Supportive Care in Cancer (2019) 27:1099–1108
https://doi.org/10.1007/s00520-018-4399-3

ORIGINAL ARTICLE

Real-world use of granulocyte colony-stimulating factor in ambulatory breast cancer patients: a cross-sectional study

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Received: 22 March 2018 / Accepted: 3 August 2018 / Published online: 11 August 2018

Abstract

Purpose To prevent febrile neutropenia (FN), European Organisation for Research and Treatment of Cancer (EORTC) guidelines recommend primary prophylaxis with granulocyte colony-stimulating factors (PPG) for patients at high risk (≥ 20%) of FN. In Belgium, the use of PPG is restricted by specific reimbursement criteria. The impact of these criteria on PPG use and adherence to guidelines is unknown.

Methods This multicentre, cross-sectional, observational study aimed to describe PPG use by FN risk category in breast cancer patients who were scheduled to receive myelosuppressive chemotherapy in outpatient clinics in Belgium during a 2-week period between 13 October and 12 December 2014.

Results In total, 490 patients were enrolled. Median age was 57.0 years. Based on their chemotherapy regimen, 53.9, 5.1 and 41.0% of patients were at a low, intermediate and high risk of FN, respectively. Overall, 39.8% of patients received PPG (17.0, 12.0 and 73.1% of those receiving low-, intermediate- and high-risk regimens, respectively). In the high-risk category, PPG was used in 89.9% of dose-dense and in 25.0% of classical chemotherapy regimens. PPG use was adherent to EORTC guidelines in 75.3% of patients (30.6% appropriate use, 44.7% appropriate non-use). EORTC guidelines would recommend PPG use in 46.1% of this study population ($n = 226$), and its use was reimbursable in Belgium in 76.1% of these patients ($n = 172$), but only 66.4% of them received PPG ($n = 150$).

Conclusions Both Belgian reimbursement criteria and physician decision-making led to a proportion of patients for whom PPG treatment was recommended but finally not receiving it.

Keywords Breast cancer · Chemotherapy · Febrile neutropenia · Granulocyte colony-stimulating factor · Prophylaxis

Introduction

Febrile neutropenia (FN) is a serious toxicity resulting from treatment with myelosuppressive chemotherapy [1, 2]. It is defined as an absolute neutrophil count (ANC) of $< 0.5 \times 10^9$/L, or a count of $< 1.0 \times 10^9$/L that is predicted to fall to $< 0.5 \times 10^9$/L within 48 h, with fever or clinical signs of sepsis [1]. FN can result in substantial morbidity and mortality and may lead to dose reductions or delays in chemotherapy administration, which in turn compromise the efficacy of cancer therapy [2]. Furthermore, 20–30% of patients with FN require hospitalisation: with a mean cost per hospitalisation in Western countries of approximately €13,500 ($15,000), FN contributes substantially to the costs of caring for patients with cancer [2–4].

Prevention of FN reduces hospital admissions, antibiotic use and the need for chemotherapy dose reductions or delays

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00520-018-4399-3) contains supplementary material, which is available to authorized users.

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[1]. Recombinant granulocyte colony-stimulating factors (G-CSFs), which promote growth and differentiation of neutrophil progenitor cells, may be used as prophylaxis to reduce the incidence, duration and severity of FN in patients receiving chemotherapy [5]. Results from randomised controlled trials and retrospective studies show that, compared with no treatment, prophylactic G-CSF significantly reduces the incidence of FN in patients with breast cancer who are receiving myelosuppressive chemotherapy [6–11].

In 2010, the European Organisation for Research and Treatment of Cancer (EORTC) updated its guidelines for use of G-CSF to reduce the incidence of chemotherapy-induced FN [1]. Recommendations are based on assessment of FN risk associated with the planned chemotherapy regimen; primary prophylactic G-CSF (PPG) is recommended for all patients receiving chemotherapy with a high FN risk (≥ 20% risk). For those receiving chemotherapy with an intermediate FN risk (10–20% risk), the decision to initiate PPG is less clear and additional factors should be considered in order to establish an overall FN risk. Risk factors for FN include age > 65 years (high risk); advanced disease; history of previous FN; no prophylaxis with antibiotics or G-CSF; poor Eastern Cooperative Oncology Group (ECOG) performance status; poor nutritional status; female sex; haemoglobin < 12 g/dL; and liver, renal or cardiovascular disease [1]. After consideration of these factors, PPG is recommended if the overall FN risk is ≥ 20%. Other guidelines provide similar recommendations [4, 12, 13].

In breast cancer, the introduction of anthracycline and taxane-based chemotherapy regimens, and the establishment of dose-dense schedules have improved outcomes [14, 15]. However, these developments mean that most chemotherapy regimens in breast cancer are associated with a high FN risk [16–19]. PPG is recommended in situations in which reductions in chemotherapy dose intensity are associated with poor prognosis [1]. Real-world observational studies have demonstrated, however, that PPG is not given to all patients at high FN risk and that the majority of FN occurs in chemotherapy cycles administered without appropriate PPG [20–24].

At the time of the study, use of PPG in Belgium was restricted by specific reimbursement criteria [22]. In breast cancer, PPG was reimbursed for patients ≥ 65 years receiving an anthracycline- and/or taxane-containing regimen in adjuvant or neo-adjuvant setting and for patients < 65 years when a regimen of concomitant anthracyclines and taxanes or a dose-dense regimen was given [25]. As secondary prophylaxis, G-CSF was reimbursed if patients experienced FN or prolonged severe neutropenia while receiving cytotoxic chemotherapy [22]. The impact of these criteria on the potential for adherence to EORTC guidelines is unknown.

This study aimed to describe the use of PPG in patients receiving chemotherapy for breast cancer in Belgium, and to describe the adherence to EORTC guidelines and the impact of Belgian reimbursement criteria in real-world practice.

Materials and methods

Study design

This multicentre observational study was conducted in 17 centres in Belgium and comprised cross-sectional and retrospective components. The study aimed to enrol 850 patients with breast cancer (BC) or non-Hodgkin lymphoma (NHL) during a 2-week recruitment period, which occurred between 13 October and 12 December 2014 and was determined by each participating centre. Eventually, 591 subjects were recruited of which 578 were eligible for the full analysis (FAS). Of the 578 subjects of the FAS, 490 were diagnosed with BC and 88 with NHL. This study reports on the patients with BC. The study protocol was approved by a central regulatory ethics committee, and written informed consent was obtained from all participants, in accordance with the ethical principles of the Declaration of Helsinki.

Objectives

The primary objective of the study was to document the use of PPG (primary prophylaxis with granulocyte colony-stimulating factors) in Belgian clinical practice for patients undergoing chemotherapy for BC or NHL in an outpatient setting. This study reports data only from patients with BC.

Participants

Patients were considered for inclusion in the study if they presented at participating outpatient clinics during the recruitment period. Individuals were considered eligible for inclusion if they were aged ≥ 18 years, had a clinical diagnosis of BC of any stage, were scheduled to receive myelosuppressive chemotherapy in the outpatient setting in Belgium and had provided written informed consent before any data recording. Patients were excluded if they had ongoing or planned concurrent participation in any interventional clinical study in which the administration of G-CSF and/or the chemotherapy schedule was determined by protocol, or if they had any disorder that compromised their ability to provide written consent.

Study sites and data collection

Included centres were selected to be representative of those treating patients with BC (in terms of region, language, size, and centre type) in order to obtain a patient population that reflected clinical practice in Belgium. Enrolment and data collection occurred on the day of the outpatient visit; patients were not further followed up after inclusion. Participating physicians completed a case report form for each eligible patient. For the cross-sectional part of the

study, physicians recorded patient- and regimen-related data for the current chemotherapy cycle at the time of inclusion. For the retrospective part of the study, physicians used patient medical records to collect data on baseline characteristics and previous chemotherapy cycles.

The primary outcome was the proportion of patients receiving PPG for chemotherapy regimens associated with a low, intermediate and high risk of FN. The EORTC definition of FN was applied: an ANC $< 0.5 \times 10^9$/L, or an ANC $< 1.0 \times 10^9$/L that is predicted to fall to $< 0.5 \times 10^9$/L within 48 h, with fever (a temperature of 38.3 °C once or of 38.0 °C for more than 1 h) or clinical signs of sepsis or fever; the ANC should be measured on the same day as these clinical signs or feverish temperature, or within 1 day of them [1]. Two FN risk assessment sets were defined:

1. Regimen-based FN risk in which patients were classified as having a low (< 10%), intermediate (10–20%) or high (≥ 20%) risk of FN according to the chemotherapy regimen they were receiving. The high-risk group was further subdivided by the type of chemotherapy regimen (classical chemotherapy regimens, administered every 3 weeks [Q3W], versus dose-dense chemotherapy, administered every 2 weeks [Q2W]).
2. Healthcare professional (HCP)-determined FN risk, as assessed by the treating physician for patients starting cycle 1 only. Patients were classified as having a low (< 10%), intermediate (10–20%) or high (≥ 20%) risk of FN. The HCP-determined FN risk was implemented, based on the EORTC guidelines [1], where a strong recommendation is made to assess the individual patient's overall FN risk before administering each cycle of chemotherapy. Such assessment would include the patient-related adverse risk factors such as elderly age, neutrophil count and others on top of the regimen-related FN risk. As stated in the guideline, this is particularly important for chemotherapy regimens associated with FN in 10–20% of patients, where 'particular attention should be given to patient-related risk factors that may increase the overall risk of FN'. With this HCP-assessment, we tried to capture this element of the guideline into our study.

Other variables for which data were recorded included patient-related FN risk factors (age ≥ 65 years, advanced disease, history of FN, no use of antibiotic prophylaxis, no use of G-CSF, poor ECOG performance and/or nutritional status, female sex, haemoglobin < 12 g/dL, liver, renal or cardiovascular disease); concomitant therapy; prevalence of different chemotherapy regimens; concordance between regimen-based FN risk assessment and HCP-determined FN risk; adherence to EORTC G-CSF guidelines; details of G-CSF administration; and use of secondary G-CSF prophylaxis (use of G-CSF in BC patients (non-metastatic or metastatic) treated with cytotoxic chemotherapy that experienced an FN or a prolonged severe neutropenia (PSN) during the course of their treatment) and adverse drug reactions (ADRs).

Statistical analyses

The analysis populations were the full analysis set (FAS; all enrolled patients who met the eligibility criteria), the regimen-based FN risk assessment set (FNAS; all patients in the FAS who received chemotherapy designated as having a low, intermediate or high FN risk), and the HCP-determined risk assessment set (HCPAS; all patients in the FNAS who entered the study at their first cycle of chemotherapy, except patients receiving a dose-dense regimen). Statistical analyses were descriptive; categorical data were summarised by the number and percentage of patients in each category, and continuous data were summarised by mean, standard deviation, median, lower and upper quartiles, and minimum and maximum values. The frequencies and patterns of missing data were informally analysed; missing data were not imputed for the analyses of outcome measures.

Results

Participants

In total, 490 patients met the eligibility criteria and were included in the study (FAS population), 46 of these patients entered the study at their first cycle of chemotherapy (=HCPAS population). Descriptive data for patient and disease characteristics in the FAS are summarised in Table 1. At enrolment, the median age was 57.0 years and 26.3% of patients were aged ≥ 65 years.

Breast cancer treatments

The use of cancer treatments in the FAS population is summarised in Table 2. The most frequently prescribed chemotherapy regimen was an anthracycline and cyclophosphamide combination followed by paclitaxel, which was prescribed to 212 patients (43.3%). This regimen was administered in a dose-dense schedule of epirubicin plus cyclophosphamide Q2W ($n = 127$, or 25.9%) or doxorubicin plus cyclophosphamide Q2W ($n = 6$, or 1.2%) and in a classical chemotherapy regimen as epirubicin plus cyclophosphamide or doxorubicin plus cyclophosphamide Q3W ($n = 79$, or 16.1%). Dose-dense regimens were more frequently used in younger patients (< 65 years) ($n = 136$; 37.7%) than in older patients (≥ 65 years) ($n = 13$; 10.1%). When considering the sequential chemotherapy treatments used, the most common planned number of chemotherapy cycles was four (4xQ3W or 4xQ2W) for a first regimen and 12 (12xQW) for a second regimen. Nearly one third of patients (30.8%) received breast-cancer-targeted therapy, most commonly trastuzumab.

Table 1 Baseline patient and disease characteristics (FAS)

Characteristic	$N = 490$
Sex, *n* (%)	
Male	1 (0.2)
Female	489 (99.8)
Age, years[a]	
Mean	56.8
SD	12.1
Median	57.0
Q1, Q3	48.0, 65.0
Minimum, maximum	25, 94
Age group, *n* (%)	
< 65 years	361 (73.7)
≥ 65 years	129 (26.3)
TNM stage at diagnosis, *n* (%)	
Stage 1	89 (18.2)
Stage 2	211 (43.1)
Stage 3	78 (15.9)
Stage 4	63 (12.9)
Unknown	49 (10.0)
Time since diagnosis, months[b]	
Mean	40.5
SD	69.5
Median	5.0
Q1, Q3	3.0, 47.1
Minimum, maximum	0, 389

FAS full analysis set, *Q* quartile, *SD* standard deviation, *TMN* tumour, node and metastasis classification

[a] No missing values

[b] Six missing values; $N = 484$

FN risk

In the FAS, based on their chemotherapy regimen, 264 (53.9%) patients were considered to have a low risk, 25 (5.1%) an intermediate risk and 201 (41.0%) a high risk of FN. Overall, three-quarters (74.1%) of the high-risk chemotherapy regimens were dose-dense (Table 3). Among patients initiating their first cycle of classical chemotherapy (HCPAS, $n = 46$), 32 (69.6%) were considered to have a low risk, 7 (15.2%) an intermediate risk and 7 (15.2%) a high risk of FN.

Regimens with a high FN risk were seldom used in the palliative care setting (stage 4 disease, 6.3%) compared with the curative setting (stage 1, 41.6%; stage 2, 50.2%; stage 3, 50.0%). High-risk regimens were also used less frequently in older patients (≥ 65 years, 23.3%, 95% CI [16.0–23.3]) than in younger patients (< 65 years, 47.4%, 95% CI [42.25–52.55]). Similarly, dose-dense regimens were used less frequently in patients receiving palliative care (3.2%) than in those receiving potentially curative treatment (stage 1, 30.3%; stage 2, 41.7%; stage 3, 33.3%), and less frequently in older patients (≥ 65 years, 10.1%) than in younger patients (< 65 years, 37.7%).

When considering patient- and disease-related risk factors for FN, 35.5% of patients had low haemoglobin levels (< 12 g/dL), 4.7% had a poor nutritional status, 5.5% had a history of previous FN and 1.4% had received antibiotic prophylaxis. Liver disease, renal disease and cardiovascular disease were present in 23.7, 4.7 and 3.1%, respectively (Supplementary Table 1, Online Resource 1).

Use of G-CSF prophylaxis

Overall, 39.8% of patients received PPG in the FAS. The use of PPG in patients who received low-, intermediate- and high-risk regimens was 17.0, 12.0 and 73.1%, respectively (Table 3). Within the high-risk group, 89.9% of patients treated with dose-dense regimens and 25.0% of those treated with classical regimens received PPG. For patients receiving high-risk dose-dense regimens, PPG use was similar for both age subgroups (< 65 years, 89.0%; ≥ 65 years, 100.0%). The use of PPG was substantially lower in younger patients (< 65 years) who were receiving high-FN risk classical chemotherapy regimens than in older patients (≥ 65 years) receiving the same regimen type (5.7 vs 64.7%, respectively).

Among patients initiating their first cycle of classical chemotherapy (HCPAS), 15.2% received PPG; 15.6% of patients at low risk of FN and 28.6% of patients at high risk of FN. Among the seven patients in the group at intermediate risk of FN, none received PPG.

Analysis of PPG use within each specific FN risk category was relatively unaffected by age and cancer stage, except that in low- and intermediate-risk groups, older patients (≥ 65 years) were more likely to receive PPG than younger patients (< 65 years) (29.3 and 28.6 vs 10.5 and 5.6% for low and intermediate FN risk, respectively) (Supplementary Table 2, Online Resource 2).

In the 72 patients (14.7%) who had experienced a serious neutropenic event (SNE) in a previous cycle, only 30 (41.7%) received secondary prophylaxis with G-CSF in at least one further chemotherapy cycle. Use of secondary prophylaxis was slightly more frequent in younger patients (< 65 years) than in older patients (≥ 65 years) (44.4 vs 33.3%). Overall, fewer SNEs in previous cycles were reported for patients who received PPG compared with those who did not (13.3% (95%CI 7.44–19.16) vs 18.3% (95%CI 13.59–23.01)). However, in the high-risk dose-dense group, patients receiving PPG were more likely to have had a previous SNE than those not receiving PPG (14.9 vs 6.7%).

Table 2 Cancer treatments overall and by age group (FAS)

	Overall ($N = 490$)	Age < 65 years ($N = 361$)	Age ≥ 65 years ($N = 129$)
Cancer treatments, *n* (%)			
Classical chemotherapy			
EC/AC Q3W plus paclitaxel	79 (16.1)	64 (17.7)	15 (11.6)
Paclitaxel	43 (8.8)	22 (6.1)	21 (16.3)
Eribulin	33 (6.7)	18 (5.0)	15 (11.6)
FEC plus docetaxel	23 (4.7)	16 (4.4)	7 (5.4)
Liposomal doxorubicin	17 (3.5)	9 (2.5)	8 (6.2)
Docetaxel	16 (3.3)	10 (2.8)	6 (4.7)
Vinorelbine	16 (3.3)	11 (3.0)	5 (3.9)
Docetaxel plus cyclophosphamide	14 (2.9)	5 (1.4)	9 (7.0)
FEC plus paclitaxel	12 (2.4)	6 (1.7)	6 (4.7)
Paclitaxel plus carboplatinum	11 (2.2)	11 (3.0)	0 (0)
TDM-1	11 (2.2)	7 (1.9)	4 (3.1)
EC/AC Q3W plus docetaxel	10 (2.0)	10 (2.8)	0 (0)
FEC	9 (1.8)	8 (2.2)	1 (0.8)
EC/AC Q3W	9 (1.8)	4 (1.1)	5 (3.9)
MMM	5 (1.0)	4 (1.1)	1 (0.8)
Vinorelbine de Gramont	4 (0.8)	1 (0.3)	3 (2.3)
EC Q3W plus carboplatinum and paclitaxel	3 (0.6)	2 (0.6)	1 (0.8)
Cisplatinum or carboplatinum only	3 (0.6)	2 (0.6)	1 (0.8)
CMF	3 (0.6)	2 (0.6)	1 (0.8)
DD chemotherapy			
EC Q2W DD plus paclitaxel	127 (25.9)	114 (31.6)	13 (10.1)
EC/AC DD Q2W plus paclitaxel and carboplatinum	16 (3.3)	16 (4.4)	0 (0)
AC DD Q2W plus paclitaxel	6 (1.2)	6 (1.7)	0 (0)
Other	20 (4.1)	13 (3.6)	7 (5.4)
Planned number of chemotherapy administrations, part 1, *n* (%)			
2	1 (0.2)	0 (0)	1 (0.8)
3	50 (10.2)	29 (8.0)	21 (16.3)
4	243 (49.6)	206 (57.1)	37 (28.7)
5	3 (0.6)	2 (0.6)	1 (0.8)
6	39 (8.0)	29 (8.0)	10 (7.8)
7	1 (0.2)	1 (0.3)	0 (0)
8	1 (0.2)	1 (0.3)	0 (0)
9	11 (2.2)	5 (1.4)	6 (4.7)
12	28 (5.7)	16 (4.4)	12 (9.3)
14	5 (1.0)	4 (1.1)	1 (0.8)
15	2 (0.4)	1 (0.3)	1 (0.8)
16	1 (0.2)	1 (0.3)	0 (0)
18	13 (2.7)	8 (2.2)	5 (3.9)
20	1 (0.2)	1 (0.3)	0 (0)
24	1 (0.2)	1 (0.3)	0 (0)
Planned number of chemotherapy cycles, part 2, *n* (%)			
3	25 (5.1)	18 (5.0)	7 (5.4)
4	29 (5.9)	29 (8.0)	0 (0)
6	1 (0.2)	1 (0.3)	0 (0)
9	12 (2.4)	8 (2.2)	4 (3.1)
12	207 (42.2)	176 (48.8)	31 (24.0)

Table 2 (continued)

	Overall ($N = 490$)	Age < 65 years ($N = 361$)	Age ≥ 65 years ($N = 129$)
18	2 (0.4)	2 (0.6)	0 (0)
Targeted therapy, *n* (%)	151 (30.8)	112 (31)	39 (30.2)
Not applicable	339 (69.2)	249 (69.0)	90 (69.8)

AC doxorubicin plus cyclophosphamide, *CMF* cyclophosphamide plus methotrexate plus 5-flurouracil, *DD* dose-dense, *EC* epirubicin plus cyclophosphamide, *FAS* full analysis set, *FEC* 5-fluorouracil plus epirubicin plus cyclophosphamide, *MMM* mitomycin plus mitoxantrone plus methotrexate, *Q2W* every 2 weeks, *Q3W* every 3 weeks

Adherence to EORTC guidelines and Belgian reimbursement criteria

The use of PPG was categorised as appropriate or inappropriate according to EORTC guidelines and to Belgian reimbursement criteria (Fig. 1). PPG use was adherent to EORTC guidelines in 75.3% ($n = 369$) of patients (30.6% appropriate use, 44.7% appropriate non-use) and non-adherent in 24.7% ($n = 121$) of patients (9.2% inappropriate use, 15.5% inappropriate non-use). Appropriate use of PPG was reimbursable in nearly all patients (147/150; 98.0%), while inappropriate use was reimbursable in half of patients (23/45; 51.1%) (Fig. 2). The proportion of appropriate non-use cases that were reimbursable was low (2.0%). However, it is noteworthy that among patients who did not receive PPG but should have according to EORTC (inappropriate non-use), PPG use was reimbursable in only one third (33.6%). In this study population, EORTC guidelines would have recommended PPG in 226 of 490 patients (46.1%). In 172 of these patients, PPG would also have been reimbursable in Belgium (76.1%), but only 150 of the 226 patients (66.3%) received PPG.

Concordance between regimen-based and HCP-determined FN risk assessment

Concordance between regimen-based and HCP-determined FN risk assessment is summarised in Table 4. Compared with the result of the regimen-based FN analysis, assessment by HCPs resulted in a higher proportion of patients deemed to have an intermediate risk (15.2% regimen-based vs 47.8% HCP-determined), while the overall proportion of high-risk patients remained the same (15.2% for both). In terms of individual category shifts: Of 32 regimen-based low-risk patients, 11 were upgraded to intermediate risk and 5 to high risk; of 7 regimen-based intermediate-risk patients, 1 was downgraded to low risk and 1 was upgraded to high risk; and of 7 patients in the regimen-based high-risk category, 6 were downgraded to intermediate risk and only 1 remained in the HCP-determined high-risk category. Reasons for the HCP-determined FN risk assessment were not recorded in this study.

Safety

No new safety signals were identified and ADRs reflected the known safety profile of G-CSF. Seven patients reported at least one ADR. These events were reported as bone pain ($n = 3$), FN ($n = 3$), influenza-like symptoms ($n = 2$), intermittent bone pain ($n = 1$), sternal and lumbosacral pain ($n = 1$), and sternal and sacroiliac pain ($n = 1$).

Discussion

In this multicentre observational study, a substantial proportion of patients received a chemotherapy regimen with a high risk of FN. Although the majority of these patients received PPG, over one quarter of patients treated with a high-risk

Table 3 Proportion of patients receiving PPG by FN risk assignment

FAS ($N = 490$)		HCPAS ($N = 46$)	
Chemotherapy FN risk group	Received PPG, *n* (%)	Chemotherapy FN risk group	Received PPG, *n* (%)
All patients	195 (39.8)	All patients	7 (15.2)
Low ($N = 264$)	45 (17.0)	Low ($N = 32$)	5 (15.6)
Intermediate ($N = 25$)	3 (12.0)	Intermediate ($N = 7$)	0 (0.0)
High ($N = 201$)	147 (73.1)	High ($N = 7$)	2 (28.6)
High—CC ($N = 52$)	13 (25.0)	High—CC ($N = 7$)	2 (28.6)
High—DD ($N = 149$)	134 (89.9)	High—DD ($N = 0$)	0 (0.0)

CC classical chemotherapy, *DD* dose-dense chemotherapy, *FAS* full analysis set, *FN* febrile neutropenia, *HCPAS* HCP-determined FN risk analysis set, *PPG* primary prophylaxis with granulocyte colony-stimulating factors

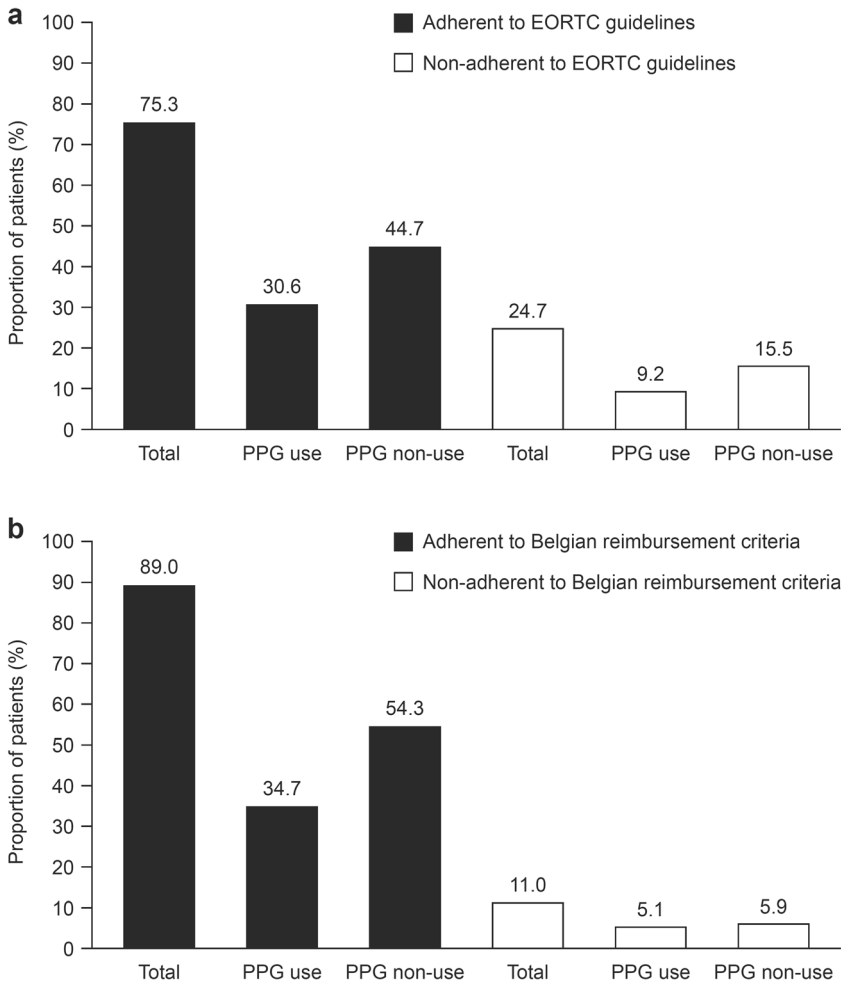

Fig. 1 Adherence to **a** EORTC guidelines and **b** Belgian reimbursement criteria (FAS, $N = 490$). EORTC European Organisation for Research and Treatment of Cancer, FAS full analysis set, G-CSF granulocyte colony-stimulating factors, PPG primary prophylaxis with G-CSF

regimen did not. The results of this study suggest that both Belgian reimbursement criteria and HCP decision-making led to a proportion of patients eligible for PPG but not receiving it.

The baseline characteristics and treatment patterns of this real-world patient group reflect those of the broad population with BC treated in clinical practice in Belgium. Almost one half of patients received an anthracycline-based regimen followed by a taxane, probably reflecting the fact that treatment regimens incorporating these agents have been shown to reduce BC mortality by approximately one third [26, 27] and are thus recommended in national and international guidelines [28, 29]. Approximately 40% of patients received high-FN risk chemotherapy regimens; of these, almost three-quarters (74%) were dose-dense regimens. Compared with classical chemotherapy regimens, dose-dense regimens have been shown to improve survival in patients with BC and are thus often used with curative intent [14, 15].

The overall proportion of patients receiving PPG was 39.8%. More than one quarter of patients treated with a high-FN risk regimen did not receive PPG. This is perhaps surprising given that PPG has been shown to reduce the incidence and severity of FN, and thus, its use is recommended in patients with BC who are receiving high-FN risk chemotherapy [1, 4, 9–13]. Poor adherence to guidelines regarding PPG use in patients at high risk of FN has, however, been reported in previous real-world studies [20, 22, 30, 31]. It should be noted that comparisons by G-CSF group can be confounded due to differences in baseline characteristics and FN risk.

In the high-risk category, the use of PPG was very common among patients receiving dose-dense therapy (89.9%) but less common among those receiving classical chemotherapy (25.0%). Furthermore, PPG use was influenced by patient age; only 6% of patients treated with high-risk classical chemotherapy who were aged < 65 years received PPG. This probably reflects Belgian reimbursement criteria; for patients aged < 65 years, PPG was reimbursed only in those who are receiving a regimen with concomitant anthracyclines and taxanes or a dose-dense regimen. This suggests that Belgian reimbursement criteria restricted PPG use in young patients who are receiving classical chemotherapy regimens. Reimbursement has previously been shown to impact PPG use [32]. Given that FN is associated with a high economic burden and that PPG has been shown to reduce

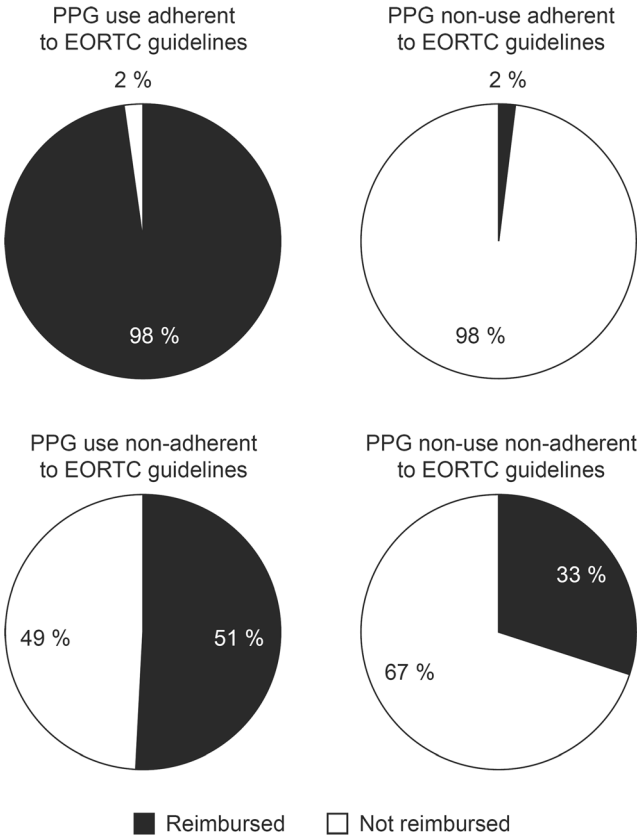

Fig. 2 Proportion of adherent and non-adherent use of PPG that is reimbursable in Belgium (FAS, $N = 490$). EORTC European Organisation for Research and Treatment of Cancer, FAS full analysis set, G-CSF granulocyte colony-stimulating factors, PPG primary prophylaxis with G-CSF

costs associated with FN, there may be economic consequences associated with failing to reimburse PPG in line with clinical guidelines [2, 33].

Our data suggest that a lack of coherence between Belgian reimbursement criteria, HCP treatment decisions and EORTC guidelines restricted access to PPG. The decision to treat or not treat with PPG was adherent to EORTC guidelines in three-quarters of patients (30.6% appropriate use, 44.7% appropriate non-use), indicating suboptimal adherence both in terms of missed opportunities to provide prophylaxis in patients at high risk and 'inappropriate' use in patients at lower risk. EORTC guidelines on use of G-CSF prophylaxis would recommend PPG in 46% of our study population, but its use was reimbursable in only 76% of these patients. Physician treatment decisions further restrict PPG use, with an additional 10% of patients who were both eligible and reimbursable for PPG not receiving treatment. Since February 1, 2018, Belgian reimbursement criteria were finally enlarged and now allow adherence to EORTC guidelines irrespective of the age of the patient.

Aside from reimbursement, there may be a number of other factors that lead to non-adherence to guidelines, such as physician experience, disease severity and treatment goals (curative vs palliative) [34]. Physicians may choose to use antibiotic prophylaxis or reduce or delay the chemotherapy dose rather than use PPG [34]. In our study, antibiotic prophylaxis, dose reductions and dose delays were reported for 0.4, 6 and 3% of cycles, respectively.

The decision on whether to treat with PPG is also influenced by how FN risk is assessed. Our study identified some discrepancies between regimen-based method and HCP-determined risk stratification. In particular, there was a trend towards increased intermediate classification with HCP-determined assignment, as has been observed in other studies [35]. Owing to a lack of guidance PPG use in patients at intermediate risk of FN, the clinical utility of this subgroup must be questioned. There remains a need for clearer information on FN risk assignment [35, 36]. Reflecting this, new guidelines on risk assignment are shortly anticipated from the Multinational Association of Supportive Care in Cancer.

This study has some limitations. Our results may overestimate adherence to guidelines in real-world practice, because physicians choosing to participate may have an increased interest in or awareness of PPG guidelines compared with the general physician population. The cross-sectional/retrospective nature of the study resulted in incomplete information on total chemotherapy planned, which potentially led to an underestimation of chemotherapy dose delays, dose reductions and discontinuations. The analysis of HCP-determined FN risk assessment was based on a relatively small number of patients and, therefore, should be interpreted with caution. Finally, these data reflect PPG use in the outpatient setting,

Table 4 Concordance between regimen-based and HCP-determined FN risk assessment (HCPAS)

HCP-determined FN risk	Regimen-based FN risk, *n* (%)			
	Low (< 10%) ($N = 32$)	Intermediate (10–20%) ($N = 7$)	High (≥ 20%) ($N = 7$)	Total ($N = 46$)
Low (< 10%)	16 (50.0)	1 (14.3)	0 (0)	17 (37.0)
Intermediate (10–20%)	11 (34.4)	5 (71.4)	6 (85.7)	22 (47.8)
High (≥ 20%)	5 (15.6)	1 (14.3)	1 (14.3)	7 (15.2)
Total	32 (69.6)	7 (15.2)	7 (15.2)	46 (100)

FN febrile neutropenia, *HCP* healthcare professional, *HCPAS* HCP-determined FN risk analysis set

and findings should not be extrapolated to the inpatient population; however, it should be noted that most patients with BC will receive treatment in the outpatient setting.

Conclusions

Our results highlight the continuing high need for PPG in patients treated for BC in Belgian clinical practice. However, Belgian reimbursement criteria prevented adherence to clinical practice guidelines for about one quarter of patients, and physician-led treatment decisions restrict treatment for a further 10% of patients. Better adherence to the EORTC guidelines within the boundaries of the current reimbursement criteria may already improve outcome.

Acknowledgments Authors had access to primary data, analyses and study reports. Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: http://www.amgen.com/datasharing.

Funding information Amgen Inc. ran and funded this study, all analyses and the medical writing support. Medical writing support, funded by Amgen Belgium, was provided by Kelly Soady PhD of Oxford PharmaGenesis, Oxford, UK.

Compliance with ethical standards

Florence Van Rijckegem, Chloë Haverbeke, Wim Wynendaele and Simon Van Belle have no conflicts of interest to disclose; Guy Jerusalem disclosed consulting fees from Amgen; Luc Somers is an external consultant to Amgen BeLux; Anke Van den broeck and Sofie Vingerhoedt are employees of Amgen BeLux.

Conflicts of interest The authors declare that they have no conflicts of interest.

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