemotherapy cycles, thus limiting dose intensity. Recombinant human granulocyte colony-stimulating factor (G-CSF) induces proliferation and differentiation of neutrophil lineage cells,[1] reduces days of neutropaenia, potentially reverses myelosuppression and reduces risk of febrile neutropaenia.[2,3] According to a meta-analysis from Kuderer, it may have an impact on early mortality and infection-related mortality,[4] but two

* *Corresponding author at:* Medical Oncology Unit, Centre Hospitalier Lyon Sud, 165, Chemin du Grand Revoyet, 69495 Pierre Bénite cedex, France. Tel.: +33 478864318; fax: +33 478864319.
E-mail address: claire.falandry@chu-lyon.fr (C. Falandry).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.04.031

other meta-analyses failed to find evidence for reduced infection-related mortality or improved overall survival.[5,6] Conditions for appropriate G-CSF use have been standardised since the first American Society of Clinical Oncology (ASCO) recommendations in 1994, updated in 2006,[7] National Comprehensive Cancer Network, European Organization for Research and Treatment of Cancer (EORTC[8]) and European Society of Medical Oncology (ESMO[9–11]) guidelines. According to the updated guidelines, the threshold to recommend prophylactic use of G-CSF was lowered from a FN risk of 40% and over to 20% and over, based on two large randomised clinical trials. Indeed, studies from Vogel et al.[12] and Timmer-Bonte et al.[13] have shown that the risk of FN is reduced substantially by primary prophylaxis with G-CSF, when the risk of FN without G-CSF is approximately 20%. Moreover, the updated guidelines proposed that the impact of other factors such as age, medical history and disease characteristics should be taken into account when the FN risk is over 10%.[7–11]

Although some settings of G-CSF prescription are now clearly identified (i.e. range of FN, patient risk factors and secondary prophylaxis), some remain debatable because of the lack of experimental data (i.e. administration time and schedule) or controversial. Moreover other covariates seem to modulate practitioners' G-CSF prescription behaviour,[14] like, for example, insurance status[15] or type of practice.[16]

Since previous data collections on G-CSF use were only partially representative of the French prescription behaviour,[17,18] a first large survey was undertaken in France in 1999 and another during 2006–2007, after the publication of the international recommendations updates in 2006.[7–11]

2. Methods

2.1. Survey methodology

The main 2006–2007 survey methodology followed a three-step method, in order to propose a patient data set representative of medical practice in France.

A first step described prospectively G-CSF prescription in 100 representative retail pharmacies that had delivered one or more G-CSF in an observation month and 50 hospital pharmacies, with a representative distribution for retail/hospital size and on the geographic territory. A set of 1071 dispensations (830 from hospital and 241 from retail pharmacies) was prospectively collected and analysed for prescribers' profession and medical practice (step 1, Table 1).

A second step selected prescriptions from the four main providers' professions (oncologists, pneumologists, haematologists and gastro-enterologists, who contributed 91.6% of prescriptions (i.e. 981 of 1071) and defined main indications and G-CSF prescription rate for each category (step 2).

Using the medical distribution defined in the second step, a representative set of 103 medical practitioners was interviewed for their G-CSF prescriptions during a 1–2 week period in seven main indications previously defined. Finally, data concerning 990 patients were prospectively collected (step 3, Table 2).

Data from a 1999 survey were analysed for comparison. This first survey included a representative set of 811 G-CSF prescriptions in six main indications (breast, ovarian, colorectal and lung cancer, Hodgkin and non-Hodgkin lymphoma) with the same design as the 2006–2007 survey.

Both surveys were funded by Chugai Pharma France. Methodology and monitoring of data collections were independently organised by a private survey agency (A+A Healthcare Marketing Research, Lyon, France). A board of experts in the field of oncology and haematology validated the drafting and final review of questionnaires.

2.2. Statistics

Proportional tests (mainly Student's *t*-tests) were used to compare different variables (e.g. age, disease stage and deci-

Table 2 – G-CSF providers pattern of practice – comparison between steps 1 and 3.

	Step 1	Step 3	
Pattern of practice	(n = 1071)	(n = 990)	
–Private clinic	231 (21.6%)	198 (20.0%)	$p = 0.38$
–Cancer centre	125 (11.7%)	166 (16.8%)	$p < 0.001$
–Public hospital	715 (66.7%)	626 (63.2%)	$p = 0.09$
–General hospital	296 (27.6%)	233 (23.5%)	$p = 0.03$
–University hospital	419 (39.1%)	393 (39.7%)	$p = 0.79$
–Oncologists	735 (68.6%)	707 (71.4%)	$p = 0.17$
–Haematologists	161 (15.0%)	179 (18.1%)	$p = 0.06$
–Pneumologists	54 (5.0%)	69 (7.0%)	$p = 0.07$
–Gastro-enterologists	31 (2.9%)	35 (3.5%)	$p = 0.41$

Table 1 – G-CSF providers characteristics (1071 G-CSF dispensations).

	Private clinics	Cancer centres	General hospitals	University hospitals	Total
Oncologists	184 (17.2%)	115 (10.7%)	187 (17.5%)	249 (23.2%)	735 (68.6%)
Haematologists	6 (0.6%)	6 (0.6%)	38 (3.5%)	111 (10.4%)	161 (15.0%)
Pneumologists	8 (0.7%)	0 (0.0%)	34 (3.2%)	12 (1.1%)	54 (5.0%)
Internists	4 (0.4%)	0 (0.0%)	15 (1.4%)	7 (0.7%)	26 (2.4%)
Radiotherapists	8 (0.7%)	0 (0.0%)	0 (0.0%)	8 (0.7%)	16 (1.5%)
Gastro-enterologists	9 (0.8%)	0 (0.0%)	17 (1.6%)	5 (0.5%)	31 (2.9%)
Dermatologists	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (0.4%)	4 (0.4%)
Infectiologists	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (0.7%)	8 (0.7%)
Other	12 (1.1%)	4 (0.4%)	5 (0.5%)	15 (1.4%)	36 (3.4%)
Total	231(21.6%)	125(11.7%)	296(27.6%)	419(39.1%)	1071(100.0%)

sional reasons) and frequency among the subpopulations analysed. Significant differences are expressed with p-values.

The software used was S-PLUS® 6.2 (Lucent Technologies).

3. Results

3.1. Description of G-CSF providers (steps 1, 2 and 3)

The 1071 G-CSF dispensations collected from 100 retail and 50 hospital pharmacies were distributed as presented in Table 1. The majority of them came from oncologists (68.6%) and were balanced between community practices: private clinics (17.2%), cancer centres having a mixed public and private status (10.7%), general hospitals (17.5%) and university hospitals (20%). Haematologists provided 15% of G-CSF dispensations, mainly in general (3.5%) and university (7.2%) hospitals. Third and fourth ranks of prescriptions came from pneumologists (5.0%) and gastro-enterologists (2.9%), mainly from general hospitals (3.2% and 1.6%, respectively).

Using these data, a representative set of 100 physicians was determined and asked prospectively about their G-CSF prescription habits. G-CSF was prescribed at a high rate in some rare indications such as testicular cancer (76%), melanoma (75%), kidney cancer (75%) and myelodysplasia (73%) but the vast majority of prescriptions (67.7%) came from most frequent solid tumours (breast, colic, rectal, gastric, lung and ovarian cancers) and lymphoma. These main seven indications were selected and a new representative set of 103 physicians was defined. These 103 providers had to fill in a questionnaire prospectively, for the next 10 patients for whom they prescribed a G-CSF.

Table 3 – Rate of primary prophylaxis by treatment place and providers' practice experience.

	Primary prophylaxis	p
All (n = 989)	487 (49.2%)	–
Treatment place		
Private clinic (n = 197)	89 (45.2%)	0.34
Cancer centre (n = 166)	70 (42.2%)	0.09
Public hospital (n = 521)	267 (51.2%)	0.03
–General hospital (n = 233)	114 (48.9%)	0.79
–University hospital (n = 288)	153 (53.1%)	0.04
Providers' practice experience		
⩽5 years (n = 108)	36 (33.3%)	<0.001
6–15 years (n = 284)	184 (64.8%)	<0.001
⩾16 years (n = 215)	74 (34.4%)	<0.001

3.2. Providers' characteristics

A total of 990 prescriptions were collected. The step 1 and step 3 prescribers' characteristic comparison is shown in Table 2. Providers from cancer centres were statistically overrepresented in step 3, compared to step 1. Conversely, general hospital providers were underrepresented. Globally, the treatment place context had a significant influence on G-CSF prescription. Whereas primary prophylaxis represented 49.0% of all G-CSF prescriptions, the rate was statistically higher in university hospital (53.1%, $p = 0.04$) and lower in cancer centres (42.2%, $p = 0.09$, Table 3). Among recently graduated providers (⩽5 years since diploma) and former ones (⩾16 years) the use of G-CSF as primary prophylaxis was significantly less (respectively, 33%, 41% and 28% for 0–5, 16–20 and >20 years since diploma, $p < 0.001$ for each category) than in 6–10 and 11–15 years since diploma providers (respectively, 66% and 63%).

The treatment place also interfered on the type of G-CSF prescribed. Globally, lenograstim, filgrastim and pegfilgrastim represented 38.2%, 19.6% and 42.2% of the 990 prescriptions, respectively. Pegylated growth factors were prescribed significantly more frequently in cancer centres and general hospital (53.0%, $p = 0.002$ and 48.9%, $p = 0.02$, respectively). Lenograstim was more frequently prescribed than filgrastim and reached 42.7% of university hospital prescriptions versus 27.3% in private clinics (Fig. 1).

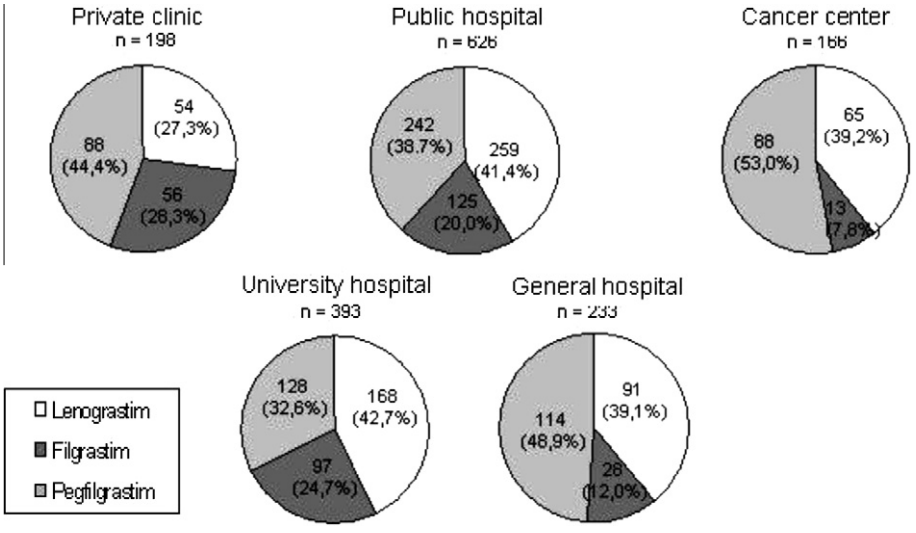

Fig. 1 – G-CSF provider characteristics.

3.3. Patient characteristics and patterns of care

The median age of patients was 61 (mean 60.2 ± 0.8, 95% confidence interval (CI)). Respectively, 609 and 381 patients were <65 and ⩾65 (respectively, 61.5% and 38.5%).

The age categories were comparable between lenograstim, filgrastim and pegfilgrastim molecules (Table 4).

3.4. G-CSF administration conditions

Globally, G-CSF was mainly prescribed after a first line chemotherapy (61.0%), in a proportion that significantly increased since 1999 (49.0%, $p < 0.001$). Almost half of G-CSF prescriptions (49.2%) corresponded to primary prophylaxis (Table 5), versus 40.6% in 1999, $p < 0.001$. At the same time, secondary prevention decreased in proportion (44.4% versus 50.9% in 1999, $p = 0.006$).

Pegylated versus daily G-CSF preferences, analysed in each indication, are shown in Fig. 2. Daily injections were more frequent in a metastatic intent (65.3%), with an overrepresentation of lenograstim, compared to filgrastim (respectively, 48.5% and 18.8%), whereas single injections of pegfilgrastim were more frequently proposed in an adjuvant setting (51.3%).

3.5. Administration schedules

G-CSF administration schedules were analysed for their start time and duration and compared to the 1999 survey data (Tables 6 and 7). For 2006–2007 survey analyses, we considered G-CSF prescribed in primary or secondary prevention intent only and the duration was considered for lenograstim and filgrastim only. For pegfilgrastim, the start time was mostly between one (D + 1) to three (D + 3) days after chemotherapy, in compliance with international recommendations.[7] Nonetheless, a substantial portion of pegfilgrastim (9.6%), lenograstim (15.3%) and filgrastim (17.6%) prescriptions was administrated during chemotherapy, as observed in 1999 for lenograstim and filgrastim (16.6%). Only a small fraction of lenograstim and filgrastim treatments exceeded 7 days (total 9.3%, 11.3% and 4.6%, respectively), whereas they were 45.3% in 1999 (Table 7).

Comparing the 1999 and 2006–2007 surveys, there was a clear downward trend in treatment duration, with a mean

Table 4 – G-CSF molecule preferences by patients' age and gender.

	All G-CSFs	Lenograstim	Filgrastim	Pegfilgrastim
Total number	990 (100%)	377 (38.1%)	195 (19.7%)	418 (42.2%)
Age	(*n* = 987)	(*n* = 377)	(*n* = 195)	(*n* = 417)
–Mean [SD]	60.2 [0.8]	60.2 [1.2]	60 [1.7]	60 [1.2]
–Median	61	61	61	61
–<50 years old	193 (19.5%)	68 (18.0%)	35 (18.0%)	89 (21.3%)
–50–59	234 (23.6%)	98 (26.0%)	44 (22.6%)	92 (22.1%)
–60–69	307 (31.0%)	119 (31.6%)	75 (33.8%)	122 (29.3%)
–⩾70 years	256 (25.9%)	92 (24.4%)	50 (25.6%)	114 (27.3%)
–Sex ratio	0.44	–	–	–

Table 5 – G-CSF preferences by treatment context – changes in proportions between 1999 and 2006–2007.

	1999	2006–2007	
	(*n* = 820)	(*n* = 989)	
Primary prevention	333 (40.6%)	487 (49.2%)	$p < 0.001$
Secondary prevention	417 (50.9%)	439 (44.4%)	$p = 0.006$
G-CSF therapy (ongoing neutropaenia)	70 (8.5%)	63 (6.4%)	$p = 0.08$
Chemotherapy line	(*n* = 818)	(*n* = 982)	
–First line	401 (49.0%)	599 (61.0%)	$p < 0.001$
–Second line	220 (26.9%)	206 (21.0%)	$p = 0.003$
–Third line and more	197 (24.1%)	177 (18.0%)	$p = 0.002$
Chemotherapy indication			
Non-Hodgkin lymphoma	(*n* = 179)	(*n* = 188) [a]	
–First line chemotherapy	109 (60.9%)	134 (71.3%)	$p = 0.03$
–Second line chemotherapy	56 (31.3%)	32 (17.0%)	$p = 0.002$
–Third line and more	14 (7.8%)	21 (11.2%)	$p = 0.27$
–High dose chemotherapy	–	6 (3.2%)	
–Mobilisation	–	4 (2.2%)	
Solid tumours	(*n* = 645)	(*n* = 799)	
–Neoadjuvant setting	78 (12.1%)	66 (8.3%)	$p = 0.016$
–Adjuvant setting	194 (30.1%)	238 (29.8%)	$p = 0.9$
–Metastatic setting	373 (57.8%)	495 (62.0%)	$p = 0.11$

a Total > 100 (more than one response possible).

duration of 5.5 days for lenograstim and filgrastim, significantly shorter than in 1999 (7.8 days).

3.6. Analyses by tumour types

In solid tumours, neoadjuvant, adjuvant and metastatic settings represented 8.3%, 9.8% and 62.0% of G-CSF prescriptions, respectively, but this distribution was highly dependent on tumour type (Table 8). Colon and ovarian cancer patients receiving G-CSFs tended to be older, as shown in Fig. 3.

3.7. Analysis of prescription compliance in breast cancer patients subgroup

We analysed G-CSFs prescriptions rules and their compliance with international guidelines in the subgroup of breast cancer patients. Patients treated with the 15 most frequent chemotherapy protocols were extracted ($n = 258$) and each protocol was identified by its FN risk rate (Table 9). According to the NCCN,[19] ASCO,[7] ESMO[11] and EORTC[8] guidelines, G-CSFs are justified in a prophylactic intent when FN risk rate is $\geqslant 20\%$. Moreover, EORTC guidelines mentioned a need for tools to evaluate the benefits of G-CSFs in elderly patients' subcategories and ASCO[7] and EORTC[8] proposed some patient-related risk factors, including age over 65 years that can extend G-CSF indication to protocols with a FN risk between 10% and 20%. The presence of these additional risk factors, such as age and intense pretreatment, were detected and asked for their participation in G-CSF administration decision. G-CSF prescriptions were first divided into $\geqslant 20\%$, from 10% to 20% and <10% FN risk rates and then classified as follows: primary intent, primary intent with additional risk factors (i.e. age, pretreatment, FN in a previous chemotherapy line), secondary

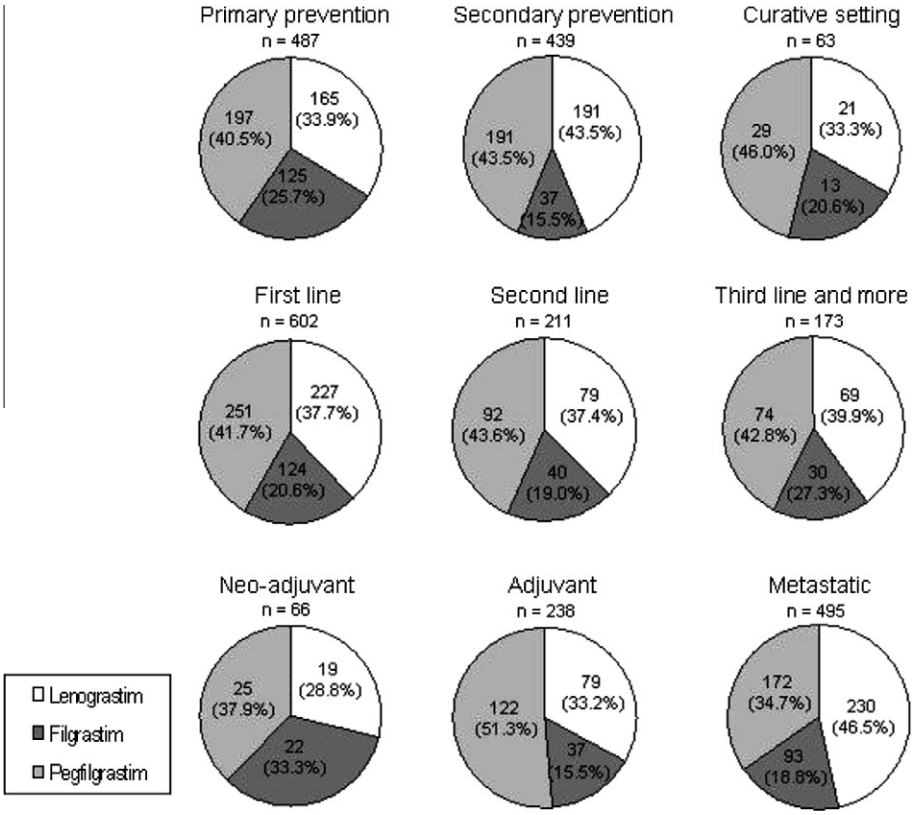

Fig. 2 – G-CSF preferences by treatment context.

Table 6 – Administration schedules in a prophylactic (primary or secondary) setting: starting time.

	Date of first injection				
	1999	2006–2007			
	All ($n = 817$)	All ($n = 923$)	Lenograstim ($n = 354$)	Filgrastim ($n = 182$)	Pegfilgrastim ($n = 387$)
Before/during chemotherapy	136 (16.6%)	124 (13.4%)	54 (15.3%)	32 (17.6%)	37 (9.6%)
From D + 1 to D + 3 (1–3 days after chemotherapy)	273 (33.4%)	606 (65.7%)	198 (55.9%)	77 (42.3%)	332 (85.8%)
D + 4 and after	408 (49.9%)	193 (20.9%)	102 (28.8%)	73 (40.1%)	18 (4.7%)

Table 7 – Administration schedules in a prophylactic (primary or secondary) setting: treatment duration.

	Treatment duration			
	1999	2006–2007		
	All (*n* = 821)	All (*n* = 572)	Lenograstim (*n* = 377)	Filgrastim (*n* = 195)
1–3 days	32 (3.9%)	63 (11.0%)	38 (10.1%)	25 (12.8%)
4	20 (2.4%)	73 (12.8%)	37 (9.8%)	36 (18.5%)
5	160 (19.5%)	202 (35.3%)	145 (38.5%)	57 (29.2%)
6	55 (6.7%)	84 (14.7%)	66 (17.5%)	18 (9.2%)
7	182 (22.2%)	97 (17.0%)	47 (12.5%)	50 (25.6%)
8 and more	372 (45.3%)	53 (9.3%)	44 (11.7%)	9 (4.6%)
10 and more	312 (38.0%)	27 (4.7%)	23 (6.1%)	4 (2.1%)

Table 8 – G-CSF prescriptions by tumour type.

	Breast	Lung	Ovary	Stomach	Colon	Rectum
Treatment context	(*n* = 279)	(*n* = 243)	(*n* = 62)	(*n* = 91)	(*n* = 115)	(*n* = 9)
–Neoadjuvant setting	17 (6%)	29 (11.9%)	3 (4.8%)	10 (11%)	6 (5.2%)	0
–Adjuvant setting	156 (56%)	34 (14.0%)	15 (24.2%)	7 (7.7%)	27 (23.5%)	0
–Metastatic setting	106 (38%)	180 (74.1%)	44 (71.0%)	74 (81.3%)	82 (71.3%)	9 (100%)
Chemotherapy line	(*n* = 281)	(*n* = 241)	(*n* = 62)	(*n* = 93)	(*n* = 116)	(*n* = 8)
–First line	146 (52.0%)	175 (72.6%)	29 (46.8%)	65 (69.9%)	59 (50.9%)	2 (25.0%)
–Second line	62 (22.1%)	47 (19.5%)	18 (29.0%)	23 (24.7%)	29 (25.0%)	1 (12.5%)
–Third line and more	53 (18.9%)	19 (7.9%)	15 (24.2%)	5 (5.4%)	28 (24.1%)	5 (62.5%)

intent, therapeutical setting, ie. during ongoing neutropaenia, in order to analyse compliance with guidelines. These results are presented in Fig. 4 and global compliance was estimated at 69.4%. It is worth noting that only one of the protocols administered (Doxorubicin–Docetaxel) has a FN risk ⩾40% and represented only 1% of G-CSF prescriptions.

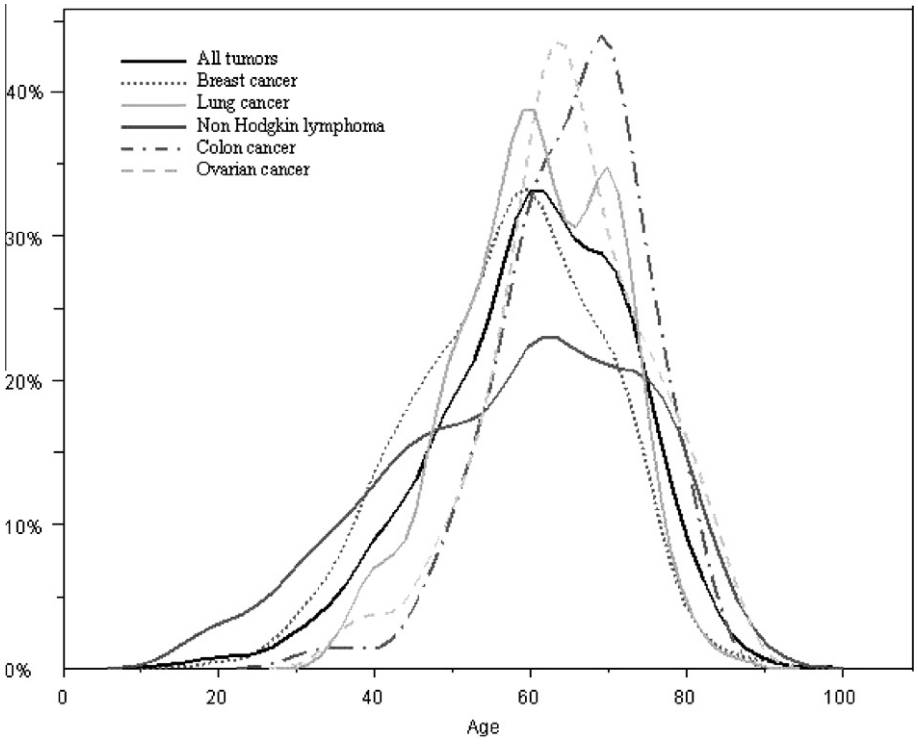

Fig. 3 – Age distribution by tumour site.

Table 9 – Top 15 chemotherapy protocols and estimated FN risk in breast cancer patients treated with G-CSF.

Estimated risk[8]	Chemotherapy protocol	No. pts (%)	Total (%)	
⩾20%	TAC 75	9 (3%)	30 (10%)	258 (87%)
	ET (Epirubicin–Docetaxel)	18 (6%)		
	AT (Adriamycin–Docetaxel)	3 (1%)		
10–20%	Docetaxel 100	58 (21%)	67 (26%)	
	Docetaxel 100 + Herceptin	6 (2%)		
	TAC 50	3 (1%)		
<10%	FEC 100	105 (35%)	161 (62%)	
	Vinorelbine Docetaxel	5 (2%)		
	FEC 75	6 (2%)		
	Vinorelbine	9 (3%)		
	Paclitaxel	17 (6%)		
	Vinorelbine 5FU	8 (3%)		
	Paclitaxel Gemcitabine	3 (1%)		
	Paclitaxel Carboplatin	4 (1%)		
	Liposomal doxorubine + cyclo-phosphamide	4 (1%)		

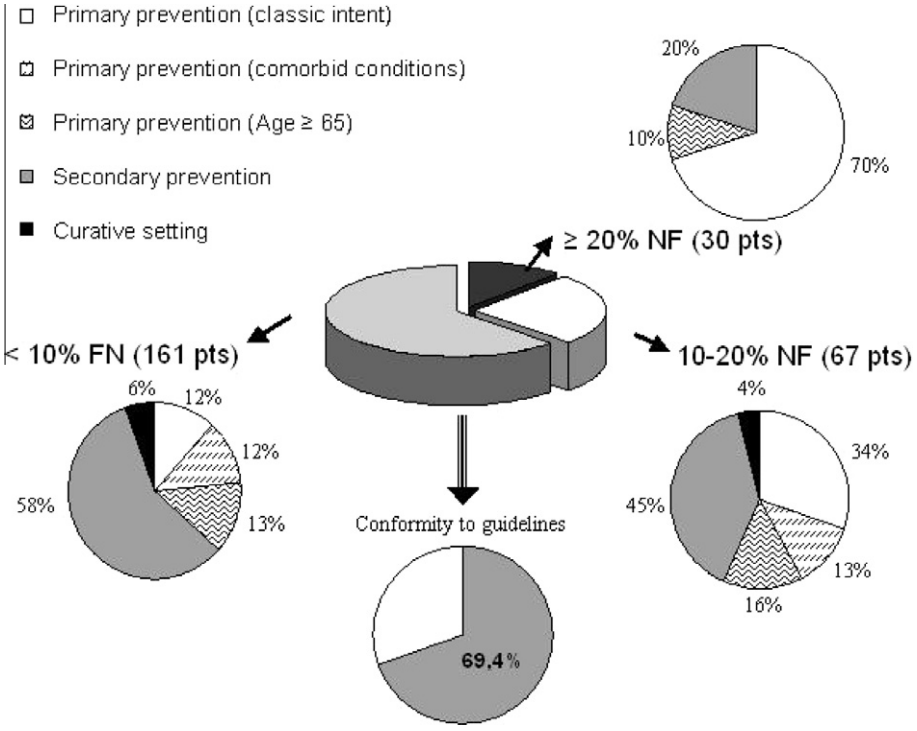

Fig. 4 – G-CSF prescription in breast cancer patient subgroup: conformity to international guidelines.

4. Discussion

These two surveys, performed in 1999 and 2006–2007, are to our knowledge the first and largest to describe G-CSF use in chemotherapy-induced febrile neutropaenia prevention in community practice at a country level.

We successively analysed providers' and patients' characteristics and their role on G-CSF prescription preferences. Concerning the role of practice context, public hospital practitioners were more likely to use G-CSFs as primary prophylaxis, cancer centre providers significantly less likely than private clinic ones, some results at the opposite of what had been observed on the United States during ASCO surveys.[16] Concerning the role of providers' practice experience, practitioners between 6 and 15 years from diploma were more likely to prescribe G-CSF. In France, a recent survey studying G-CSF prescription as adjuvant treatment for chronic hepatitis C stated young age (<45), practice in university hospital and a high number of patients treated as significant covariates associated with a high G-CSF prescription rate.[20] Our results are, in a different indication, in accordance with this previous survey, even though the number of patients treated by each provider was not verified. These different surveys highlight some heterogeneity in community practice between countries, more dependent in France on the providers' practice context than on public versus liberal practice.

Compared to 1999, G-CSFs are more frequently prescribed after a first line chemotherapy (61.0% versus 49.0%, $p < 0.001$) and as primary prophylaxis (49.2% versus 40.6%, $p < 0.001$), a trend that can be interpreted both as a consequence of NCCN, ASCO, ESMO and EORTC guidelines updates and as the use of more myelotoxic chemotherapy combinations. Conversely, therapeutical prescriptions as adjunct therapy for the treatment of febrile neutropaenia were less frequent (6.4% versus 8.5%, $p = 0.08$) in accordance with ASCO and EORTC 2006 guidelines that do not recommend it for FN in routine practice, but take into account FN duration and risk factors.[7,8]

Since the pegfilgrastim authorisation, single injection schedules have increased and reached 42.2% of the prescriptions in the 2006–2007 survey, whereas lenograstim and filgrastim accounted for 38.1% and 19.7% of prescriptions, respectively. During the same period, the duration of daily injections significantly decreased, as only 9.3% of treatments exceeded 7 days in 2006–2007, versus 45.3% in 1999. These two tendencies are contradictory, as a pegfilgrastim injection is equivalent to daily injections for a prolonged period of 11 days[21,22] that is twice the average duration of daily G-CSF treatmentin of our 2006–2007 cohort (5.5 days).

Daily injections remain more frequent, especially in a metastatic setting. In this context, short daily G-CSF schemas are prescribed not only as primary or secondary prophylaxis but also in order to maintain dose intensity.

Overall, G-CSF seems to be prescribed earlier and with extended indications.

For long survivors, a possible risk of myelodysplasia (MDS) or acute myeloid leukaemia (AML) remains questionable on the basis of epidemiologic studies. Indeed, two successive publications of the Surveillance, Epidemiology and End Result (SEER) program have reported controversial data. The first report from Hershman stated among breast cancer patients who had received between 1991 and 1999 an adjuvant chemotherapy that the risk of myeloid malignancies (AML and MDS) was twice as high among patients treated with G-CSF (hazard ratio (HR) = 2.24, 95% CI = 1.22–4.08).[23] However, these data were not confirmed by a second analysis from Patt et al. on AML risk.[24] Comparable doubts arose from CALGB study 9741[25] and a meta-analysis from this group.[26] However, potential confounders have been proposed, as anthracycline treatment or age. In Patt's retrospective study on SEER data, the adjusted hazard ratio for AML 10-year risk with adjuvant chemotherapy versus none was 1.53 (95% CI = 1.14–2.06) but G-CSF use within the first year of diagnosis did not convey a significantly increased risk of AML (HR = 1.14; 95% CI = 0.67–1.92). Nonetheless, a prolonged haematologic follow-up should be carried out for long survivors, notably in the adjuvant setting.

In the breast tumour subgroup, our results highlight a globally good compliance (69.4%) of G-CSF prescription indications with international guidelines. This analysis must take into account that 18.9% of G-CSF prescriptions in this subgroup were provided after a third line of chemotherapy, 38% in a metastatic setting. In these situations short G-CSF treatments (1–3 injections) are sometimes proposed both to maintain the dose intensity and to prevent neutropaenia, whenever no real febrile neutropaenia was documented. Since they allow to maintain dose intensity[13,27–35] but do not improve survival in solid tumours[28,33,36–39] and lymphoma,[5,40–42] these indications remain feasible but debated in international guidelines.[7,8]

Nonetheless, 13.4% of total G-CSF treatments were initiated before the end of the chemotherapy, whereas too early treatment initiation was clearly identified to increase myelosuppression.[43] For this concern, our results advocate, in the next international guidelines on G-CSFs use, for some highlights on the recommended and prohibited administration schedules, as G-CSF should not be started before one day after the end of chemotherapy infusion.

Conflict of interest statement

C.F. has no conflict of interest to disclose. M.C., G.C. and G.F. participated to a scientific board and held consultant arrangements for protocol validation with Chugai Pharma France.

Acknowledgements

The authors wish to thank the prescribers who completed the questionnaires, the board of experts who worked on the first survey, in 1999 [oncologists: G. Ganem (Jean Bernard Center, Le Mans), J.P. Lotz (Tenon Hospital, Paris), E. Pujade-Lauraine (Hôtel-Dieu Hospital, Paris), D. Serin (Sainte-Catherine de Sienne Clinic, Avignon), M. Spielmann (Gustave Roussy Institute, Villejuif), L. Zelek (Avicennes Hospital, Bobigny) and haematologists: T. Facon (Claude Huriez Hospital, Lille), C. Ghandour (Sevigné Clinic, Cesson-Sévigné), F. Guilhot (Jean Bernard Hospital, Poitiers), J.P. Marolleau (South Hospital, Amiens), J.F. Rossi (Hôpital Lapeyronie Hospital, Montpellier)], A+A Healthcare Marketing Research and Chugai Pharma France.

REFERENCES

1. Asano S. Human granulocyte colony-stimulating factor: its basic aspects and clinical applications. *Am J Pediatr Hematol Oncol* 1991;**13**(4):400–13.
2. Ozer H, Armitage JO, Bennett CL, et al. 2000 Update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. American Society of Clinical Oncology Growth Factors Expert Panel. *J Clin Oncol* 2000;**18**(20):3558–85.
3. Komrokji RS, Lyman GH. The colony-stimulating factors: use to prevent and treat neutropenia and its complications. *Expert Opin Biol Ther* 2004;**4**(12):1897–910.
4. Kuderer NM, Dale DC, Crawford J, Lyman GH. 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* 2007;**25**(21):3158–67.
5. Bohlius J, Herbst C, Reiser M, Schwarzer G, Engert A. Granulopoiesis-stimulating factors to prevent adverse effects in the treatment of malignant lymphoma. *Cochrane Database Syst Rev* 2008;(4):CD003189.
6. Sung L, Nathan PC, Alibhai SM, Tomlinson GA, Beyene J. Meta-analysis: effect of prophylactic hematopoietic colony-stimulating factors on mortality and outcomes of infection. *Ann Intern Med* 2007;**147**(6):400–11.

7. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol* 2006;**24**(19):3187–205.
8. Aapro MS, Cameron DA, Pettengell R, et al. 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* 2006;**42**(15):2433–53.
9. Greil R, Jost LM. ESMO recommendations for the application of hematopoietic growth factors. *Ann Oncol* 2005;**16**(Suppl 1):i80–2.
10. Greil R, Psenak O. Hematopoietic growth factors: ESMO recommendations for the application. *Ann Oncol* 2007;**18**(Suppl 2):ii89–91.
11. Greil R, Psenak O, Roila F. Hematopoietic growth factors: ESMO recommendations for the applications. *Ann Oncol* 2008;**19**(Suppl 2):ii116–8.
12. Vogel CL, Wojtukiewicz MZ, Carroll RR, et al. First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: a multicenter, double-blind, placebo-controlled phase III study. *J Clin Oncol* 2005;**23**(6):1178–84.
13. Timmer-Bonte JN, de Boo TM, Smit HJ, et al. Prevention of chemotherapy-induced febrile neutropenia by prophylactic antibiotics plus or minus granulocyte colony-stimulating factor in small-cell lung cancer: a Dutch Randomized Phase III Study. *J Clin Oncol* 2005;**23**(31):7974–84.
14. Swanson G, Bergstrom K, Stump E, Miyahara T, Herfindal ET. Growth factor usage patterns and outcomes in the community setting: collection through a practice-based computerized clinical information system. *J Clin Oncol* 2000;**18**(8):1764–70.
15. Harlan LC, Greene AL, Clegg LX, et al. Insurance status and the use of guideline therapy in the treatment of selected cancers. *J Clin Oncol* 2005;**23**(36):9079–88.
16. Bennett CL, Smith TJ, Weeks JC, et al. Use of hematopoietic colony-stimulating factors: the American Society of Clinical Oncology survey. The Health Services Research Committee of the American Society of Clinical Oncology. *J Clin Oncol* 1996;**14**(9):2511–20.
17. Gautie L, Canal P, Menguy A, et al. Analysis of hematopoietic growth factor prescriptions in 19 French Cancer Centers. *Bull Cancer* 1998;**85**(12):1043–8.
18. Maurice-Tison S, Schuller MP, Salamon R. Prescription d'un facteur de croissance hématopoïétique, le lénograstime, en pratique courante. Résultats et commentaires, à partir d'une enquête nationale réalisée d'avril 1995 à mars 1996. *La Presse Médicale* 1998;**27**(24):1203–12.
19. McNeil C. NCCN guidelines advocate wider use of colony-stimulating factor. *J Natl Cancer Inst* 2005;**97**(10):710–1.
20. Thevenot T, Cadranel JF, Di Martino V, et al. A national French survey on the use of growth factors as adjuvant treatment of chronic hepatitis C. *Hepatology* 2007;**45**(2):377–83.
21. Green MD, Koelbl H, Baselga J, et al. A randomized double-blind multicenter phase III study of fixed-dose single-administration pegfilgrastim versus daily filgrastim in patients receiving myelosuppressive chemotherapy. *Ann Oncol* 2003;**14**(1):29–35.
22. Holmes FA, O'Shaughnessy JA, Vukelja S, et al. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. *J Clin Oncol* 2002;**20**(3):727–31.
23. Hershman D, Neugut AI, Jacobson JS, et al. Acute myeloid leukemia or myelodysplastic syndrome following use of granulocyte colony-stimulating factors during breast cancer adjuvant chemotherapy. *J Natl Cancer Inst* 2007;**99**(3):196–205.
24. Patt DA, Duan Z, Fang S, Hortobagyi GN, Giordano SH. Acute myeloid leukemia after adjuvant breast cancer therapy in older women: understanding risk. *J Clin Oncol* 2007;**25**(25):3871–6.
25. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol* 2003;**21**(8):1431–9.
26. Muss HB, Woolf S, Berry D, et al. Adjuvant chemotherapy in older and younger women with lymph node-positive breast cancer. *Jama* 2005;**293**(9):1073–81.
27. Fossa SD, Kaye SB, Mead GM, et al. Filgrastim during combination chemotherapy of patients with poor-prognosis metastatic germ cell malignancy. European Organization for Research and Treatment of Cancer, Genito-Urinary Group, and the Medical Research Council Testicular Cancer Working Party, Cambridge, United Kingdom. *J Clin Oncol* 1998;**16**(2):716–24.
28. Masutani M, Ochi Y, Kadota A, et al. Dose-intensive weekly alternating chemotherapy for patients with small cell lung cancer: randomized trial, can it improve survival of patients with good prognostic factors? *Oncol Rep* 2000;**7**(2):305–10.
29. Gisselbrecht C, Haioun C, Lepage E, et al. Placebo-controlled phase III study of lenograstim (glycosylated recombinant human granulocyte colony-stimulating factor) in aggressive non-Hodgkin's lymphoma: factors influencing chemotherapy administration. Groupe d'Etude des Lymphomes de l'Adulte. *Leuk Lymphoma* 1997;**25**(3–4):289–300.
30. Vaughn DJ, Malkowicz SB, Zoltick B, et al. Paclitaxel plus carboplatin in advanced carcinoma of the urothelium: an active and tolerable outpatient regimen. *J Clin Oncol* 1998;**16**(1):255–60.
31. Masutani M, Tsujino I, Fujie T, et al. Moderate dose-intensive chemotherapy for patients with non-small cell lung cancer: randomized trial, can it improve survival of patients with good performance status? *Oncol Rep* 1999;**6**(5):1045–50.
32. Lyman GH, Kuderer NM, Djulbegovic B. Prophylactic granulocyte colony-stimulating factor in patients receiving dose-intensive cancer chemotherapy: a meta-analysis. *Am J Med* 2002;**112**(5):406–11.
33. Gatzemeier U, Kleisbauer JP, Drings P, et al. Lenograstim as support for ACE chemotherapy of small-cell lung cancer: a phase III, multicenter, randomized study. *Am J Clin Oncol* 2000;**23**(4):393–400.
34. Hackshaw A, Sweetenham J, Knight A. Are prophylactic haematopoietic growth factors of value in the management of patients with aggressive non-Hodgkin's lymphoma? *Brit J Cancer* 2004;**90**(7):1302–5.
35. Hidalgo M, Mendiola C, Lopez-Vega JM, et al. A multicenter randomized phase II trial of granulocyte-colony stimulating factor-supported, platinum-based chemotherapy with flexible midcycle cisplatin administration in patients with advanced ovarian carcinoma. PSAMOMA Cooperative Group, Spain. *Cancer* 1998;**83**(4):719–25.
36. Levine MN, Bramwell VH, Pritchard KI, et al. Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1998;**16**(8):2651–8.
37. Papaldo P, Lopez M, Marolla P, et al. Impact of five prophylactic filgrastim schedules on hematologic toxicity in early breast cancer patients treated with epirubicin and cyclophosphamide. *J Clin Oncol* 2005;**23**(28):6908–18.

38. Crawford J, Ozer H, Stoller R, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. *New Engl J Med* 1991;**325**(3): 164–70.
39. Trillet-Lenoir V, Green J, Manegold C, et al. Recombinant granulocyte colony stimulating factor reduces the infectious complications of cytotoxic chemotherapy. *Eur J Cancer* 1993;**29A**(3):319–24.
40. Lyman GH, Dale DC, Friedberg J, Crawford J, Fisher RI. Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkin's lymphoma: a nationwide study. *J Clin Oncol* 2004;**22**(21):4302–11.
41. Bohlius J, Reiser M, Schwarzer G, Engert A. Impact of granulocyte colony-stimulating factor (CSF) and granulocyte-macrophage CSF in patients with malignant lymphoma: a systematic review. *Brit J Haematol* 2003;**122**(3):413–23.
42. Burton C, Linch D, Hoskin P, et al. A phase III trial comparing CHOP to PMitCEBO with or without G-CSF in patients aged 60 plus with aggressive non-Hodgkin's lymphoma. *Brit J Cancer* 2006;**94**(6):806–13.
43. Tjan-Heijnen VC, Biesma B, Festen J, et al. Enhanced myelotoxicity due to granulocyte colony-stimulating factor administration until 48 hours before the next chemotherapy course in patients with small-cell lung carcinoma. *J Clin Oncol* 1998;**16**(8):2708–14.