Granocyte-colony Stimulating Factor (G-CSF) Has Significant Efficacy as Secondary Prophylaxis of Chemotherapy-induced Neutropenia in Patients with Solid Tumors: Results of a Prospective Study

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Abstract. *Aim: To carry out a prospective, multicenter and observational study describing prophylactic strategies [cycle delay, dose-reduction, (G-CSF) prescription] to prevent recurrence of neutropenic events (NE) in patients with solid tumors, and identify potential predictive factors of NE recurrence. Patients and Methods: Patients ≥18 years old with an NE in a previous chemotherapy cycle (cycle A) without G-CSF support, followed for four cycles (B to E) were included in the study. NE was defined as any neutropenia grade 1-4, febrile or not, which impacted on subsequent chemotherapy cycles (cycle delay, or reduction, or prophylactic G-CSF). Results: Data of 548 patients were analyzed, 378 (69%) were female, with a mean (SD) age of 61.7 (12.3) years. WHO PS: 0-1: 88.3%, incidence of breast cancer: 40%, metastatic disease: 53.3%. Following the first NE episode, 44.5% of patients had cycle delay, 22.3% dose reduction and 466 (85%) received prophylactic G-CSF. NE recurrence rates were: 21.2% at cycle B, 18.6% at cycle C, 11.5% at cycle D and 12.9% at cycle E. G-CSF support (hazard ratio: 0.32 , 0.24-0.43, p<0.001) was associated with lower NE recurrence. Pegfilgrastim seemed to offer the highest protection (hazard ratio; HR=0.23, 95% CI: 0.16-0.32; p<0.001). Conclusion: Secondary G-CSF prophylaxis has significant efficacy in reducing the incidence of NE and should be considered as a valuable option.*

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Neutropenia is a common side-effect of cancer chemotherapy in patients with solid tumors. Febrile neutropenia (FN), defined by grade 4 neutropenia and >38.0˚C fever is the complication of most concern. It is associated with severe morbidity and increased risk of mortality (1-3). A correlation between the dose/dosing schedule and neutropenia has been established for most cytotoxic agents (4, 5). However the risk of developing life-threatening complications after an episode of severe neutropenia (*i.e.* FN) is variable from one patient to another due to individual risk factors. Some risk factors can be considered in predicting the risk of neutropenia and are well-established in international guidelines in the primary prophylaxis setting (5, 6). These are: age (>65 years old and older), advanced disease, altered patient condition [poor *performance status* (*PS*) and/or nutritional status], pre-existing condition (active infection, open wound, recent surgery), previous FN, previous irradiation to pelvis, and impaired renal or liver function.

Granulocyte colony stimulating factors (G-CSF) reduce the severity and duration of neutropenia and FN (7, 8). In

a recent meta-analysis of randomized clinical trials of solid tumors (9), overall survival was better in the subgroup of patients who received primary G-CSF prophylaxis, with a higher dose-intensity of chemotherapy. While primary G-CSF prophylaxis use is well-endorsed by all international societies (5, 6, 10, 11), secondary G-CSF is restricted to patients who experienced a neutropenic complication from a previous cycle of chemotherapy, and who did not receive primary prophylaxis. In such patients, a reduced dose of chemotherapy may compromise treatment efficacy and outcome (12-14). In some clinical situations, however, dose reduction or chemotherapy delay may be a reasonable strategy in the palliative setting. Limited published data are currently available on the use of secondary G-CSF prophylaxis.

We designed this prospective, multicenter and observational study to describe the prophylactic strategies – cycle delay, dose-reduction, G-CSF prescription – developed to prevent the recurrence of a neutropenic event (NE), subsequently to a previous episode in patients with solid tumors, and to evaluate their respective efficacy (primary endpoint). Secondary objectives were to assess the recurrence rate of NE and identify factors predictive of recurrence.

Patients and Methods

Study design and patient selection. The study was conducted between February 2010 and June 2011 among 62 cancer centers in France, treating patients with all types of solid tumors. The study was conducted in accordance with the principles of the Declaration of Helsinki and the international directives (ICH3) for non-interventional studies. No ethical approval was required by the French authorities at the time of initiation of the study as the study was a non-interventional one.

To be eligible, patients with solid tumours had to be aged ≥18 years old (no upper limit of age), and experience an NE during a previous cycle (reference cycle A) of chemotherapy without G-CSF support, which required cycle delay and/or dose reduction and/or prescription of prophylactic G-CSF in the subsequent cycle of the same chemotherapy. Patients with hematological malignancies, those who received concomitant radiotherapy or were participating in a clinical trial were not eligible. Chemotherapy was administered as per physician decision and according to institution practice. Prophylactic G-CSF was given as per standard practice and the summary of product characteristics. No additional procedures were required during the study period. Patients were followed up to four consecutive cycles (cycles B to E).

Demographics (age, gender), cancer history (tumor type, previous treatments for cancer), chemotherapy regimen (type, number of previous lines, number of cycles received), physical examination (WHO *PS*, height, weight), hepatic and renal tests, presence of significant co-morbidities (concomitant wound, active infection, or recent surgery) were collected at study entry. NE (type, severity, duration) and its impact on the subsequent cycle (cycle delay, dose reduction, or use of prophylactic G-CSF) with type, modalities of prescription, duration and number of administrations by cycle, were recorded at each cycle.

Statistical methods. The sample size was calculated to include a total of 600 patients to detect significance with an α error of 5% and a statistical power of 80%, of i) an effect of G-CSF in reducing by 50% the risk of occurrence of a second NE following a first episode, assuming use of G-CSF in 20% or more patients and an NE recurrence rate of 50%, and ii) any risk factor that would increase or reduce the recurrence rate of a NE by 2, if the frequency of this factor is >5% in the analyzed population.

NE was defined as any episode of FN (*i.e.* single temperature ≥38.3˚C orally or ≥38.0˚C over one hour and neutrophils <500/mm^3 or <1000//mm^3 or decline of neutrophils to ≤500/mm^3 over the next 48 h), or any episode of neutropenia with a significant impact on the next cycle of chemotherapies by cycle delay, dose reduction or prescription of G-CSF.

Prophylactic strategies were defined as any of the following measures developed subsequently to the first NE: cycle delay and/or dose reduction and/or prescription of prophylactic G-CSF, and stratified in two categories according to G-CSF prescription or not: the first category was defined as any prophylactic strategy with G-CSF (*i.e.* prophylactic G-CSF alone or prophylactic G-CSF with cycle delay and/or dose reduction), and the second as any prophylactic strategy without G-CSF (*i.e.* cycle delay, or dose reduction, or cycle delay and dose reduction).

Descriptive statistics were used for patient demographics, disease characteristics and prophylactic strategies (mean and standard deviations for the continuous data, frequency and percentages for categorical data).

Univariate analyses using a log-rank test were first carried out to establish the existence or absence of a link between predictive variables and NE. Predictive variables that were studied in the model included prophylactic strategies as defined above and risk factors defined by the National Comprehensive Cancer Network (NCCN) guidelines (6): age (years and classes: <65 years, ≥65 years), BMI (<18.5, 18.5-30, ≥30), prior chemotherapy (none/metastatic disease/other), prior radiotherapy (yes/no), primary tumor type (all localization yes/no), disease extent (loco regional/metastatic), prior episode of FN during previous line of chemotherapy, concomitant infection, open wound, prior history of surgery (within 3 months prior to study entry), WHO PS (0/1/2 or more), renal dysfunction (creatinine clearance <30 ml/min, 30-60, >60 ml/min), hepatic dysfunction [total bilirubin >1.5 × upper limit of normal (ULN) and/or Alanine transaminase (ALT)>2 × ULN; yes/no].

Only variables with a statistical *p*-value <0.20 were introduced into the Cox regression model (PHREG procedure using SAS® Software, SAS Institute, Cary, NC, USA) for the multivariate analysis. Hazard ratios (HRs) per factor and their two-tailed 95% (CI), and *p*-values were calculated.The analyses were performed on NE, as the number of patients with FN and neutropenic fever was too small in the subsequent cycles to perform the analysis by type of event.

Results

Patient and disease characteristics at study entry. A total of 548 eligible and evaluable patients were included in the analysis. Patients and disease characteristics are shown in Table I. The median age was 63 (SD: 12.3) years (range 18 to 92 years), of whom 43.6% were aged ≥65 years old. Primary tumor type was mainly breast cancer (40.0%). More

than half of the patients (53.3%) were treated for metastatic disease, as first line for 59.9%. One hundred and three patients (18.8%) had undergone previous radiotherapy and 53.1% had history of surgery within three months prior to study entry. The majority of patients (88.3%) had a good *PS* (0 or 1). No clinically significant co-morbidities were present; only 10.8% of the patients presented an active infection and 1.8% had a skin injury (open wound). A total of 45 (8.2%) patients had abnormal hepatic tests. Mean (± SD) serum creatinine clearance was 82.6±29.8 ml/min (Cockcroft formula).

Chemotherapy regimens and neutropenic events during the first cycle (cycle A). Chemotherapy consisted mainly of 5-fluorouracil-epirubicin and cyclophosphamide (FEC100) (9.5%), paclitaxel/carboplatin (7.1%) and 5-fluorouracil, leucovorin and oxaliplatin (FOLFOX)/capecitabine (6.9%). The median duration of cycle A was 21 days (range 7 to 68 days). During cycle A, 88 (16.1%) patients experienced FN, 42 (7.7%) neutropenic fever, and 418 (76.3%) neutropenia (all grades) without fever, of grade 3-4 was observed in 264 (63.2%) patients. Cycle B was delayed in 244 (44.5%) patients and chemotherapy dose was reduced in 122 (22.3%) patients. Prophylactic G-CSF was given to 466 (85.0%) patients, of whom 278 (59.7%) received pegfilgrastim, 127 (27.3%) lenograstim, 48 (10.3%) filgrastim, and 10 (2.1%) a biosimilar.

Incidence of NE and prophylactic strategies in the subsequent cycles (cycles B through E). A total of 344 (62.7%) patients completed four cycles of chemotherapy. Table II summarizes cycle duration, incidence of NE and prophylactic strategies by cycle. The proportion of patients who experienced a NE recurrence, including FN, was low across all cycles. The incidence of cycle delay and chemotherapy dose reduction decreased with further cycles of chemotherapy. Median number of G-CSF administrations in the subsequent cycles, excluding pegfilgrastim (administered as a single dose) was 5 (range 1 to 10). A small proportion of patients received prophylactic antibiotics; 6 patients in cycle B, 4 in cycle C, 2 in cycle D and none in cycle E. Ten patients required hospitalization following an episode of FN or neutropenic fever. Nine deaths were reported, none of them were related to NE.

Factors predictive of recurrence of NE in the subsequent cycles. As shown in Table III, the univariate analysis identified four co-variates that were potentially associated with a greater rate of NE recurrence: prior episode of FN, primary tumor type (lung and colorectal), metastatic disease and prior radiotherapy, while breast cancer and prophylactic strategy with G-CSF were associated with a lower NE incidence. In the multivariate analysis, only prophylactic strategy with G-CSF was found to be statistically associated with a lower recurrence rate of NE (HR=0.32, 95% CI: 0.24-0.43; $p<0.001$) (Figure 1). The proportion of patients who experienced a NE was 29.0% when receiving G-CSF *versus* 68.0% for patients who did not. Mean (±SD) time to NE recurrence was 102.1 (1.9) days in G-CSF treated-patients, compared to 62.3 (3.0) days in the other group. Furthermore,

Table I. *Patient and disease characteristics at study entry.*

Patient characteristics	N=548
Gender (n; %)	
Male	170 (31.0)
Female	378 (69.0)
Age (years)	
Mean (±SD)	61.7±12.3
Median (range)	63 (18-92)
≥65 (n; %)	239 (43.6)
Median BMI (kg/m^2) (range)	24 (15-41)
BMI by class (n; %)	
<18.5	24 (4.4)
18.5-30	459 (83.8)
≥30	62 (11.3)
Missing data	3 (0.5)
Performance status (n ;%)	
0	235 (42.9)
1	249 (45.4)
2	52 (9.5)
3	3 (0.5)
Missing data	9 (1.6)
Primary tumor type (n; %)	
Breast	219 (40.0)
Colorectal	86 (15.7)
Lung	65 (11.9)
Ovarian	54 (9.9)
Other[a]	124 (22.6)
Chemotherapy setting at inclusion (n, %)	
Neo-adjuvant	56 (10.2)
Adjuvant	200 (36.5)
Metastatic	292 (53.3)
Main chemotherapy regimens (n; %) (frequency ≥4%)	
FEC100	52 (9.5)
Paclitaxel + carboplatin	39 (7.1)
FOLFOX/capecitabine	38 (6.9)
Docetaxel at 100 mg/m^2	22 (4.0)
Other*	397 (72.5)

[a]Cervix, stomach, prostate, pancreas, and other. FEC100: 5-fluorouracil at 500-600 mg/m^2, epirubicin at 100 mg/m^2 and cyclophosphamide at 600 mg/m^2; FOLFOX: 5-fluorouracil, leucovorin and oxaliplatin. *other: Adriamycin-cyclophosphamide; Adriamycin-cyclophosphamide, paclitaxel; Caelyx; docetaxel at 75 mg/m^2; docetaxel at 100 mg/m^2; doxorubicin-docetaxel; epirubicin-cyclophosphamide; capecitabine-oxaliplatin; etoposide-cisplatin; 5-fluorouracil-leucovorin-irinotecan; 5-fluorouracil-leucovorin; gemcitabine-cisplatin; vironelbine; paclitaxel; paclitaxel-bevacizumab; taxotere-cyclophosphamide; taxotere- carboplatin-herceptin; taxotere-adriamycin-cyclophosphamide; bleomycin-etoposide-cisplatin; topotecan; other.

Table II. *Incidence of neutropenic events and its impact on the prophylactic strategies by cycle (N=548, all cycles).*

	Cycle				
	A (No prophylactic G-CSF) N=548	B (Initiation of G-CSF) N=548	C N=548	D N=442	E N=344
Cycle Duration (days)					
Mean (±SD)	24.2±7.5	20.3±4.7	20.2±4.7	19.7±5.0	19.6±5.1
Median (range)	21 (7-68)	21 (7-35)	21 (7-42)	21 (5; 37)	21 (7; 37)
Neutropenic events (NE) by cycle					
Number of patients with at least one NE N (%)	548 (100)	116 (21.2)	102 (18.6)	51 (11.5)	48 (12.9)
Febrile neutropenia N (%)	88 (16.1)	3 (0.5)	4 (0.7)	0	1 (0.3)
Median duration (days) (range)	-	8 (1-10)	10 (4-13)	-	4 (4-4)
Neutropenic fever N (%)	42 (7.7)	2 (0.4)	4 (0.7)	1 (0.2)	0
Median duration (days) (range)	-	5(4-6)	3(1-23)	5(5-5)	-
Median worst grade (range)	3 (1-3)	2 (1-3)	3 (3-3)	3 (3-3)	-
Neutropenia without fever (N; %)	418 (76.3)	111 (20.3)	95 (17.3)	50 (11.3)	47 (13.7)
Grade 3-4 (N; %)	264 (63.2)	45 (40.5)	23 (24.2)	13 (26.0)	9 (19.2)
Prophylactic strategies* (by cycle)					
Cycle delay N (%)	-	244 (44.5)	44 (8.0)	23 (5.2)	18 (5.2)
Dose reduction N (%)	-	122 (22.3)	27 (4.9)	17 (3.8)	12 (3.5)
% of dose reduction±SD		23.7±13.3	24±13.7	19.2±10.3	24.8±4.9
Prophylactic G-CSF N (%)	-	466 (85.0)	413 (75.4)	332 (75.1)	247 (71.8)
Type of G-CSF N (%)					
Pegfilgrastim	-	278 (59.7)	253 (61.3)	211 (63.6)	152 (61.5)
Filgrastim	-	48 (10.3)	39 (9.4)	30 (9.0)	22 (8.9)
Lenograstim	-	127 (27.3)	11 (26.9)	84 (25.3)	67 (27.1)
Biosimilars	-	10 (2.1)	9 (2.2)	6 (1.8)	6 (2.4)
Number of G-CSF administrations (excluded pegfilgrastim)					
Mean (±SD)	-	4.4±1.6	4.6±1.5	4.5±1.6	4.6±1.5
Median (range)	-	5 (1-10)	5 (1-9)	5 (1-9)	5 (1-9)
Prophylactic antibiotics (N, %)		6 (1.1)	4 (0.7)	2 (0.5)	0

*Prophylactic strategies included cycle delay and/or dose reduction and/or prophylactic G-CSF.

the HR for NE recurrence was 0.23 (95% CI: 0.16-0.32; $p<0.001$) in the group of patients who received pegfilgratim and 0.49 (95% CI: 0.35-0.69); $p<0.001$) for those receiving G-CSF daily, compared to no G-CSF support (Figure 2).

Discussion

We designed this study to describe the prophylactic strategies developed to prevent NE recurrence following a first episode in a cohort of patients treated for solid tumors and to identify factors predictive of recurrence. From a clinical point of view, the choice of NE as the main criteria in this study makes sense as not only FN, but also chemotherapy delay and/or dose-reduction can have a deleterious impact on a patient's quality of life, efficacy of chemotherapy and the hospital organization.

Out of the 548 patients who experienced a NE during the first cycle without G-CSF support, 88 (16.1%) experienced FN, 42 (7.7%) a neutropenic fever and 418 (76.3) neutropenia (any grade) without fever. These events resulted in delay of

Table III. *Factors with p-value <0.20 in the univariate analysis assessing recurrence of neutropenic events, by log-rank test (N=548; all cycles).*

Variables	Modality	Neutropenic events N (%)	No neutropenic events N (%)	Mean time from the first event (SD)	Log-rank *p*-Value
Primary tumor type					
Lung cancer	No	167 (34.6)	315 (65.4)	97.2 (1.9)	0.064
	Yes	32 (49.2)	33 (50.8)	85.6 (4.8)	
Breast cancer	No	138 (41.9)	191 (58.1)	91.9 (2.4)	0.003
	Yes	61 (28.0)	157 (72.0)	84.6 (1.9)	
Colorectal cancer	No	159 (34.5)	302 (65.5)	98.0 (1.9)	0.009
	Yes	40 (46.5)	46 (53.5)	72.8 (3.6)	
Disease extent	Metastatic	118 (40.5)	173 (59.5)	93.1 (2.4)	0.078
	Other	81 (31.6)	175 (68.4)	89.7 (2.1)	
Prior radiotherapy	No	155 (35.0)	288 (65.0)	97.5 (2.0)	0.125
	Yes	43 (41.7)	60 (58.3)	75.8 (3.2)	
Prior episode of	No	156 (34.7)	293 (65.3)	97.3 (2.0)	0.174
febrile neutropenia*	Yes	42 (43.3)	55 (56.7)	87.5 (4.1)	
Treatment measure	With G-CSF	132 (29.5)	316 (70.5)	102.1 (1.9)	<0.001
	Without G-CSF	67 (67.7)	32 (32.3)	62.3 (3.0)	

*In a previous line of chemotherapy.

chemotherapy in 44.5% of the patients, dose reduction in 22.3% of the patients and use of secondary G-CSF prophylaxis in 85.0% of the patients in the subsequent cycle (cycle B). Of note, 40% of the study cohort had breast cancer, and almost half (46.7%) of them were treated with a curative intent.

The recurrence of an NE, including FN, was low across all subsequent cycles. The proportion of patients having experienced at least one NE decreased with further cycles of chemotherapy. Similarly, FN rates decreased dramatically from 16.1% in cycle A to 0.3% in cycle E. Importantly the rate of iterative cycle delay and dose reduction decreased significantly in all cycles, while approximately two-thirds of the patients continued to receive prophylactic G-CSF in the subsequent cycles. These results suggest that secondary G-CSF prophylaxis is common practice for patients with solid tumors, both to prevent recurrence of FN, and to maintain chemotherapy dose-intensity. In a recent survey conducted by Falandry *et al*. between 2006 and 2007 (15), after the publication of the international recommendations update in 2006 on the use of G-CSF on a large cohort of 990 patients with solid tumor (15), 44.4% of G-CSF prescriptions were given as secondary prophylaxis. Moreover, in patients with breast cancer, 38% of G-CSF prescriptions were given in a metastatic setting and as third-line for 18.9% of them.

As an exploratory analysis, we used risk factors that are validated for FN in the primary prophylaxis setting to identify factors predictive of recurrence, to which we added the prophylactic strategies (taking into account the use or not of G-CSF). In our study, advanced age was not found to be a factor predictive of NE recurrence. This may be explained by the widespread use of prophylactic G-CSF in our cohort of patients, including the elderly patients. This may suggest that use of prophylactic G-CSF may have protected them from developing subsequent NE. The efficacy of G-CSF in elderly patients in primary prophylaxis was demonstrated in a phase III study by Balducci *et al*. (16). Only a prophylactic approach that included G-CSF was found to be an independent predictor of lower recurrence rate of NE (HR: 0.32, 95% CI: 0.24-0.43; $p<0.001$) in the multivariate analysis. Patients who received secondary prophylactic G-CSF, had three-fold lower risk of NE recurrence compared to patients who did not. The mean (±SD) time for recurrence from the first event was longer (102.1±1.9 days) in G-CSF-treated patients, compared to 62.3±3.0 days in the group of patients who did not receive prophylactic G-CSF. Moreover, pegfilgrastim seemed to offer the highest protection, (HR=0.23, 95% CI: 0.16-0.32; $p<0.001$). There is now a growing body of evidence suggesting that pegfilgrastim, a pegylated formulation of filgrastim is more effective than filgrastim or other daily G-CSF, in the primary prophylaxis setting (17, 18).

In conclusion, our study shows that secondary G-CSF prophylaxis has significant efficacy in reducing the incidence of chemotherapy-induced NE, and should be considered as a valuable option for an optimal delivery of standard chemotherapy in patients with solid tumors. Further clinical trials are needed to confirm our results.

Disclosure

GF is a consultant for Amgen; all remaining Authors have declared no conflicts of interest. The Authors have full control of all primary data and agree to allow the journal to review the data if requested. This work was in part supported by Amgen France SAS.

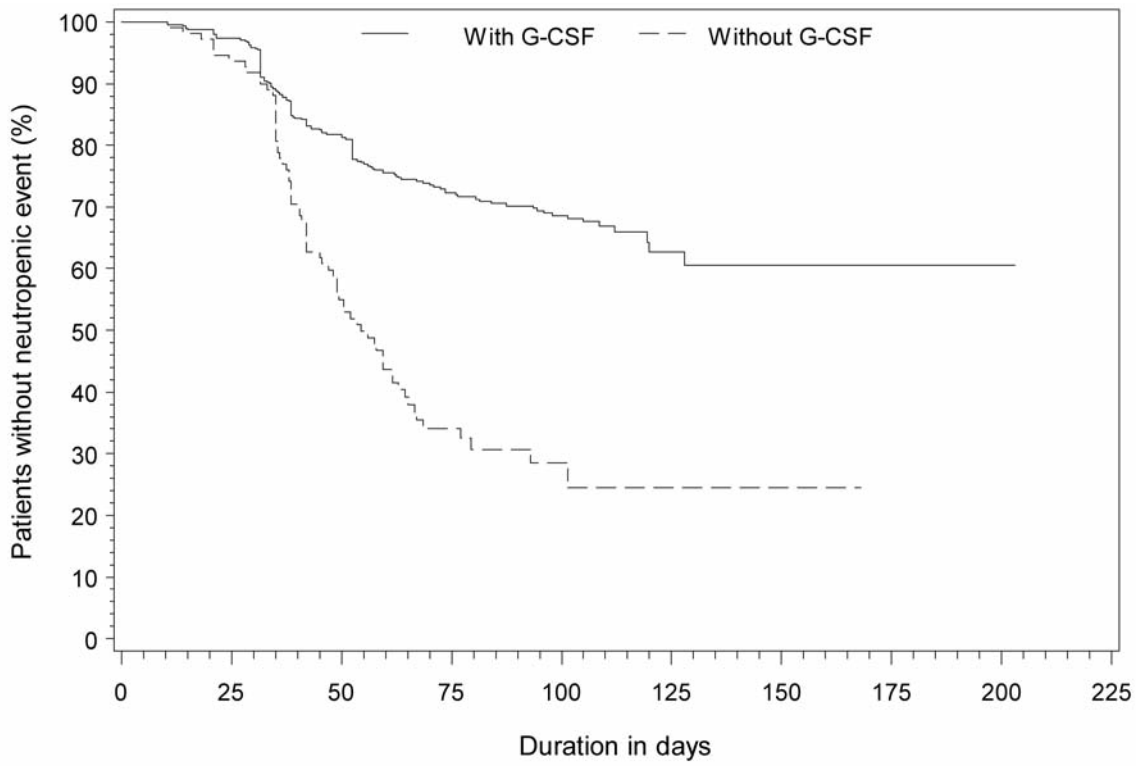

Figure 1. *Incidence of neutropenic events in the subsequent cycles according to the prophylactic strategy with or without Granocyte Colony Stimulating Factor (G-CSF) by the Kaplan-Meier curve for the time to recurrence of neutropenic event (N=548; all cycles).*

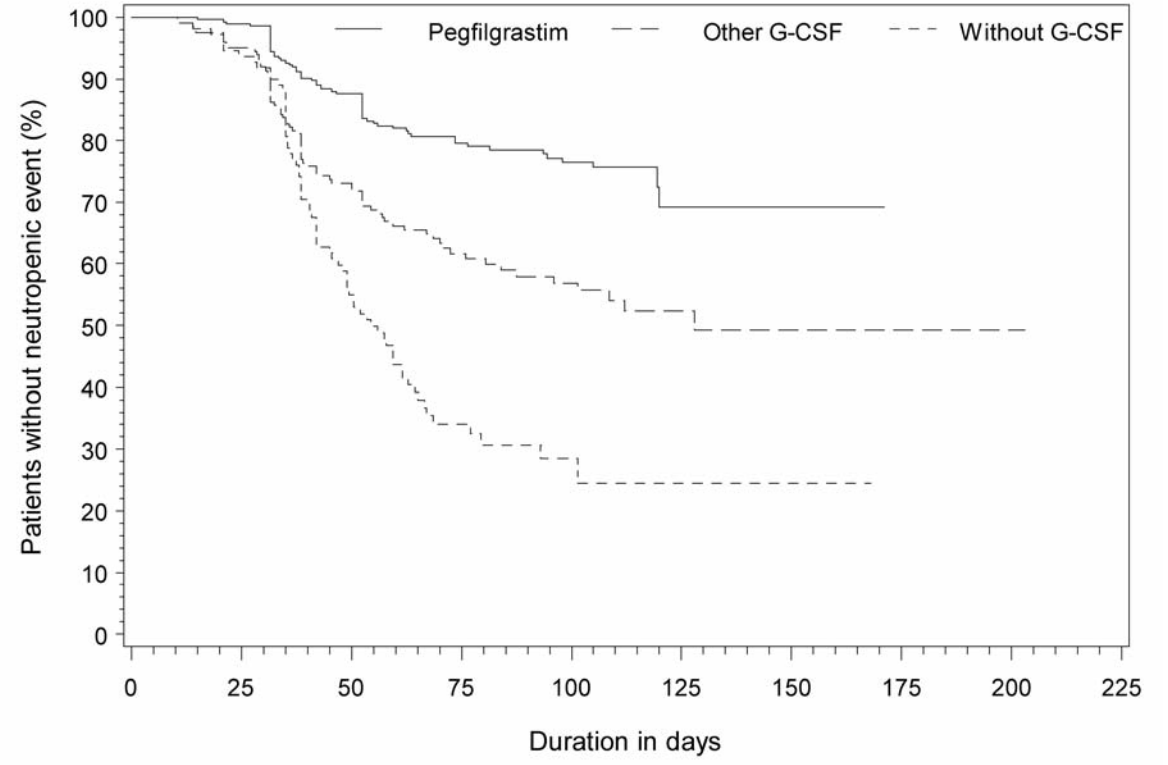

Figure 2. *Incidence of neutropenic events in the subsequent cycles according to the type of G-CSF by the Kaplan-Meier curve for the time-to-recurrence of neutropenic events (N=548; all cycles).*

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References

1 Kuderer NM, Dale DC, Crawford J, Coster LE and Lyman GH: Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. Cancer *106*: 2258-2266, 2006.

2 Courteney DM, Aldeen AZ, Gorman SM, Handler JA, Trifilio SM, Parada JP, Yarnold PR and Bennett CL: Cancer-associated neutropenic fever: Clinical outcome and economic costs of emergency department care. Oncologist *12*: 1019-1026, 2007.

3 Elting LS, Lu C, Escalante CP, Giordano SH, Trent JC, Cooksley C, Avritscher EB.C, Shih YT, Ensor J, Bekele BN, Gralla RJ, Talcott JA and Rolston K: Outcomes and cost of outpatient or inpatient management of 712 patients with febrile neutropenia. J Clin Oncol *26*: 606-611, 2008.

4 Chabner BA: Antimitotic drugs. Cancer Chemother Biol Response Modif *14*: 55-56, 1993.

5 Aapro MS, Cameron DA, Pettengell R, Bohlius J, Crawford J, Ellis M, Kearney N, Lyman GH, Tjan-Heijnen VC, Walewski J, Weber DC, Zielinski C; European Organisation for Research and Treatment of Cancer (EORTC) Granulocyte Colony-Stimulating Factor (G-CSF) Guidelines Working Party: EORTC guidelines for the use of granulocyte-colony stimulating factors to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphomas and solid tumours. Eur J Cancer *42*: 2433-2453, 2006.

6 National Comprehensive Cancer Network: Practice Guidelines in Oncology V1.2012. Myeloid Growth Factors. Available at: http://www.nccn.or/professionals/physician_gls/PDF/myeloid_growth.pdf. Last accessed October 20, 2012.

7 Crawford J, Ozer H, Stoller R, Johnson D, Lyman G, Tabbara I, Kris M, Grons J, Picozzi V, Rausch G, Smith R, Gradishar W, Yahanda A, Vincent M, Stewart M and Glaspy J: Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small cell lung cancer. N Engl J Med *325*: 164-170, 1991.

8 Dale D: Current management of chemotherapy-induced neutropenia: The role of colony-stimulating factors. Semin Oncol *30*: 3-9, 2003.

9 Lyman GH, Dale DC, Wolff DA, Culakova E, Poniewierski MS, Kuderer NM and Crawford J: Acute myeloid leukemia or myelodysplasic syndrome in randomized clinical trials of cancer chemotherapy with granocyte colony-stimulating factor: a systemic review. J Clin Oncol *28*: 2914-2924, 2010.

10 Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, Bennett CL, Cantor SB, Crawford JC, Cross SJ, Demetri G, Desch CE, Pizzo PA, Schiffer A, Schwartzberg L, Somerfield MR, Somlo G, Wade JC, Wade JL, Winn RJ, Wozniak AJ and Wolff AC: 2006 Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guidelines. J Clin Oncol *24*: 3187-3205, 2006.

11 Aapro M, Crawford J and Kamioner D: Prophylaxis of chemotherapy-induced febrile neutropenia with granulocyte colony stimulating factors: Where are we now? Support Care Cancer *18*: 529-541, 2010.

12 Bosly A, Bron D, Van Hoof A, De Bock R, Berneman Z, Ferrant A, Kaufman L, Dauwe M and Verhoef G: Achievement of optimal average relative dose intensity and correlation with survival in diffuse large B-cell lymphoma patients treated with CHOP. Ann Hematol *87*: 277-283, 2008.

13 Chirivella I, Bermejo B, Insa A, Pérez-Fidalgo A, Magro A, Rosello S, Garcia-Garre E, Martin P, Bosch A and Lluch A: Optimal delivery of anthracycline-based chemotherapy in the adjuvant setting improves outcome of breast cancer patients. Breast Cancer Res Treat *114*: 479-484, 2009

14 Pettengell R, Schwenkglenks M and Bosly A: Association of reduced relative dose intensity and survival in lymphoma patients receiving CHOP-21 chemotherapy. Ann Hematol *87*: 429-430, 2008.

15 Falandry C, Campone M, Cartron G, Guerin D and Freyer G: Trends in G-CSF use in 990 patients after EORTC and ASCO guidelines. Eur J Cancer *46*: 2389-2398, 2010.

16 Balducci L, Al-Halawani H, Charu V, Tam J, Shalin S, Dreiling L and Ershler WB: Elderly cancer patients receiving chemotherapy benefit from first-cycle pegfilgrastim. Oncologist *12*: 1416-1424, 2007.

17 Kuderer NM, Dale DC, Crawford J and Lyman GH: Impact of primary prophylaxis with granulocyte colony stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: A systemic review. J Clin Oncol *25*: 3158-3167, 2007.

18 Pinto L, Liu Z, Doan Q, Bernal M, Dubois R and Lyman G: Comparison of pegfilgrastim with filgrastim on febrile neutropenia, grade IV neutropenia and bone pain: A meta-analysis of randomized controlled trials. Curr Med Res Opin *23*: 2283-2295, 2007.

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