available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Febrile neutropenia and related complications in breast cancer patients receiving pegfilgrastim primary prophylaxis versus current practice neutropaenia management: Results from an integrated analysis ☆

G. von Minckwitz[a,*], M. Schwenkglenks[b], T. Skacel[c], G.H. Lyman[d], A. Lopez Pousa[e], P. Bacon[c], V. Easton[f], M.S. Aapro[g]

[a]German Breast Group, c/o GBG Forschungs GmbH, University of Frankfurt, Frankfurt, Schleussner Str. 42, 63263 Neu-Isenburg, Germany
[b]European Center of Pharmaceutical Medicine, University of Basel, Basel, Switzerland
[c]Medical affairs, Amgen (Europe) GmbH, Zug, Switzerland
[d]Division of Medical Oncology, Duke University Medical Center, Durham, NC, USA
[e]Department of Medical Oncology, Hospital Sant Pau, Barcelona, Spain
[f]Biostatistics, Amgen Ltd., Cambridge, UK
[g]Institut Multidisciplinaire d'Oncologie, Genolier, Switzerland

ARTICLE INFO

Article history:
Received 17 June 2008
Received in revised form
24 October 2008
Accepted 17 November 2008
Available online 26 December 2008

Keywords:
Breast neoplasms
Drug therapy
Granulocyte colony-stimulating factor
Neutropaenia/chemically induced
Pegfilgrastim
Human
Primary prevention
Taxane

ABSTRACT

Granulocyte colony-stimulating factors (G-CSFs) reduce febrile neutropaenia (FN) incidence but may be used inconsistently in current practice (CP). This study compared the efficacy of pegfilgrastim primary prophylaxis (PPP) with CP neutropaenia management in breast cancer. Individual patient data (N = 2282) from 11 clinical trials and observational studies using chemotherapy regimens with ⩾15% FN risk and PPP (6 mg, all cycles) or CP (no G-CSF or any cycle G-CSF/pegfilgrastim) were included in an integrated analysis. Most patients received docetaxel-containing regimens. A generalised linear mixed model was fitted (N = 2210). Neutropaenia prophylaxis (PPP versus CP), age and disease stage influenced the incidence of FN. Overall, FN was less frequent with PPP than with CP (odds ratio [OR]: 0.124; 95% confidence interval [CI]: 0.08, 0.194; $P < 0.0001$). Odds for cycle 1 FN, dose reductions ⩾ 15% and FN-related hospitalisation were also significantly lower with PPP. These data support PPP in breast cancer patients receiving chemotherapy with moderately high/high FN risk.

© 2008 Elsevier Ltd. All rights reserved.

1. Introduction

The evolution of more efficacious chemotherapeutic regimens for breast cancer has in some cases, e.g. taxane-containing regimens, been accompanied by an increased risk of clinically significant myelosuppression and febrile neutropaenia (FN). Despite treatment with broad-spectrum anti-infective agents, FN is still associated

☆ This study was supported by Amgen (Europe) GmbH.
* *Corresponding author:* Tel.: +49 69 6102 798740; fax: +49 69 6102 7987440.
E-mail address: Minckwitz@germanbreastgroup.de (G. von Minckwitz).
0959-8049/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2008.11.021

with relatively high rates of in-hospital mortality (up to 10%).[1]

FN may lead to chemotherapy dose delays or dose reductions in subsequent cycles, resulting in reduced relative dose intensity (RDI). In a study by Bonadonna and colleagues, fewer patients who received <85% of the optimal dose of adjuvant cyclophosphamide, methotrexate and fluorouracil (CMF) were alive at 20 years' follow-up compared with those who received ⩾85% of the optimal dose (29% versus 52%, respectively).[2] Furthermore, in a more recent study of breast cancer patients receiving anthracycline-containing adjuvant chemotherapy, the multivariate adjusted hazard ratio for disease-free survival at 10 years was 0.64 (95% confidence interval [CI]: 0.43, 0.96) for patients receiving ⩾85% versus <85% RDI.[3] While RDI achieved may in part be a reflection of other factors such as age and co-morbidity, these data suggest that failure to receive planned dose contributes to poorer survival. In metastatic disease, ensuring optimal RDI may be less critical, but is a consideration when prolonging life is the aim of treatment.[4,5]

Prophylactic granulocyte colony-stimulating factors (G-CSFs) reduce the incidence of FN and shorten the duration of neutropaenia.[6,7] Standard G-CSFs, such as filgrastim, require daily administration. In contrast, pegfilgrastim[8,9] has neutrophil-regulated pharmacokinetics; it is therefore active only while neutrophil count is low and can be administered once per cycle.[10] By aiding neutrophil recovery, G-CSF prophylaxis may facilitate delivery of planned chemotherapy.

FN frequently occurs in the first cycle of chemotherapy,[11] suggesting a benefit from primary G-CSF prophylaxis in high-risk patients. However, evidence suggests that current practice use of G-CSFs does not adequately protect patients from FN. G-CSFs are often given for relatively short courses and not from the first cycle.[12,13] The purpose of this integrated analysis of individual patient data from breast cancer studies was to compare pegfilgrastim primary prophylaxis (PPP) with current practice (CP) neutropaenia management for prevention of FN and related events.

2. Patients and methods

2.1. Study identification

We conducted a Medline literature search (August 2005) to identify common breast cancer chemotherapy regimens associated with FN risk ⩾15%. No date limits were used, but publications were limited to human data and English language. Search terms included taxoids, (pegylated)doxorubicin, Adriamycin, epirubicin, docetaxel, paclitaxel, cyclophosphamide, methotrexate and fluorouracil. These terms were then combined with the terms febrile neutropaenia, neutropaenia, leucopaenia and infection. The search produced 513 relevant articles and was supplemented by a review of data from a retrospective study of cancer care in Europe.[14]

Through manual scanning of the search results, we identified the following chemotherapy regimens as conferring FN risk ⩾ 15%:

- AT or ET: doxorubicin 50–60 mg/m^2 (A) or epirubicin 75–100 mg/m^2 (E) + paclitaxel 175–250 mg/m^2 (T).
- ADoc or EDoc: A(E) + docetaxel 75–100 mg/m^2 (Doc).
- DocAC or DocEC: DocA(E) + cyclophosphamide (C).
- Doc monotherapy 100 mg/m^2.
- AC-Doc or EC-Doc.
- A(E) + carboplatin (Cb) AUC 4–6.
- Gemcitabine 750–1200 mg/m^2 + A 30–60 mg/m^2 (E 50–150 mg/m^2) + T.
- Vinorelbine 20–35 mg/m^2 + Cb.

Vinorelbine + Cb and A(E) + Cb are not in common use, therefore they were not included in the next stage of the analysis. Completed breast cancer studies involving the use of the other regimens (from cycle 1) were eligible for the present analysis if

(i) They were phase II–IV interventional clinical trials performed in accordance with good clinical practice or well-designed prospective observational/retrospective studies.
(ii) They included supportive care with protocol-driven pegfilgrastim (Neulasta®, Amgen, Thousand Oaks, CA, USA) primary prophylaxis from cycle 1 (PPP group) or CP neutropaenia management, which was conservatively defined as any currently used approach including no G-CSF, daily G-CSF (filgrastim or lenograstim) in any cycle or pegfilgrastim in any cycle.

A total of 19 eligible studies were identified from the original literature review and supplementary searches of the clinical trial database at Amgen (including investigator-led studies funded [in part] by Amgen) and abstracts from the American Society of Clinical Oncology annual meeting (2000–2005). The key consideration for final inclusion in the analysis was timely access to individual patient data (by February 2006), which had to include FN. Accordingly, eight randomised clinical trials, two prospective observational trials and one retrospective trial were included in the integrated analysis (Table 1).[8,9,11,15–22] Data from specific arms of these studies were included in the analysis depending on whether they met the criteria for PPP or CP. Patients receiving 2-weekly treatment cycles were excluded.

2.2. Outcome measures

The primary outcome measure was the proportion of patients with FN across all cycles. FN was defined as in the individual studies (see Table 1). Secondary outcome measures included the proportion of patients with FN in cycle 1, hospitalisation due to FN, the incidence of chemotherapy dose delays (>3 days) and dose reductions (⩾15%), and grades 3–4 haematological toxicities.

2.3. Integrated analysis and statistical modelling

We carried out an integrated analysis of the individual patient data. Descriptive summaries of demographic and disease characteristics for included patients were prepared by study

Table 1 – Studies and patients eligible for the integrated analysis.

Study	ID	Study type (and, where applicable, patients randomised [N])	Regimen	Disease stage	Pegfilgrastim primary prophylaxis (PPP)	Current practice neutropaenia management (CP)
Included studies and patients						
Vogel et al.[11*]	Med	RCT (PPP [N = 463] versus placebo [N = 465])	Doc	I–IV	N = 462 PPP arm (FN: 6 [1%])	N = 465 placebo arm (secondary prophylaxis pegfilgrastim) (FN: 78 [17%])
Holmes et al.[8*]	Med	RCT (PPP [N = 154] versus PP filgrastim)	ADoc	II–IV	N = 150 PPP arm (FN: 14 [9%])	
Holmes et al.[20*]	Med	RCT (PPP [N = 108[versus PP filgrastim)	ADoc	II–IV	N = 108 PPP arm (FN: 15 [14%])	
Green et al.[9*]	Med	RCT (PPP [N = 78] versus PP filgrastim)	ADoc	II–IV	N = 77 PPP arm (FN: 10 [13%])	
Kaufman et al.[21*]	Db	RCT (PPP [N = 45] day 0 versus day 1)	Various	II–IV	N = 43 PPP Day 1 arm (FN: 5 [12%])	
Balducci et al.[17†]	Db	RCT (PPP [N = 8] versus post cycle 1)	Various	I–IV	N = 7 PPP arm (FN: 1 [14%])	
Ozer et al.[22*]	Db	Prospective open-label (PPP N = 89)	Various	I–IV	N = 89 PPP. Single arm trial (FN: 5 [6%])	
Von Minckwitz et al., 2008[15‡¶]	As	Cohorts from RCT (PPP N = 624; PP ciprofloxacin N = 248)	DocAC	I–III	N = 367 PPP or PPP + ciprofloxacin (FN: 13 [4%])	N = 248 primary prophylaxis ciprofloxacin. G-CSF not precluded (FN: 54 [22%])
Lopez Pousa et al.[16†]	Db	Prospective observational	Various	I–IV		N = 72 any/no G-CSF (FN: 9 [13%])
Pettengell et al.[19§]	Db	Prospective observational	Various	I–III		N = 50 any/no G-CSF (FN: 4 [8%])
Morrison et al.[18†]	Db	Retrospective	Various	I–IV		N = 144 any/no G-CSF (FN: 16 [11%])
Studies excluded by lack of access to individual patient data						
Nabholtz et al. J Clin Oncol 2001	Med	Single arm with G-CSF support	DocAC	IV		Secondary prophylaxis
Nabholtz et al. J Clin Oncol 2003	Med	RCT with G-CSF support	ADoc	IV		Secondary prophylaxis
Alba et al. J Clin Oncol 2004	Med	RCT with G-CSF support	ADoc	IV		Secondary prophylaxis
O'Shaughnessy et al. J Clin Oncol 2002	Med	RCT with G-CSF support	Doc	IV		Therapeutic G-CSF use
Biganzoli et al. J Clin Oncol 2002	Med	RCT with G-CSF support	AT	IV		Unspecified G-CSF
Jassem et al. J Clin Oncol 2001	Med	RCT with G-CSF support	AT	IV		Unspecified G-CSF
Zielinski et al. ASCO 2003. #26	As	RCT with G-CSF support	GET	IV		Unspecificed G-CSF
Martin et al. ASCO 2005. #604	As	RCT with G-CSF support	DocAC	I–III		G-CSF prophylaxis

A, doxorubicin; Doc, docetaxel; C, cyclophosphamide; G, gemcitabine; G-CSF, granulocyte colony-stimulating factor; RCT, randomised clinical trial.
ID, identified by; As, ASCO abstract; Db, database of studies with Amgen funding; Med, Medline search.
In these studies, febrile neutropaenia was defined as: *absolute neutrophils count (ANC) $< 0.5 \times 10^9$/L and temperature $\geqslant$ 38.2 °C; †ANC $< 1.0 \times 10^9$/L and temperature $\geqslant$ 38.0 °C; ‡ANC $< 1.0 \times 10^9$/L and three oral temperature measurements > 38.0 °C or a single measurement > 38.5 °C; §ANC $< 0.5 \times 10^9$/L and temperature $\geqslant$ 38.0 °C. The individual study FN rates were calculated as part of this analysis. ¶In the study by Von Minckwitz, pegfilgrastim/G-CSF was not the study article. These agents were specified as supportive care in the protocol. Patients who should have received pegfilgrastim from cycle 1 but did not, were excluded from this analysis.

and for the integrated populations within each treatment group (PPP versus CP). By cycle, G-CSF use was characterised in terms of type of G-CSF administered and number of doses of daily G-CSF.

A three-step approach was taken for the comparative analysis. Firstly, the homogeneity of patient populations was assessed within the PPP and CP groups. In the second step, homogeneity between these treatment groups was assessed. Finally, a generalised linear mixed model was fitted to the primary outcome measure using SAS software (Proc Glimmix procedure). Type of neutropaenia prophylaxis (PPP or CP) was included in the modelling process as a fixed effect and the study was included as a random effect. The following baseline covariates were also assessed for significant effect on FN: age (years), disease stage (I–III versus IV) and prior chemo/radiotherapy (yes/no). Eastern Cooperative Oncology Group (ECOG) performance status was not considered as a covariate as study inclusion criteria meant that nearly all patients were categorised ECOG 0–1. Covariates of clinical importance were considered for inclusion in the model at the 25% significance level.[23]

A similar modelling process was used to determine factors affecting the incidence of FN in cycle 1. Secondary outcome measures were assumed to be FN related, therefore covariates identified as predictors of FN were automatically included in the model for each of these outcomes. Adjusted proportions for outcome measures were derived from the model using least squares means. These adjusted values predict the incidence of outcome measures in the PPP and CP groups, after allowing for the effects of those covariates identified as influencing FN.

Sensitivity analyses were performed to assess the robustness of the results for the primary outcome measure. Firstly, patients receiving G-CSF primary prophylaxis (any G-CSF given within 7 days of the last chemotherapy dose in cycle 1) were removed from the CP group. Subgroup analyses on the two largest studies and the remaining group of 'smaller' studies were also planned.

3. Results

3.1. Patient disposition

Data on 1569 PPP and 979 CP patients were available for analysis. However, 266 patients in the PPP group were excluded as they did not receive pegfilgrastim from cycle 1. A total of 2282 patients (1303 PPP and 979 CP) treated 'per protocol' were therefore included in the integrated analysis.

Most patients were planned to receive four or six cycles of chemotherapy. In all, 79% of patients received their planned number of cycles.

3.2. Baseline demographics, disease characteristics and chemotherapy regimen

The 'within group' variability of patient characteristics from the different studies was judged to be acceptable (data not shown), and data were combined into a single dataset. Baseline characteristics of the combined populations are shown in Table 2, along with the chemotherapy regimens received. Whilst slight differences were noted (e.g. use of ADoc was greater in the PPP group, and Doc monotherapy was more common in the CP group), the variability between the PPP and CP groups was low and they were considered sufficiently well balanced to allow comparison via statistical modelling.

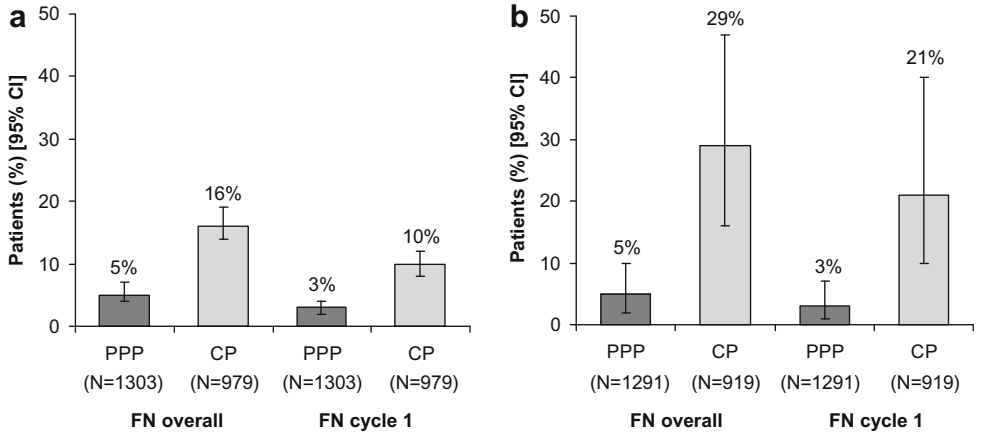
3.3. G-CSF use

In the PPP group, all patients received pegfilgrastim in cycle 1 and almost all cycles thereafter. In the CP group, 739 patients (75%) did not receive G-CSF in cycle 1, and a similar propor-

Table 2 – Patient demographics at baseline, disease characteristics and treatment.

	PPP (N = 1303)	CP (N = 979)
Age, years (mean ± SD)	51.4 ± 10.4	52.0 ± 9.9
Female, *n* (%)	1296 (99)	974 (99)
Menopausal (⩾50 years), *n* (%)	721 (55)	565 (58)
Race, n (%)		
Caucasian	684 (52)	418 (43)
Hispanic	172 (13)	151 (15)
Other	80 (6)	90 (9)
Unknown	367 (28)	320 (33)
ECOG status n (%)		
0–1	1262 (97)	832 (85)
Unknown	5 (<1)	108 (11)
Disease stage, n (%)		
Stage I	19 (1)	13 (1)
Stage II	568 (44)	355 (36)
Stage III	346 (27)	278 (28)
Stage IV	361 (28)	273 (28)
Unknown	9 (1)	60 (6)
Prior therapy, n (%)		
None	868 (67)	547 (56)
Chemotherapy	210 (16)	209 (21)
Radiotherapy	29 (2)	22 (2)
Both	154 (12)	127 (13)
Unknown	42 (3)	74 (8)
Histology, n (%)		
Adenocarcinoma	338 (26)	0 (0)
Unknown	965 (74)	979 (100)
Estrogen receptor status, n (%)		
Negative	344 (26)	220 (22)
Positive	473 (36)	264 (27)
Unknown	486 (37)	495 (51)
Study chemotherapy regimen, n (%)		
AT/ET	4 (<1)/2 (<1)	4 (<1)/2 (<1)
ADoc/EDoc	346 (27)/6 (<1)	32 (3)/32 (3)
DocAC	410 (31)	265 (27)
Doc	480 (37)	488 (50)
AC-Doc / EC-Doc	50 (4)/5 (<1)	131 (13)/23 (2)
ACb	0 (0)	2 (<1)

A, doxorubicin; C, cyclophosphamide; Cb, carboplatin; CP, current practice neutropaenia management; Doc, docetaxel; E, epirubicin; T, paclitaxel; ECOG, Eastern Cooperative Oncology Group; PPP, pegfilgrastim primary prophylaxis.
'Unknown' also used to categorise patients for whom these data were not collected.
'DocAC' sometimes referred to as 'TAC', where T indicates docetaxel.



CP, current practice neutropenia management; FN, febrile neutropenia; PPP, pegfilgrastim primary prophylaxis.

Fig. 1 – (a) Descriptive (unadjusted) and (b) adjusted proportions of patients with febrile neutropaenia (FN) over all cycles and during cycle 1. Adjusted proportions predict patients with FN after allowing for differences in study, age and disease stage.

Table 3 – Generalised, linear mixed model of factors affecting the incidence of febrile neutropaenia (FN), chemotherapy delivery parameters, FN-related hospitalisation and grades 3–4 haematological toxicity.

	Estimate	Standard error	*P* value	Odds ratio (OR) (95% confidence interval [CI])
Primary outcome measure				
Overall FN (*N* = 2210)				
Group (PPP versus CP)	–2.0853	0.2258	<0.0001	0.124 (0.08, 0.194)
Age (per additional year)	0.01956	0.007351	0.0078	1.02 (1.005, 1.035)
Stage (I–III versus IV)	–0.3370	0.1885	0.0739	0.714 (0.493, 1.033)
Secondary outcome measures				
Cycle 1 FN (*N* = 2210)				
Group (PPP versus CP)	–2.2300	0.3225	<0.0001	0.108 (0.057, 0.203)
Age (per additional year)	0.01929	0.009313	0.0384	1.019 (1.001, 1.038)
Stage (I–III versus IV)	–0.5354	0.2289	0.0194	0.585 (0.374, 0.917)
Dose reduction ⩾ 15% (*N* = 2210)				
Group (PPP versus CP)	–0.5475	0.1823	0.0027	0.578 (0.405, 0.827)
Age (per additional year)	0.01345	0.007332	0.0668	1.014 (0.999, 1.028)
Stage (I–III versus IV)	–0.5206	0.1685	0.0020	0.594 (0.427, 0.827)
Dose delay > 3 days (*N* = 2210)				
Group (PPP versus CP)	–0.05529	0.1357	0.6839	0.946 (0.725, 1.236)
Age (per additional year)	0.006841	0.005870	0.2440	1.007 (0.995, 1.019)
Stage (I–III versus IV)	–0.00170	0.1619	0.9916	0.998 (0.727, 1.371)
FN hospitalisation (*N* = 2210)				
Group (PPP versus CP)	–1.5871	0.2546	<0.0001	0.205 (0.124, 0.338)
Age (per additional year)	0.02258	0.009046	0.0126	1.023 (1.005, 1.041)
Stage (I–III versus IV)	–0.7858	0.2158	0.0003	0.456 (0.298, 0.696)
Grades 3–4[a] neutropaenia (*N* = 1983)				
Group (PPP versus CP)	–3.1797	0.1504	<0.0001	0.042 (0.031, 0.056)
Age (per additional year)	0.01687	0.006182	0.0064	1.017 (1.005, 1.029)
Stage (I–III versus IV)	0.2319	0.1575	0.1411	1.261 (0.926, 1.717)
Grades 3–4[a] leucopaenia (*N* = 2132)				
Group (PPP versus CP)	–2.8379	0.1504	<0.0001	0.059 (0.044, 0.079)
Age (per additional year)	0.02106	0.005481	0.0001	1.021 (1.01, 1.032)
Stage (I–III versus IV)	0.004360	0.1472	0.9764	1.004 (0.753, 1.341)

CP, current practice neutropaenia management; PPP, pegfilgrastim primary prophylaxis.
N = 2210 as data are missing age alone (3 patients), disease stage alone (68 patients) and age/disease stage (1 patient).
a National Cancer Institute Common Toxicity Criteria grades.

tion remained without G-CSF support by cycle 4. Of those remaining in the study at cycle 6 ($N = 374$), almost half (184 [49%]) were receiving some form of G-CSF. Among 61 CP patients for whom data on duration of daily G-CSF use were available, 30 (49%) received less than seven daily doses of G-CSF in cycle 1. Overall, daily G-CSF was most frequently administered at five to seven doses per cycle. In cycles 1–4, 11–13% of patients in the CP group received pegfilgrastim only, as did 78 (21%) of those still on study at cycle 6.

3.4. *FN outcome measures*

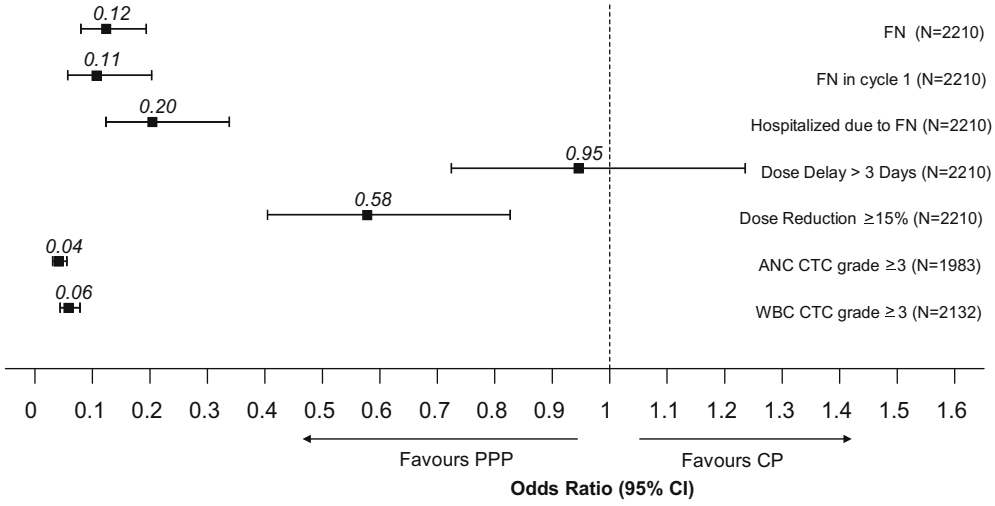
Descriptive analysis showed the incidence of overall FN to be lower in the PPP group than in the CP group (Fig. 1a). A similar difference was noted for cycle 1 FN. Of those who experienced cycle 1 FN in the PPP ($N = 34$) and CP ($N = 95$) groups and continued to cycle 2, 15% and 9% had a subsequent FN event.

In the model, type of neutropaenia prophylaxis (PPP versus CP), age and disease stage (but not prior chemo/radiotherapy) were found to influence overall FN, with increased risk of FN for older patients and for those with stage IV disease (Table 3).

With regard to type of prophylaxis, the odds for FN occurrence were statistically significantly lower in the PPP group compared with the CP group ($P < 0.0001$) (Fig. 2). Similarly, neutropaenia prophylaxis, age and disease stage were significant predictors of cycle 1 FN. On the basis of the model, the rates of FN (overall and cycle 1), after adjusting for baseline differences in study, disease stage and age, showed a greater advantage for PPP over CP (Fig. 1a and b).

To aid clinical interpretation of the model, Table 4 shows the predicted rates of overall FN according to patient age and disease stage depending on whether they were given PPP or CP support. Furthermore, an additional sensitivity analysis was performed in which chemotherapy regimen was included in the model in place of study. Here, chemotherapy regimen group was found to be a predictor of FN and relative to Doc or AC-Doc, the odds of experiencing FN were increased with DocAC (odds ratio [OR]: 2.0; 95% CI: 1.363, 2.935) and with ADoc (OR: 3.759; 95% CI: 2.370, 5.964).

When patients receiving G-CSF primary prophylaxis ($N = 161$) were excluded from the CP group, similar findings to the main analysis were observed. The odds for FN over



*Mixed model analysis with arm, age and stage as fixed effects and study as a random effect. ANC, absolute neutrophil count; CTC, common toxicity criteria; WBC, white blood cell count (leucopenia).

Fig. 2 – Odds ratios* for febrile neutropaenia (FN), related outcomes and haematological toxicity for patients receiving pegfilgrastim primary prophylaxis (PPP) versus current practice (CP) neutropaenia management.

Table 4 – Predicted proportions of breast cancer patients experiencing febrile neutropaenia (FN) over all cycles as a function of age and disease stage.

Age at baseline (years)	Proportion of patients with FN (95% confidence interval [CI]) Disease stage at baseline			
	I–III		IV	
	PPP ($N = 930$)	CP ($N = 646$)	PPP ($N = 361$)	CP ($N = 273$)
40	3% (2%, 6%)	22% (12%, 36%)	5% (2%, 9%)	28% (16%, 45%)
50	4% (2%, 8%)	25% (15%, 40%)	6% (3%, 11%)	32% (19%, 49%)
60	5% (3%, 9%)	29% (17%, 45%)	7% (3%, 13%)	37% (22%, 54%)
70	6% (3%, 11%)	33% (20%, 50%)	8% (4%, 15%)	41% (25%, 60%)

CP, current practice neutropaenia management; PPP, pegfilgrastim primary prophylaxis.
Proportions derived from generalised linear mixed model.

all cycles were again significantly lower with PPP compared with CP (OR: 0.126; 95% CI: 0.082, 0.195; $P < 0.0001$). Analysis of the two largest studies alone ($N = 1507$) also showed consistent findings; the odds ratio for FN was 0.096 (PPP versus CP; 95% CI: 0.058, 0.158; $P < 0.0001$). It was not possible to apply the final model to small studies alone, since each study contributed patients to only one group.

3.5. *Chemotherapy delivery*

Fig. 3a shows the findings of the descriptive analyses of chemotherapy dose delays and dose reductions.

Type of neutropaenia prophylaxis, age and disease stage influenced chemotherapy dose reductions (⩾15%), but did not affect the incidence of chemotherapy dose delays (>3 days) (Table 3; Fig. 2). The odds for requiring a dose reduction were significantly lower among patients receiving PPP rather than CP. When adjusted for baseline variability, the difference between the proportions of PPP and CP patients requiring dose reductions narrowed (with overlapping CIs), but was little changed with respect to dose delays (Fig. 3b).

3.6. *Hospitalisation due to FN*

FN-related hospitalisation was influenced by neutropaenia prophylaxis (PPP versus CP), age and disease stage. The odds for FN-related hospitalisation were significantly lower in the PPP group compared with the CP group (Table 3; Fig. 2), accordingly lower proportions of PPP patients experienced FN-related hospitalisation than those receiving CP (Fig. 3a and b).

3.7. *Haematological toxicity*

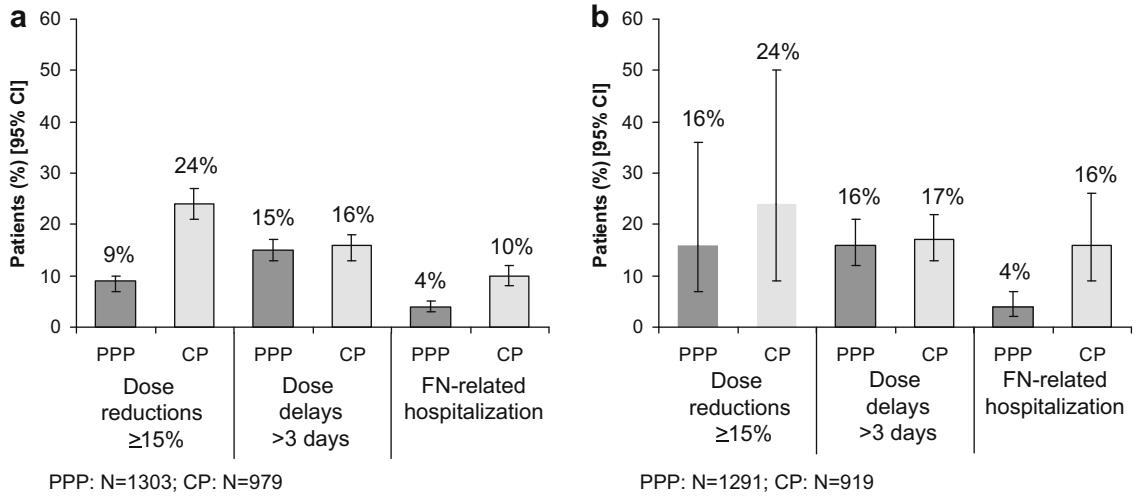
In descriptive analyses, the incidence of grades 3–4 neutropaenia was 39% (514/1303) (95% CI: 37%, 42%) and 72% (708/979) (69%, 75%) for the PPP and CP groups, respectively. Grades 3–4 leucopaenia was observed in 47% (603/1303) (44%, 49%) and 67% (655/979) (64%, 70%) of PPP and CP patients, respectively.

Type of neutropaenia prophylaxis and age, but not disease stage, influenced grades 3–4 neutropaenia and leucopaenia in the model. The odds for developing either of these adverse events were significantly lower in the PPP versus the CP group (Table 3; Fig. 2). The adjusted proportions (95% CI) of patients with grades 3–4 neutropaenia were 47% (1072/1983) (9%, 89%) and 96% (911/1983) (70%, 99%), respectively, while the values for leucopaenia were 47% (1288/2132) (15%, 82%) and 94% (844/2132) (74%, 99%), respectively.

4. Discussion

In this integrated analysis of over 2200 breast cancer patients receiving chemotherapy with moderately high to high FN risk, PPP from the first cycle provided significantly better protection from FN than CP neutropaenia management. Similarly, patients receiving PPP were significantly less likely to experience grades 3–4 neutropaenia, require chemotherapy dose reductions or be hospitalised due to FN. The proportions of patients with FN adjusted for study, age and disease stage showed a greater advantage for PPP over CP than the descriptive data from the unmodelled dataset. As a higher proportion of PPP patients received more myelotoxic chemotherapy regimens such as DocAC and ADoc, this predicted increase in FN for CP patients when the groups were balanced by the model is unsurprising. The model also indicates that FN risk could be as high as 41% in elderly patients with stage IV disease receiving CP.

CP neutropaenia management varied considerably. Three-quarters of patients did not receive G-CSF in the first cycle and that proportion did not increase in cycle 2 despite the substantial number of patients with cycle 1 FN. Nevertheless, the CP group is an acceptable representation of neutro-



CP, current practice neutropenia management; FN, febrile neutropenia; PPP, pegfilgrastim primary prophylaxis.

Fig. 3 – (a) Descriptive (unadjusted) and (b) adjusted proportions of patients with dose reductions/delays and febrile neutropaenia (FN)-related hospitalisations. Adjusted proportions predict patients with FN, after allowing for differences in study, age and disease stage.

paenia management. Trials using ADoc and Doc show that G-CSF is often reserved for secondary prophylaxis[24,25] and the use of short courses is also quite common.[26,27] Furthermore, delayed G-CSF use is not unusual.[13,18] The largest population included in the CP arm was drawn from a randomised trial that stipulated secondary prophylaxis for Doc monotherapy.[11] This was CP at the time and, according to European guidelines, it remains so for patients with no additional risk factors for FN. Similarly, in the GEPARTRIO trial,[15] ciprofloxacin was regarded as sufficient prophylaxis for DocAC during the pilot phase, but G-CSF was not precluded and over 50% of patients received it at some point during treatment.

Our findings reflect other studies comparing pegfilgrastim with various filgrastim regimens. For example, in a previous analysis of the GEPARTRIO study, patients receiving PPP had a statistically significantly lower rate of FN than those receiving G-CSF on days 5–10 of 3-weekly DocAC cycles (7% versus 18%, respectively; $P < 0.001$).[15] The cohort of patients receiving daily G-CSF was not included in the present analysis as patients received the agent per protocol as primary prophylaxis. Results from a retrospective, single-centre experience comparing pegfilgrastim with a median of 6 days G-CSF use in patients ($N = 118$) receiving E(Doc or T) are less conclusive (FN incidence 3.3% versus 9.1% for daily G-CSF; $P = 0.445$).[28] Phase III trials suggest that pegfilgrastim and a median of 10–11 daily doses of filgrastim in patients receiving ADoc chemotherapy are similarly efficacious for preventing FN and allowing neutrophil recovery, but a pooled analysis of the trials suggests that pegfilgrastim could in fact be advantageous in this respect (FN: 11% versus 19%; relative risk: 0.56 [95% CI: 0.35, 0.89]).[8,9,29]

The link we have shown between FN, increasing age and advanced disease stage reflects the patient risk factors highlighted in recent European guidelines.[4] With respect to age, this observation is of particular importance, as to our knowledge, it is the first time such a relationship has been comprehensively demonstrated in the breast cancer setting. At the descriptive level, our data show that patients experiencing FN despite PPP are at high risk of further FN events. Such patients should be closely monitored.

In the present analysis, dose delays were not affected by type of neutropaenia prophylaxis, but the odds for dose reduction were significantly lower with PPP versus CP. Physicians may prefer to dose reduce rather than to delay giving treatment, but these outcomes may also be affected by protocol instructions on dose adjustments. PPP was also associated with fewer FN-related hospitalisations than CP, confirming the findings of a previous study that showed the risk of hospitalisation for neutropaenia or that infection increased with decreasing days of daily G-CSF use.[30]

Current guidelines recommend G-CSF primary prophylaxis for patients at overall FN risk $\geqslant 20\%$.[4,31] Our data relate to chemotherapy regimens with $\geqslant 15\%$ FN risk, but nevertheless lend weight to this recommendation. DocAC is associated with 21–24% FN risk and ADoc with 33–48% FN risk.[4] Doc monotherapy is associated with 16–17% FN risk, but physicians should consider primary prophylaxis in patients with concomitant risk factors (e.g. older age, late-stage disease).[4,11] Adequate G-CSF prophylaxis is potentially life saving in the adjuvant setting as it not only decreases the risk of FN but also facilitates delivery of chemotherapy. For example, a large meta-analysis showed that lack of G-CSF prophylaxis was associated with reduced chemotherapy dose intensity in breast cancer patients.[32] Furthermore, another recent meta-analysis has shown that primary prophylaxis with G-CSF (5–14 days treatment) in patients receiving chemotherapy for solid tumours or lymphomas was associated with lower risk of infection-related mortality and early mortality than placebo/secondary G-CSF prophylaxis.[33]

A prospective randomised trial comparing PPP with CP is difficult to perform with the possible biases introduced into 'current practice', while a classic meta-analysis was precluded by some studies not contributing patients to both treatment groups. The present integrated analysis of individual patient data is therefore a valid approach. Indeed, it offers advantages over analyses based on aggregated data (e.g. full adjustment for patient characteristics).[34] The analysis must be viewed within the context of the databases searched and may be limited by the unavailability of patient data from some studies. Two studies contributed most patients and were key drivers of the results, however, variability in constituent population size is a feature of many combined analyses. A greater advantage for PPP was shown in a sensitivity analysis of these studies alone, indicating the overall results to be a more conservative estimate of its efficacy.

In conclusion, the present analysis supports use of PPP in patients receiving chemotherapy with moderately high to high risk of FN – both to avoid FN and to enable delivery of planned treatment.

Conflict of interest statement

G. von Minckwitz has received research funding from Amgen, Sanofi-Aventis and F. Hoffman La-Roche. He has acted as a consultant to Amgen and received honoraria.

Matthias Schwenkglenks has acted as a consultant to Amgen and has received research funding.

G. Lyman has received research funding from Amgen. He has received honoraria from Amgen and Ortho Biotech.

A. Lopez Pousa has received research funding from Amgen.

M. Aapro has received research funding from Amgen, F. Hoffman La-Roche and Sanofi-Aventis. He has participated in advisory boards and speaker bureau for these companies.

Authors P. Bacon, V. Easton and T. Skacel are employees of Amgen, with stock options.

Acknowledgements

This study was supported by Amgen (Europe) GmbH. Amgen authors participated in the design and conduct of the analysis. Statistical support was also provided by Susan Lawrinson and Jon Cooke of Amgen Ltd. (Uxbridge, UK), while Anne Whitehead (University of Reading, UK) acted as a statistical consultant. Editorial support was provided by Gavin Worth of Amgen (Europe) GmbH (Zug, Switzerland).

REFERENCES

1. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. *Cancer* 2006;**106**:2258–66.
2. Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: the results of 20 years of follow-up. *New Engl J Med* 1995;**332**:901–6.
3. Chirivella I, Bermejo B, Insa A, et al. Optimal delivery of anthracycline-based chemotherapy in the adjuvant setting improves outcome of breast cancer patients. *Breast Cancer Res Treat* 2008. epub..
4. 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**:2433–53.
5. Hryniuk W, Frei E, Wright FA. A single scale for comparing dose-intensity of all chemotherapy regimens in breast cancer: summation of dose intensity. *J Clin Oncol* 1998;**16**:3137–47.
6. 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**:164–70.
7. 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**:319–24.
8. 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**:727–31.
9. 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**:29–35.
10. Johnston E, Crawford J, Blackwell S, et al. Randomized, dose-escalation study of SD/01 compared with daily filgrastim in patients receiving chemotherapy. *J Clin Oncol* 2000;**18**:2522–8.
11. 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**:1178–84.
12. Scott SD, Chrischilles EA, Link BK, Delgado DJ, Fridman M, Stolshek BS. Days of prophylactic filgrastim use to reduce febrile neutropenia in patients with non-Hodgkin's lymphoma treated with chemotherapy. *J Manage Care Pharm* 2003;**9**(2 Suppl.):15–21.
13. Koumakis G, Vassilomanolakis M, Barbounis V, et al. Optimal timing (preemptive versus supportive) of granulocyte colony-stimulating factor administration following high-dose cyclophosphamide. *Oncology* 1999;**56**:28–35.
14. Schwenkglenks M, Jackisch C, Constenla M, et al. Neutropenic event risk and impaired chemotherapy delivery in six European audits of breast cancer treatment. *Support Care Cancer* 2006;**14**:901–9.
15. Von Minckwitz G, Kümmel S, du Bois A, et al. Pegfilgrastim ± ciprofloxacin for primary prophylaxis with TAC (docetaxel/doxorubicin/cyclophosphamide) chemotherapy for breast cancer. Results from the GEPARTRIO Study. *Ann Oncol* 2008;**19**:292–8.
16. Lopez Pousa A, Rifa J, Casas Fernandez de Tejerina A, et al. Risk assessment model for first-cycle chemotherapy-induced neutropenia (CIN) among breast cancer (BrCa) patients. On behalf of the DELFOS Study Group. *Ann Oncol* 2006;**17**(Suppl. 9): ix296. Abstract no. 1028P.
17. Balducci L, Al-Halawani H, Charu V, et al. Elderly cancer patients receiving chemotherapy benefit from first cycle pegfilgrastim. *Oncologist* 2007;**12**:1416–24.
18. Morrison VA, Wong M, Hershman D, Campos LT, Ding B, Malin J. 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 Manage Care Pharm* 2007;**13**:337–48.
19. Pettengell P, Schwenkglenks M, Leonard R, et alfor the Impact of Neutropenia in Chemotherapy – European Study Group (INC-EU). *Support Care Cancer* 2008;**22**:33. E-publication ahead of print.
20. Holmes FA, Jones SE, O'Shaughnessy J, et al. Comparable efficacy and safety profiles of once-per-cycle pegfilgrastim and daily injection filgrastim in chemotherapy-induced neutropenia: a multicenter dose-finding study in women with breast cancer. *Ann Oncol* 2002;**13**:903–9.
21. Kaufman PA, Paroly W, Rinaldi D, et al. Randomized double-blind phase 2 study evaluating same-day versus next-day administration of pegfilgrastim with docetaxel, doxorubicin, and cyclophosphamide (TAC) in women with early stage and advanced breast cancer. *Breast Cancer Res Treat* 2004;**88** (1 Suppl.):22–3. Abstract no. 1054.
22. Ozer H, Mirtsching B, Rader M, et al. Neutropenic events in community practices reduced by first and subsequent cycle pegfilgrastim use. *Oncologist* 2007;**12**:484–94.
23. Bendel RB, Afifi AA. Comparison of stopping rules in forward stepwise regression. *J Am Stat Assoc* 1977;**72**:46–53.
24. Bontenbal M, Creemers GJ, Braun HJ, et al. Phase II to III study comparing doxorubicin and docetaxel with fluorouracil, doxorubicin, and cyclophosphamide as first-line chemotherapy in patients with metastatic breast cancer: results of a Dutch Community Setting Trial for the Clinical Trial Group of the Comprehensive Cancer Centre. *J Clin Oncol* 2005;**23**:7081–8.
25. Harvey V, Mouridsen H, Semiglazov V, et al. Phase III trial comparing three doses of docetaxel for second-line treatment of advanced breast cancer. *J Clin Oncol* 2006;**24**:4963–70.
26. Martin M, Lluch A, Segui MA, et al. Toxicity and health-related quality of life in breast cancer patients receiving adjuvant docetaxel, doxorubicin, cyclophosphamide (TAC) or 5-fluorouracil, doxorubicin and cyclophosphamide (FAC): impact of adding primary prophylactic granulocyte-colony stimulating factor to the TAC regimen. *Ann Oncol* 2006;**17**:1205–12.
27. Polyzos A, Tsavaris N, Kosmas C, et al. Docetaxel and epirubicin supported by granulocyte colony-stimulating factor first-line in advanced breast cancer. *Anticancer Res* 2003;**23**:2917–23.
28. Schippinger W, Holub R, Dandachi N, Bauernhofer T, Samonigg H. Frequency of febrile neutropenia in breast cancer patients receiving epirubicin and docetaxel/paclitaxel with colony-stimulating growth factors: a comparison of filgrastim or lenograstim with pegfilgrastim. *Oncology* 2006;**70**:290–3.
29. Siena S, Piccart MJ, Holmes FA, Glaspy J, Hackett J, Renwick JJ. A combined analysis of two pivotal randomized trials of a single dose of pegfilgrastim per chemotherapy cycle and daily Filgrastim in patients with stage II–IV breast cancer. *Oncol Rep* 2003;**10**:715–24.
30. Weycker D, Hackett J, Edelsberg JS, Oster G, Glass AG. Are shorter courses of filgrastim prophylaxis associated with increased risk of hospitalization? *Ann Pharmacother* 2006;**40**:402–7.

31. 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**:3187–205.
32. Lyman GH, Dale DC, Crawford J. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. *J Clin Oncol* 2003;**21**:4524–31.
33. 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**:3158–67.
34. Lyman GH, Kuderer NM. The strengths and limitations of meta-analyses based on aggregate data. *BMC Med Res Methodol* 2005;**5**:14.