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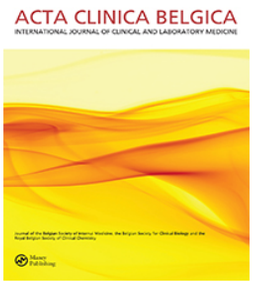

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# Neutropenia management in patients receiving myelosuppressive polychemotherapy for early breast cancer in Belgium: BRONS study results

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**ABSTRACT**

**Background**: Chemotherapy plays an important role in the treatment of early breast cancer (EBC). Granulocyte-colony stimulating factors (G-CSF) can reduce the risk of febrile neutropenia as primary prophylaxis (PP) or secondary prophylaxis (SP). The BRONS study investigated the incidence of serious neutropenic events (SNE) and G-CSF use in a Belgian population of EBC patients treated with myelosuppressive polychemotherapy.

**Methods**: Conducted in 2011, this study was a prospective, multicentre, observational trial involving 260 patients. The primary endpoint was the incidence of SNE defined as either febrile neutropenia (FN) or prolonged severe neutropenia (PSN; neutrophil count $\leq 0.5 \times 10^9$ for at least five days). Secondary endpoints included a description of the chemotherapeutic regimens prescribed and G-CSF use.

**Results**: Nine percent of patients were treated with a dose-dense regimen (DD) and 91% received classical chemotherapy (CC). PP with G-CSF (PPG) was given to 20% of patients (100% in DD and 11% in CC). Eighteen percent of patients presented a SNE (4% in DD and 20% in CC) of which 15% were FN and 3% PSN. SNE occurrence was 8% in the PPG subgroup and 21% in the no-PPG subgroup. In the DD subgroup, all patients received PPG and no FN was reported. Twenty six adverse events related to G-CSF were reported in 8.2% of patients and two of these were classified as severe.

**Conclusion**: This observational study highlights the high incidence of SNE with CC regimens in patients who do not receive PPG. It also confirms the safe profile of DD regimens with G-CSF support.

**KEYWORDS**
Breast cancer; neutropenia; G-CSF; prophylaxis; chemotherapy

## Introduction

Breast cancer (BC) is the most frequently diagnosed cancer and the leading cause of cancer-related death in Belgian women with an incidence and mortality of 147.5 and 29.5 per 100,000 cases in 2012, respectively [1]. While chemotherapy plays an important role in the adjuvant/neoadjuvant setting, its precise indications remain a matter of debate. The decision to initiate chemotherapy should be based on tumour biology (expression of hormone receptors, human epidermal growth factor receptor 2 (HER2) status, histological grade, Ki67), tumour extension (size, nodal status, lymphovascular invasion) and a patient's comorbidities and preferences. Different scoring systems calculating the individual risk of relapse and death from BC have been developed (Adjuvant online! [2]; PREDICT Tool [3]). Genomic tests may also help with the decision of selected patients. Adjuvant/neoadjuvant chemotherapy is now recommended in most high risk (HR) luminal B patients, HER2-positive and triple negative BC [4]. Different treatment regimens have been evaluated with the sequential use of an anthracycline-taxane regimen demonstrating superiority in terms of disease-free survival (DFS) and overall survival (OS) over an anthracycline-based regimen alone [5].

Attention has also focused on trying to reduce the toxicity of chemotherapy regimens whilst maintaining their optimal efficacy. Haematological toxicity remains one of the main concerns due to the associated risk of infectious complications that correlates with the duration of grade 4 neutropenia and the depth of the neutrophil count nadir [6]. FN still occurs in eight out of every 1000 patients receiving (neo)adjuvant chemotherapy [7]. Such events can lead to delays in subsequent cycles and can negatively affect pre-planned dose delivery that can impair outcomes (DFS and OS) [8]. Prevention of FN remains a major concern.

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Primary prophylaxis (PP) with granulocyte-colony stimulating factors (G-CSF) can reduce the related need for hospital admission, intravenous antibiotics, and dose delay or dose reduction [9].

G-CSF can be used as PP or secondary prophylaxis (SP) [10]. EORTC [11] and ESMO [12] guidelines recommend the use of G-CSF as PP for chemotherapy regimens where the risk of FN is superior to 20% (HR). For chemotherapy regimens with a 10–20% probability of FN (intermediate risk, IR), the recommendation is to evaluate the individual risk by considering other prognostic factors (age > 65 years, advanced disease, history of prior FN, mucositis, poor performance status and/or cardiovascular disease) [12]. In BC, filgrastim (plasma half-life of 3–4 h and daily sub-cutaneous administration) and pegfilgrastim (prolonged plasma half-life and only one administration) are the most investigated molecules. Two phase 3 studies confirmed the non-inferiority of pegfilgrastim over filgrastim in terms of efficacy and safety as PP in patients who received combined doxorubicin (60 mg/m$^2$) and docetaxel (75 mg/m$^2$) [13,14]. Thereafter, a meta-analysis of five different trials (including these two phase 3 studies) established the superiority of pegfilgrastim over filgrastim to reduce the incidence of FN [15].

In 2009, the Belgian government decided to reimburse PP with G-CSF (PPG) for early breast cancer (EBC) patients undergoing adjuvant or neoadjuvant chemotherapy who meet the following criteria: (i) age ≥65 years treated with a regimen that includes an anthracycline and/or taxane and (ii) patients treated concomitantly with an anthracycline and a taxane, or a dose-dense (DD) regimen (i.e. epirubicin and cyclophosphamide two weekly followed by weekly paclitaxel), irrespective of age.

The BRONS study prospectively investigated the management of neutropenia in a Belgian population of EBC patients treated with myelosuppressive polychemotherapy. The incidence of serious neutropenic events (SNE), choice and administration of chemotherapy, and use of G-CSF in a daily clinical practice, is described.

## Methods

### Study design and population

This trial was designed as a prospective, multicentre, observational study. Fifteen sites in Belgium were selected to participate with the objective to represent the landscape of BC centers in Belgium. Patients were required to be ≥18 years old, diagnosed with EBC, and scheduled for myelosuppressive adjuvant or neoadjuvant polychemotherapy including an anthracycline (A) and/or taxanes (T), or a DD regimen. No previous enrolment in a clinical trial with protocol-specified G-CSF use was allowed. The choice of chemotherapy and G-CSF were at the discretion of the medical oncologist in charge. This study was sponsored and financed by Amgen (Brussels, Belgium). The manuscript was written by the investigators.

### Endpoints and objectives

The primary endpoint of the study was to evaluate the incidence of SNE, defined as FN [absolute neutrophil count (ANC) ≤ 0.5 × 10$^9$ and fever >38°C], or prolonged severe neutropenia (PSN; ANC ≤0.5 × 10$^9$ for at least 5 days), in the overall population and in different sub-groups: DD and classical chemotherapy (CC) regimens; PPG and no PPG). Secondary endpoints included a description of (i) PPG use by type of chemotherapeutic regimen, including anthracycline (A), taxane (T), concomitant anthracycline/taxane (AT), sequential anthracycline-taxane (A-T), sequential taxane-anthracycline (T-A) or classical CMF (Cx) (Table 1); (ii) PPG use by regimen 'FN-risk' category defined as high (H), intermediate (I), low (L) or undefined if

Table 1. Type and reference doses of classical chemotherapy (CC) regimens.

| | Type | Product 1 | Product 2 | Product 3 | Product 4 |
|---|---|---|---|---|---|
| High risk | | | | | |
| FEC-D | A-T | Fluorouracil: 500 | Epirubicin: 100 | Cyclophosphamide: 500 | Docetaxel: 100 |
| D-FEC | T-A | Docetaxel: 100 | Fluorouracil: 500 | Epirubicin: 100 | Cyclophosphamide: 500 |
| EC-D | A-T | Epirubicin: 90 | Cyclophosphamide: 600 | Docetaxel: 100 | |
| AC-D | A-T | Doxorubicin: 60 | Cyclophosphamide: 600 | Docetaxel: 100 | |
| Intermediate risk | | | | | |
| FEC | A | Fluorouracil: 500 | Epirubicin: 100 | Cyclophosphamide: 500 | |
| FEC-P80 | A-T | Fluorouracil: 500 | Epirubicin: 100 | Cyclophosphamide: 500 | Paclitaxel (*) : 80 |
| FEC-P175 | A-T | Fluorouracil: 500 | Epirubicin: 100 | Cyclophosphamide: 500 | Paclitaxel: 175 |
| TC | T | Docetaxel: 75 | Cyclophosphamide: 600 | | |
| XDOC | T | Capecitabine: 2500 | Docetaxel: 75 | | |
| Low risk | | | | | |
| EC | A | Epirubicin: 90 | Cyclophosphamide: 600 | | |
| AC | A | Doxorubicin: 60 | Cyclophosphamide: 600 | | |
| AC-P80 | A-T | Doxorubicin: 60 | Cyclophosphamide: 600 | Paclitaxel (*) : 80 | |
| CMF ** | Cx | Fluorouracil: 600 | Cyclophosphamide: 100 | Methotrexate: 40 | Fluorouracil: 600 |

*Doses reflect 3-weekly frequency of administration except for doses marked with an asterix (*) which are given on a weekly basis, and the CMF regimen marked ** (classical CMF) which is given in a 28-day regimen, with fluorouracil and methotrexate administered intravenously on days 1 and 8, and cyclophosphamide administered orally on days 1–14.*

planned dose <90% of reference dose (U); (iii) PPG use by age (<65 years or ≥65 years); (iv) estimation of PSN and FN by regimen 'FN-risk' category (H, I, L, U), PPG use (yes, no), and age (<65 years, ≥65 years); (v) chemotherapy administration (dose delays and dose reductions) by category of regimen, PPG use and age; (vi) occurrence of neutropenia and unplanned hospital admissions or visits.

### *Statistical analysis*

The statistical analysis was purely descriptive.

## Results

### *Population and treatment characteristics*

Two hundred and sixty patients were recruited from 14 of the 15 selected Belgian centres between 6/12/2010 and 19/08/2011. The last round of chemotherapy was administered on 02/02/2012. Two hundred and fifty-four patients were evaluable for the primary endpoint (Figure 1). Twenty-four patients (9%) received a DD regimen and 230 patients (91%) were treated with CC. CC was considered to be of HR for FN in 75% of these patients, IR in 17%, low risk in 2% and undefined risk in 6%.

The demographics and tumour characteristics are described in Table 2. Patients treated with DD were on average 10 years younger than those who received CC (44.4 versus 54.4 years, respectively) had a lower body mass index (BMI) and body surface area (BSA), were in better general condition according to ECOG performance status, and presented more aggressive tumours based on histological grade and hormonal status. In the CC group, 85% of the patients were aged <65 years. There were no relevant differences in patient and tumour characteristics across the regimen FN-risk groups receiving CC.

Treatment characteristics are listed in Table 3. All 24 patients in the DD group were treated with an A-T regimen. Of these, 92% received combined epirubicin/cyclophosphamide followed by paclitaxel (DD EC-P). All DD patients received PPG. In the CC group, the majority of patients (83%) were treated with an A-T regimen and of these 93% received combined 5-fluorourcil/epirubicin/cyclophosphamide followed by docetaxel (FEC-D). Eleven percent were treated with an A-based regimen and 5% with a T-based regimen. Seventy-five percent of the CC regimens were classified as being at HR of FN, yet only 11% of the patients who received CC also received PPG, and all were aged ≥65 years, in line with the Belgian reimbursement criteria at the time. HR regimens consisted of FEC-D

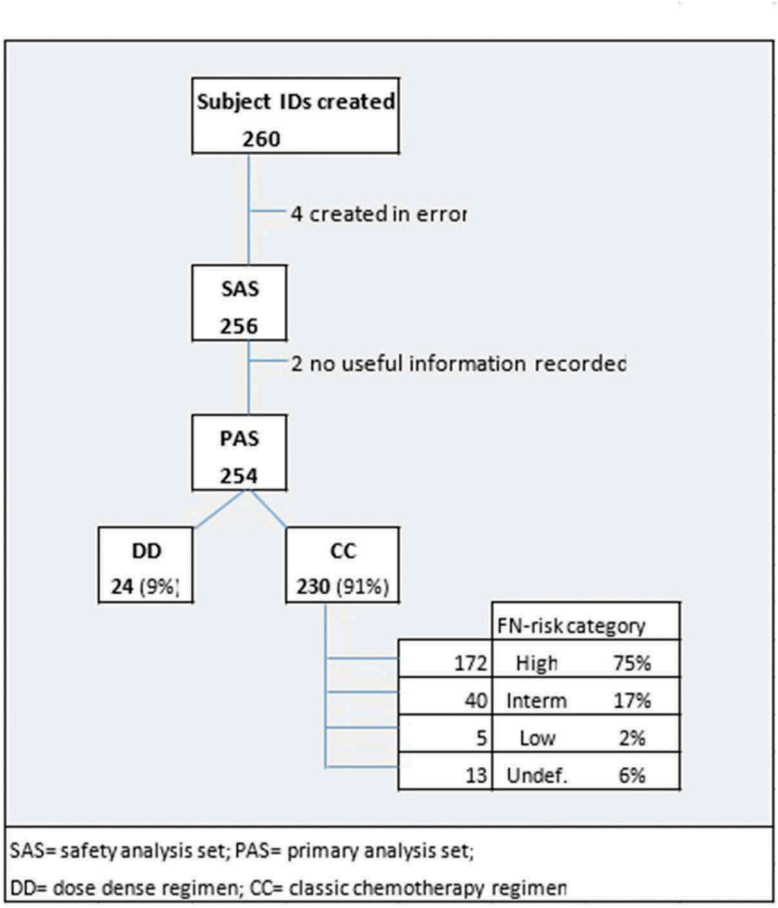


Figure 1. Flowchart of the BRONS study.

Table 2. Patient demographics, performance status, histological grade and hormone status.

| Demographics | | ALL (*N*) 254 | % 100% | DD (*N*) 24 | % 9% | CC (*N*) 230 | % 91% |
|---|---|---|---|---|---|---|---|
| Age | Mean (years) | **53,4** | | 44,4 | | 54,4 | |
| | Min/max (years) | **29,2/82,2** | | 33,6/67 | | 29,2/82,2 | |
| | <65 years | **219** | **86%** | 23 | 96% | 196 | 85% |
| Gender | Male | **1** | **0,4%** | | | 1 | |
| Etnhicity | White/caucasion | **249** | **98%** | | | | |
| BMI | Mean (ratio) | **26,34** | | 23,22 | | 26,66 | |
| BSA | Mean ($m^2$) | **1,75** | | 1,68 | | 1,76 | |
| PS | ECOG 0 | **218** | **90%** | 23 | 96% | 195 | 89% |
| Histological grade | Grade 1 | **23** | **9%** | 0 | 0% | 23 | 10% |
| | Grade 2 | **90** | **36%** | 4 | 17% | 86 | 38% |
| | Grade 3 | **133** | **53%** | 20 | 83% | 113 | 49% |
| Stage (AJCC 7th) | Stage I | **62** | **24%** | 9 | 38% | 53 | 23% |
| | Stage IIa | **83** | **33%** | 9 | 38% | 74 | 32% |
| | Stage IIb | **57** | **22%** | 1 | 4% | 56 | 24% |
| | Stage IIIa | **30** | **12%** | 4 | 17% | 26 | 11% |
| | Stage IIIb | **5** | **2%** | 0 | 0% | 5 | 2% |
| | Stage IIIc | **12** | **5%** | 1 | 4% | 11 | 5% |
| | Stage IV | **3** | **1%** | 0 | 0% | 3 | 1% |
| | Unknown | **2** | **1%** | 0 | 0% | 2 | 1% |
| Hormonal status | ER+ | **184** | **73%** | 13 | 54% | 171 | 74% |
| | PR+ | **152** | **60%** | 8 | 33% | 144 | 63% |
| | HER-2 +++ | **61** | **24%** | 6 | 25% | 55 | 24% |
| Comorbidities | 0 | **182** | **72%** | 22 | 92% | 160 | |
| | Any significant | **72** | **28%** | 2 | 8% | 70 | 30% |
| | 1 | **39** | **15%** | 1 | 4% | 38 | 17% |

DD = dose-dense regimen; CC = lassical chemotherapy; BMI = body mass index; BSA = body surface area; PS = performance status; AJCC = American Joint Committee on Cancer; ER = estrogen receptor; PR = progesterone receptor; HER-2 = human epidermal growth factor receptor 2

Table 3. Treatment characteristics.

| Treatment | | ALL (*N*) | ALL (%) | DD (*N*) | DD (%) | CC (*N*) | CC (%) |
|---|---|---|---|---|---|---|---|
| Chemotherapy | A-T/T-A | **214** | **84%** | 24 | 100% | 190 | 83% |
| Category | A | **26** | **10%** | | | 26 | 11% |
| | T | **11** | **4%** | | | 11 | 5% |
| | Other | **3** | **1%** | | | 3 | 1% |
| Regimen FN-risk | High | **196** | **77%** | 24 | 100% | 172 | 75% |
| Category | Intermediate | **40** | **16%** | | | 40 | 17% |
| | Low | **5** | **2%** | | | 5 | 2% |
| | Undefined | **13** | **5%** | | | 13 | 6% |
| G-CSF use | PPG given | **50** | **20%** | 24 | 100% | 26 | 11% |

DD = dose-dense regimen; CC = classical chemotherapy; A = anthracycline; T = taxane; FN = febrile neutropenia; G-CSF = granulocyte-colony stimulating factor; PPG = primary prophylaxis with G-CSF.

in 98%, D-FEC in 0.6%, AC-D in 0.6% and EC-D in 0.6% of patients (data not shown).

## Primary endpoint

Results of the primary objective are summarised in Table 4. Eighteen percent (46/254) of the patients experienced at least one SNE consisting of FN in 15% and PSN in 3%. In the DD group, 1 out of 24 patients (4%) presented with a SNE consisting of PSN. In the CC group, 45 out of 230 patients (20%) presented with a SNE (17% FN and 3% PSN). Irrespective of PPG, SNE occurred in 20% of patients aged <65 years and in 15% of those aged ≥65 years.

The planned analysis of the PPG subgroups showed that 8% and 21% of the population experienced a SNE in the PPG and no-PPG subgroups, respectively. In the HR CC regimens, a SNE occurred in 8% of patients in the PPG subgroup and in 23% in the no-PPG subgroup. Within the IR group, SNE were reported in 20% and 17% of patients treated with or without PPG, respectively.

Six patients ≥65 years did not receive PPG although they were eligible under the Belgian reimbursement criteria. In CC patients <65 years who did not receive PPG, 40 out of 196 (20%) experienced a SNE. An analysis of age and use or omission of PPG in regimens at HR of FN (DD and HR CC, 196 patients) demonstrated that SNE occurred in 4% of patients aged <65 years who received PPG (all treated by DD), 8% of patients aged ≥65 years who received PPG, 22% of no-PPG patients aged <65 years, and 33% of no-PPG patients aged ≥65 years.

## Secondary endpoints

### Febrile neutropenia

No patient in the DD group experienced FN. In the CC subgroup, 7% of the patients who received PPG experienced FN (all were treated by IR regimens) compared to 18% in the no-PPG population (mostly patients treated by HR regimens).

### G-CSF administration

Fifty-six percent of the overall population (142/254 patients) received G-CSF at one time (Table 5). All patients treated with DD regimens received pegfilgrastim as PPG. In the CC subgroup, 118 patients (51%) were treated with G-CSF either as PPG (23%), or for chemotherapy-induced neutropenia or SP (77%). In the 'no-PPG planned' subgroup in which patients received a CC regimen without PPG from the first cycle, 45% (91/203 patients) eventually

Table 4. Number and percentage of subjects experiencing at least one SNE.

| | | ALL *N* (%) | DD *N* (%) | CC *N* (%) | High *N* (%) | Int *N* (%) | Low *N* (%) | Undef. *N* (%) |
|---|---|---|---|---|---|---|---|---|
| Population | ***N* = 254** | **254 (100%)** | 24 (9%) | 230 (91%) | 172 (75%) | 40 (17%) | 5 (2%) | 13 (6%) |
| | At least 1 SNE (*N*) | **46** | 1 | 45 | 37 | 7 | 0 | 1 |
| | (% of pop.) | **18%** | 4% | 20% | 22% | 18% | 0% | 8% |
| Age group (year) | **<65 (*N*)** | **219** | 23 | 196 | 154 | 29 | 4 | 9 |
| | At least 1 SNE (*N*) | **41** | 1 | 40 | 34 | 5 | 0 | 1 |
| | (% of <65) | **19%** | 4% | 20% | 22% | 17% | 0% | 11% |
| | **≥65 (*N*)** | **35** | 1 | 34 | 18 | 11 | 1 | 4 |
| | At least 1 SNE (*N*) | **5** | 0 | 5 | 3 | 2 | 0 | 0 |
| | (% of ≥65) | **14%** | 0% | 15% | 17% | 18% | 0% | 0% |
| Planned G-CSF | **PPG (*N*)** | **51** | 24 | 27 | 12 | 10 | 1 | 4 |
| | At least 1 SNE (*N*) | **4** | 1 | 3 | 1 | 2 | 0 | 0 |
| | (% of PPG) | **8%** | 4% | 11% | 8% | 20% | 0% | 0% |
| | **No PPG (*N*)** | **203** | 0 | 203 | 160 | 30 | 4 | 9 |
| | At least 1 SNE (*N*) | **42** | | 42 | 36 | 5 | 0 | 1 |
| | (% of no PPG) | **21%** | | 21% | 23% | 17% | 0% | 11% |
| Age+G-CSF | **PPG & <65 (*N*)** | **23** | 23 | 0 | | | | |
| | At least 1 SNE (*N*) | **1** | 1 | | | | | |
| | (% of PPG & <65) | **4%** | 4% | | | | | |
| | **PPG & ≥ 65 (*N*)** | **28** | 1 | 27 | 12 | 10 | 1 | 4 |
| | At least 1 SNE (*N*) | **3** | 0 | 3 | 1 | 2 | 0 | 0 |
| | (% of PPG & ≥ 65) | **11%** | 0% | 11% | 8% | 20% | 0% | 0% |
| | **No PPG & <65 (*N*)** | **196** | 0 | 196 | 154 | 29 | 4 | 9 |
| | At least 1 SNE (*N*) | **40** | | 40 | 34 | 5 | 0 | 1 |
| | (% of no PPG & <65) | **20%** | | 20% | 22% | 17% | 0% | 11% |
| | **No PPG ≥ 65 (*N*)** | **7** | 0 | 7 | 6 | 1 | 0 | 0 |
| | At least 1 SNE (*N*) | **2** | | 2 | 2 | 0 | | |
| | (% of no PPG & ≥ 65) | **29%** | | 29% | 33% | 0% | | |

DD = dose-dense regimen; CC = classical chemotherapy; High = high risk of febrile neutropenia (FN); Int = intermediate risk of FN; Low = low risk of FN; Undef = undefined risk of FN; SNE = serious neutropenic event; G-CSF = granulocyte-colony stimulating Factor; PPG = primary prophylaxis with G-CSF.

Table 5. G-CSF use.

| | G-CSF administration ? | ALL (*N* = 254) *N* (%) | DD (*N* = 24) *N* (%) | CC (*N* = 230) *N* (%) |
|---|---|---|---|---|
| ALL *N* = 254 | No | **112 (44%)** | 0 (0%) | 112 (49%) |
| | Yes | **142 (56%)** | 24 | (100%) |
| 118 (51%) | | | | |
| | Peg. only | **119** | 24 | 95 |
| | (% of Yes) | **84%** | 100% | 81% |
| | Daily G-CSF & Peg. | **23** | 0 | 23 |
| | (% of Yes) | **16%** | 0% | 19% |
| No PPG planned from 1st cycle *N* = 203 | No (*N*) | **112** | 0 | 112 |
| | (%) | **55%** | 0% | 55% |
| | Yes (*N*) | **91** | 0 | 91 |
| | (%) | **45%** | 0% | 45% |
| | Peg. only (*N*) | **68** | 0 | 68 |
| | (% of Yes) | **75%** | 0% | 75% |
| | Daily G-CSF & Peg. | **23** | 0 | 23 |
| | (% of Yes) | **34%** | 0% | 34% |
| PPG plannedplanned from 1st cycle *N* = 51 | No (*N*) | **0** | 0 | 0 |
| | (%) | **0%** | 0% | 0% |
| | Yes (*N*) | **51** | 24 | 27 |
| | (%) | **100%** | 47% | 53% |
| | Peg. only | **51** | 24 | 27 |
| | (% of Yes) | **100%** | 100% | 100% |
| | Daily G-CSF & Peg. | **0** | 0 | 0 |
| | (% of Yes) | **0%** | 0% | 0% |

G-CSF = granulocyte-colony stimulating factor; DD = dose-dense regimen; CC = classical chemotherapy; Peg. = pegfilgrastim; PPG = primary prophylaxis with G-CSF.

received G-CSF. Among these 91 patients, 68 (75%) received pegfilgrastim alone, and 23 (25%) received both pegfilgrastim and daily G-CSF which was given with therapeutic intent to 17 patients (83%) and with prophylactic intent to four patients (17%).

### *Dose delays*

Forty patients (16% in the PPG subgroup and 16% in the no-PPG subgroup) had at least one cycle of chemotherapy delayed for more than three days mainly due to FN or chemo-induced neutropenia (CIN) (15), subject preference (11) or logistics (7). The rate of dose delays within the DD or CC regimens were not recorded.

Dose reductions occurred in 31 patients representing 12% of the overall population. In the DD regimen subgroup, only two subjects (8%) required dose reduction (data not shown). In PPG and no-PPG population, dose had to be reduced in 20% and 10%, respectively.

### *Haematological toxicities*

Of the patients who received CC, 65% experienced grade 3 (G3) or grade 4 (G4) neutropenia (grade 3, 16%; grade 4, 49%). There was proportionally more neutropenia in the no-PPG subgroup compared to the PPG subgroup (69% versus 23% of patients, respectively). Conversely, 88% of patients treated with a DD regimen were free of G3-G4 neutropenia including those aged ≥65 years. Thirty-five patients in the overall population (14%) were treated with broad spectrum intravenous antibiotics (all were from the CC subgroup), and 50 patients (20%) experienced an unplanned hospital admission (8% in the DD regimen

group and 21% in the CC group). There were no major differences with regards to age, PPG-use and FN-risk regimen subgroups in admitted patients. Hospital admission was primarily due to FN and CIN (47%) (data not shown).

### *Adverse drug reactions*

Adverse drug reactions (ADR) specific to G-CSF use were reported in 21 patients (8% of the general population), and consisted of pyrexia (1), spinal pain (1), back pain (6), bone pain (6), musculoskeletal pain (9), pain in one or more extremities (1) and headache (2). Seventeen of these ADRs were classified as mild, seven as moderate, and two as severe: 1 bone pain and 1 headache.

### *Exploratory analysis*

The type of chemotherapy prescribed by participating centres was analysed and showed that only four out of the 14 centres (29%) used DD regimens in 24 of the 254 patients (9%). FEC-D was the most frequently used regimen (70% of patients). Paclitaxel was used in 23 out of the 24 DD regimen patients (96%), and docetaxel in 193 out of the 203 CC patients (95%). In the FEC-D subgroup, PPG was used in 8% of patients. Overall, 20% of the FEC-D patients experienced a SNE (FN in 17% and PSN in 3%).

An analysis of the use of PPG in accordance with the Belgian reimbursement criteria or EORTC guidelines demonstrated that all 50 patients who were treated with PPG met the reimbursement criteria. According to the EORTC recommendations, 172 patients who received a CC regimen at HR of FN were eligible for PPG, but only 14 (8%) received it.

## Discussion

This study set out to prospectively evaluate the rate of SNE experienced by patients treated with adjuvant chemotherapy for EBC in Belgium. An overall rate of 18% was found with 15% and 3% of patients experiencing FN and PSN, respectively. Further analysis demonstrated that SNE occurred in 4% of patients treated with a DD regimen and in 20% of those treated with CC. Medical oncologists also adhered to the reimbursement criteria as all PPG prescriptions met the reimbursement guidelines. BRONS study is a small multicentre observational trial that therefore requires cautious data interpretation. There is no information regarding frequency of full blood count analysis and most patient have probable not underwent repeated blood sampling between chemotherapy dosing. PSN is therefore probably underestimated for methodological reason. Nevertheless, this study provides a very good overview of the use of adjuvant chemotherapy and G-CSF in EBC in Belgium.

It is worth highlighting that BRONS was conducted in 2011 when FEC-docetaxel was still the leading regimen in the adjuvant setting. Since then, new practice changing data have emerged. First, the addition of 5-fluorouracil to an anthracycline-taxane regimen was shown not to offer any advantage in terms of DFS and only led to more toxicity [16]. Second, weekly paclitaxel and 3-weekly docetaxel were shown to be superior to 3-weekly paclitaxel in terms of DFS [17]. In the same study, only weekly paclitaxel demonstrated an OS advantage and appeared to be less toxic, with the exception of peripheral neuropathy. It has now also been shown that anthracyclines may be omitted for small (<3 cm), node negative, HER-2 positive tumours [18]. Consequently, a clear trend in favour of epirubicin/cyclophosphamide three weekly for four cycles followed by paclitaxel weekly for 12 cycles (4EC-12Pac) came to the fore in the adjuvant setting, as noted in the 2014 Belgian Society of Medical Oncology (BSMO) Breast Cancer Task Force report. This report also recommended that DD regimens be reserved for specific situations, such as triple negative BC and node positive patients [19].

Secondary endpoints included an analysis of neutropenic events according to treatment regimen, enabling comparison between the rates of SNE in the BRONS study with data from pivotal studies although this comparison has many methodological limitations.

The FEC-D regimen was validated in the PACS01 trial which reported G3-G4 neutropenia in 28.1% of patients on day 21, and an 11.2% rate of FN [20]. This regimen was given to 70% of patients in the BRONS study with a corresponding rate of FN of 17%. In the PACS01 trial, all patients were node positive and the median age was 50 years. The mean age of patients receiving CC in the BRONS study was 54.4 years, and node negative patients were also included. Within the limitations of cross-trial comparisons, FEC-D appears to be more toxic in BRONS study participants compared to those in PACS01. Other clinical trials have indicated a rate of FN in excess of 20% with the FEC-D regimen [21]. This highlights the need to confirm pivotal study data in more real life and specific populations.

With regards to DD regimens, data from the phase 3 trial comparing FEC with 2-weekly EC plus PPG followed by paclitaxel or 3-weekly EC followed by paclitaxel (2 weekly in this study) showed that 10% of patients experienced G3-G4 neutropenia in the ddEC-P population [16]. This is consistent with the rate of 12.5% of G3-G4 neutropenia found in the DD BRONS population. It confirms the feasibility of DD regimens and their lower risk of neutropenic events, as pointed out in a meta-analysis of four other DD studies in adjuvant BC [22].

Sparano and colleagues reported a FN rate of 8% in the AC-paclitaxel weekly arm (7% during AC cycles

and 1% during paclitaxel cycles) compared to 22% in the AC-docetaxel 3-weekly arm (6% during AC cycles and 16% during docetaxel cycles), highlighting the favourable haematological safety profile of weekly paclitaxel [17]. Based on this data, EC/AC followed by weekly paclitaxel can be classified as being at low risk of FN and PPG is not warranted. Conversely, 3-weekly docetaxel-based regimens, such as AC-D and FEC-D seem to have a HR of FN. One of the reasons for the continued use of docetaxel is that it produces far less neuropathy than paclitaxel, as clearly reported [17] and permits less visits to hospitals.

At the time of the study, Belgian government reimbursed the cost of G-CSF as PP against FN only in EBC patients treated with an anthracycline and/or taxane who are ≥65 years old. This seems to be in line with the BRONS study findings. In the overall population, we saw a clear relationship trend between age and risk of SNE: 4% in the PPG and age <65 years population (all treated by DD), 11% in the PPG and age ≥65 years, 20% in the no-PPG and age <65 years, and 29% in the no-PPG and age ≥65 years. If we focus on FN in the no-PPG patients treated with HR CC regimens (FEC-D in 98.2%), FN occurred in 19% who were <65 years old and in 33% aged ≥65 years (Table 6). As a result and based on EORTC/ESMO guidelines and classification, FEC-D may be classified as an HR regimen in patients ≥65 years and an IR regimen in patients <65 years among whom the rate of FN remains non-negligible.

In conclusion, regarding FEC-D patients, this analysis supports the new Belgian reimbursement criteria for PPG updated in February 2018. Indeed, PPG reimbursement can now also be offered to patients treated with IR regimen when additional risk factors would be present or in order to prevent any dose delay/dose reduction in an adjuvant curative setting. BRONS data also confirm that the age of patients remains an important FN-risk factor. It opens the question to reliable prognostic tools designed to predict an accurate FN-risk, especially for young patients treated by low risk regimens like the now commonly used EC/AC-P regimen.

Table 6. Febrile neutropenia outcome by age group and planned G-CSF strategy.

| | | ALL *N* | CC *N* (% of all) | High *N* (% of all) |
|---|---|---|---|---|
| Population | ***N* = 254** | **254** | 230 (91%) | 172 (75%) |
| | At least 1 FN (*N*) | **38** | 38 | 31 |
| | (% of pop.) | **15%** | 17% | 18% |
| **Age + G-CSF** | **PPG & <65 (*N*)** | **23** | 0 | 0 |
| | At least 1 FN (*N*) | **0** | | |
| | (% of PPG & <65) | **0%** | | |
| | **PPG & ≥ 65 (*N*)** | **28** | 27 | 12 |
| | At least 1 FN (*N*) | **2** | 2 | 0 |
| | (% of PPG & ≥ 65) | **7%** | 7% | |
| | **No PPG & <65 (*N*)** | **196** | 196 | 154 |
| | At least 1 FN (*N*) | **34** | 34 | 29 |
| | (% of no PPG & <65) | **17%** | 17% | 19% |
| | **No PPG ≥ 65 (*N*)** | **7** | 7 | 6 |
| | At least 1 FN (*N*) | **2** | 2 | 2 |
| | (% of no PPG & ≥ 65) | **29%** | 29% | 33% |

CC = Classical chemotherapy; High = High risk of febrile neutropenia; FN = Febrile neutropenia; G-CSF = Granulocyte-Colony Stimulating Factor; PPG = Primary Prophylaxis with G-CSF.

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