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ORIGINAL RESEARCH



## Management and cost analysis of cancer patients treated with G-CSF: a cohort study based on the French national healthcare insurance database

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### ABSTRACT

**Objectives:** To describe the management and costs associated with G-CSF therapy in cancer patients in France.

**Methods:** This study analyzed a representative random population sample from the French national healthcare insurance database, focusing on 1,612 patients with hematological or solid malignancies who were reimbursed in 2013 or 2014 for at least one G-CSF treatment dispensed in a retail pharmacy. Patient characteristics and treatment costs were analyzed according to the type of cancer. Then the costs and characteristics of patients associated with the use of different G-CSF products were analyzed in the sub-set of breast cancer patients.

**Results:** The most frequent malignancies in the database population were breast cancer (23.3%), hematological malignancies (22.2%), and lung cancer (12.4%). The reimbursed G-CSF was pegfilgrastim in 34.1% of cases, lenograstim in 26.7%, and filgrastim in 17.9%. More than one G-CSF product was reimbursed to 21.3% of patients. The total annual reimbursed health expenses per patient, according to the type of G-CSF, were €27,001, €24,511, and €20,802 for patients treated with filgrastim, lenograstim, and pegfilgrastim, respectively. Ambulatory care accounted for, respectively, 35%, 38%, and 41% of those costs. In patients with breast cancer, ambulatory care cost was €7,915 with filgrastim, €7,750 with lenograstim, and €6,989 with pegfilgrastim, and the respective cost of G-CSF was €1,733, €1,559, and €3,668.

**Conclusion:** All available G-CSF products have been shown to be effective in cancer patients, and both daily G-CSFs and pegylated G-CSF are recommended in international guidelines. Nevertheless, this analysis of G-CSF reimbursement indicates that the choice of product can markedly affect the total cost of ambulatory care.

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### Introduction

Chemotherapy-induced neutropenia can lead to sepsis and other life-threatening infections, usually after the first treatment cycles<sup>1–6</sup>. Neutropenia can also lead to treatment delays and dose reductions, thus compromising the efficacy of subsequent treatment cycles<sup>7–11</sup>.

International guidelines recommend the use of granulocyte colony-stimulating factor (G-CSF) to prevent febrile neutropenia and, thereby, reduce the need for hospitalization and antibiotic therapy in patients at risk<sup>12–14</sup>. The guidelines of the American Society of Oncology (ASCO), updated in 2015, those of the National Comprehensive Cancer Network (NCCN), issued in 2016, and the 2006 EORTC guidelines updated in 2010 recommend primary G-CSF prophylaxis in patients who have a  $\geq 20\%$  risk of febrile neutropenia on the basis of patient- and treatment-related factors<sup>12–14</sup>. The 2010 EORTC guidelines recommend systematic G-CSF therapy on a case-by-case basis when chemotherapy regimen is associated with febrile neutropenia in 10–20% of patients, taking into account patient-related factors, such as age over 65 years<sup>12</sup>.

Three G-CSF products are currently available, namely filgrastim, lenograstim, and pegfilgrastim. Filgrastim and lenograstim are administered as a series of daily injections, whereas pegfilgrastim is injected only once per chemotherapy cycle. In a systematic review and meta-analysis published in 2007, these products were found to significantly reduce the incidence of febrile neutropenia, with a relative risk of 0.54 (95% CI = 0.43–0.67;  $p < .001$ )<sup>15</sup>. The 2015 update of the ASCO guidelines states that the choice of G-CSF depends on convenience, cost, and the clinical situation<sup>13</sup>.

The efficiency of G-CSF is still controversial in the US<sup>16</sup>, and the level of cost-effectiveness is directly related to the cost of the G-CSF, the rate of the febrile neutropenia<sup>17</sup> induced by the chemotherapy, and could be influenced by other societal costs<sup>18</sup>. A recent review<sup>19</sup> on G-CSF use shows that various determinants should be taken into account by the physician when prescribing G-CSF, and cost is part of these determinants.

The main aim of this study was to describe the management costs of G-CSF-treated cancer patients according to the type of malignancy and the choice of G-CSF product, based

on a cohort drawn from the French national healthcare insurance database during the period 2013–2014. Ambulatory care costs were analyzed separately.

## Materials and methods

### Data source

This retrospective study was based on a sample known as the *Echantillon Généraliste des Bénéficiaires* (EGB), extracted from the French national healthcare insurance database, which covers ~90% of the French population. The EGB is a 1/97 representative random sample of the entire database, and comprises more than 600,000 individuals<sup>20,21</sup>. The database contains patient characteristics (age gender and exemption of copayment), all outpatient reimbursed medical costs, prescriptions, administered laboratory exams and private and public hospital data, and vital status. Data on drugs, with the dates of prescription and the quantities dispensed, have been available since 2003. Previous studies have used this database to analyze drug utilization and exposure<sup>22–24</sup>, and results are considered as relevant for the French population by the Sickness Funds and the HTA French agency (Haute Autorité de Santé).

### Study population

Patients who were reimbursed for at least one G-CSF treatment including biosimilars between January 1, 2013 until December 31, 2014 were identified, and those with a diagnosis of hematological malignancy or solid cancer were included in the study. The G-CSF products available in France (lenograstim, filgrastim (originator and biosimilars), and pegfilgrastim) were identified from the Anatomical Therapeutic Chemical (ATC: L03AA) classification of medicines (WHO).

The data available on G-CSF treatment included the G-CSF product, the dispensing date, and the number of units dispensed in retail pharmacies, where G-CSF is usually dispensed in France<sup>25</sup>. The database contains no information on in-hospital G-CSF consumption. The other extracted variables were age, gender, the administrative area (zip code), the specialty of the prescribing physician, the number of hospitalizations (related/unrelated to chemotherapy/G-CSF treatment), the number of patients receiving free complementary universal health insurance or full healthcare coverage for a chronic disease, and all healthcare resources reimbursed by the French Sickness Funds.

### Statistical analysis

The analyses were essentially descriptive, and no specific hypothesis was tested. Qualitative variables are described as numbers and percentages and quantitative variables as the mean, median, and IQ. Descriptive analyses were performed according to the G-CSF product and the type of cancer. Patients presenting with multiple cancer were grouped together. Characteristics of patients were described in the year of the first delivery of G-CSF over the study period

(2013 or 2014). The duration of treatment with each G-CSF product was estimated, between the first delivery and the last delivery of G-CSF observed during the 2-year period, from the number of units dispensed by the pharmacy multiplied by the mean number of dispensing dates. For pegfilgrastim, a correction multiplication factor of 11 days was used, according to the results of a pivotal clinical trial<sup>26</sup>.

### Economic analysis

The healthcare payer's perspective was adopted, and costs were complete costs. The total cost calculated for the year 2013 or 2014 for each patient included all items eligible for reimbursement: medical fees, drugs, laboratory tests, nursing care, physiotherapy, medical devices, transportation, and hospitalization. Hospitalization could be either outpatient (= day care hospital) or inpatient hospitalization (at least 1 night stay). Ambulatory and hospitalization costs were separately analysed, because ambulatory costs are collected for each reimbursed item by the Sickness Funds, and hospitalization costs are estimated from a national cost estimate of their DRG.

Annual costs were estimated for the whole population and according to the type of cancer. To avoid bias, annual costs were only considered for the year during which G-CSF was dispensed, and costs were those of the entire year. Total costs for patients who were treated during the whole 2-year study period were halved.

A separate cost analysis was performed according to the G-CSF product in the most represented sub-set of patients (i.e. with breast cancer). Moreover, the breast cancer sub-group was deemed more homogeneous than the hematological malignancies sub-group, since the latter comprises different entities such as Non-Hodgkin Lymphoma and Acute Leukemia, with very different patient management. We described the costs of the patients according to their main available characteristics, in order to present the real-life use in France of the different types of G-CSF.

SAS software version 9.3 (SAS Institute, Cary, NC) was used for statistical analyses.

## Results

### Pharmacoepidemiology and consumed resources

#### Characteristics of patients identified in the database

During the study period 2013–2014, 1,662 patients received at least one reimbursement for G-CSF out of a total of 627,418 patients in the EGB database. Fifty of these patients had no recorded cancer diagnosis and were excluded. The study population, therefore, consisted of 1,612 cancer patients who received G-CSF, and their main characteristics are described in Table 1.

The most frequent malignancies were breast cancer (23.3%), hematological malignancies (22.2%), lung cancer (12.4%), and colorectal cancer (5.8%). Mean age was 62 years (SD = 13.7) (ranging from 57 years (SD = 12.4) in the breast cancer group to 65 years (SD = 11.4) in the colorectal cancer

**Table 1.** Patients characteristics and G-CSF product according to cancer type.

	Breast cancer (n = 375)	Hematological malignancy <sup>b</sup> (n = 358)	Lung cancer (n = 201)	Colorectal cancer (n = 95)	Other solid tumors <sup>c</sup> (n = 583)	Total patients included (n = 1,612)	p
Men, %	1.1	53	67	59	57	44.5	<.0001
Age (years), mean (SD)	56.6 (12.4)	64.0 (16.6)	63.9 (9.3)	64.7 (11.4)	63.0 (13.7)	62 (14)	<.0001
Died in 2013/2014, n (%)	31 (8.3%)	63 (17.6%)	98 (48.8%)	25 (26.3%)	219 (37.6%)	27.0	<.0001
G-CSF product <sup>a</sup> , %							
Filgrastim	17	49	30	38	31	32	<.0001
Lenograstim	33	49	38	57	43	42	<.0001
Pegfilgrastim	66	36	54	26	47	49	<.0001
Interval between chemotherapy cures $\geq 18$ days, %	83	67	68	50	61	68	<.0001

<sup>a</sup>At least one G-CSF product during the study period (the total of the column can exceed 100%).

<sup>b</sup>Hodgkin lymphoma = 35, Other lymphoma = 187, multiple myeloma = 70, lymphoid leukemia = 49, myeloid leukemia = 15, others = 2.

<sup>c</sup>Other solid tumors: Female genital organs = 80, Male genital organ = 52, Urinary tract = 32, Head and Neck = 37, Other digestive cancer = 109, other localization = 47, and two simultaneous cancer diagnoses = 226.

SD, standard deviation.

group), and 55.5% of the patients were women. Other solid tumors ( $n = 583$ , 36%) such as female/male genital organs ( $n = 80/52$ ), urinary tract ( $n = 32$ ), Head and Neck ( $n = 37$ ), other digestive cancer ( $n = 109$ ) and patients with two simultaneous cancer diagnoses ( $n = 226$ ) were also described in Table 1.

Characteristics of patients were also compared according to the type of G-CSF consumed during the study period: the proportion of males was greater in the filgrastim group (52.8%) than in the others groups (38.7%, 46.2%, respectively, in the pegfilgrastim and lenograstim groups;  $p = .001$ ); there was no statistical difference (5%) between these three groups on age and rate of death ( $p = .16$  and  $p = .12$ ).

Only 5.4% of patients had CMU-c health insurance (a surrogate marker of poverty), and 83.5% of patients had full healthcare coverage for at least one chronic disease (cancer 76%, diabetes 8.5%, hypertension 4.2%, chronic ischemic heart disease 3.0%, atherosclerosis 2.0%, ...).

### G-CSF reimbursement for cancer patients

Patients who were prescribed only one G-CSF product received pegfilgrastim in 34.1% of cases, lenograstim in 26.7%, and filgrastim in 17.9%. Among the patients who were prescribed filgrastim, 78% received biosimilars ( $n = 231$ ), and only 57 patients received filgrastim originator. More than one G-CSF product was prescribed to 21.3% of patients. Out of the 288 patients treated with filgrastim alone, 226 were prescribed the syringes containing 30 MU of filgrastim, 49 were prescribed the 48 MU syringes, and 23 patients received both doses.

A total of 23,904 G-CSF units were dispensed to the 1,612 patients over the study period. The mean number of dispensing dates per patient was between 4.0 (SD = 4.0) for lenograstim or pegfilgrastim and 4.3 (SD = 4.6) for filgrastim, and the mean number of units dispensed ranged from 4.3 (SD = 3.2) for pegfilgrastim to 19.1 (SD = 19) for filgrastim and lenograstim. The estimated average treatment duration per year was 19.1 days (SD = 19) with lenograstim and filgrastim, and 46.8 days (SD = 36) with pegfilgrastim.

Since no difference was observed between filgrastim originator and biosimilar, and because of small sample sizes, their data were pooled in subsequent analyses.

Regarding the use of G-CSF products according to the cancer type, it is noteworthy that, respectively, 66% and 54% of patients with breast cancer and lung cancer received pegfilgrastim, whereas, respectively, 49% and 57% of patients with hematological malignancies and colorectal cancer received lenograstim (Table 1).

### Hospitalization of patients treated with G-CSF

The total number of hospitalizations was 29,969. Almost all the patients were hospitalized at least once ( $n = 1,599$ ; 99%), either for day care outpatient hospital or for in-patient stay. The average number of admissions for hospital day care was 15 (including 10 for chemotherapy) and the average number of hospital stays was 5. The mean duration of hospital stay was 4.8 days (median = 2 days; SD = 8). The average cumulative length of hospital stays was 26 days (median = 15 days).

Most hospitalizations were related to cancer treatment: chemotherapy (54% of hospitalizations), irradiation (41.3%), venous access placement (5.5%), or transfusion of labile blood products (4.5%). There were very few hospitalizations for post-chemotherapy aplasia/neutropenia (0.1%) or infections/fever (0.1%).

Three hundred patients (18.6%) had at least one radiotherapy treatment during the study period: 28.0% in the breast cancer group, 8.1% in the hematological malignancies group, 30.0% in the lung cancer group, and 6.3% in the colorectal cancer group.

### Nursing care

Within 10 days after G-CSF dispensation, respectively, 88%, 86%, and 82% of patients treated with lenograstim, filgrastim, and pegfilgrastim were reimbursed for nursing care.

### Economic analysis

#### Global population

Costs reimbursed for ambulatory care according to the type of cancer are described in Table 2. The more expensive ambulatory items were G-CSF expenses for solid tumors and pharmacy expenses for hematological malignancies. G-CSF represented 39% of the total cost of ambulatory care for

**Table 2.** Treatment costs reimbursed by the French national healthcare insurance for cancer patients according to the main types of cancer (€).

Mean; Median (Q1–Q3)	Breast cancer (n = 375)	Hematological malignancy (n = 358)	Lung cancer (n = 201)	Colorectal cancer (n = 95)	Other cancer (n = 583)	Total (n = 1,612)	p
Medical fees	€810; 434 (201–999)	€341; 165 (46–391)	€899; 373 (117–1,002)	€728; 449 (203–933)	€761; 358 (131–773)	€695; 326 (115–760)	<.0001
Pharmacy and derived products <sup>a</sup>	€791; 375 (158–812)	€5,126; 1,030 (223–3,232)	€1,885; 1,006 (365–2,410)	€1,793; 891 (504–2,436)	€1,950; 864 (311–2,166)	€2,368; 679 (236–2,047)	<.0001
G-CSF <sup>b</sup>	€3,017; 2,947 (1,487–4,017)	€2,904; 2,158 (1,173–3,964)	€2,487; 1,964 (982–3,748)	€2,654; 1,486 (793–3,447)	€2,589; 1,964 (982–3,509)	€2,750; 2,033 (982–3,929)	<.0001
Ambulatory cancer treatment	€1,143; 104 (0–829)	€397; 0 (0–19)	€1,485; 0 (0–0)	€461; 0 (0–0)	€1,327; 0 (0–0)	€1,046; 0 (0–167)	<.0001
Nursing care	€357; 143 (51–354)	€411; 156 (51–385)	€691; 236 (67–614)	€992; 472 (204–1,225)	€884; 262 (90–782)	€639; 209 (68–561)	<.0001
Laboratory tests	€154; 61 (7–207)	€262; 182 (67–367)	€278; 180 (61–400)	€374; 295 (168–541)	€268; 191 (65–388)	€248; 159 (45–346)	<.0001
Medical devices, dressings, etc.	€226; 94 (2–167)	€205; 27 (0–149)	€546; 120 (4–325)	€1,111; 617 (295–1,123)	€841; 164 (16–730)	€536; 114 (2–375)	<.0001
Transport	€1,132; 462 (69–1,534)	€901; 305 (0–1,038)	€1,341; 641 (80–1,916)	€1,282; 451 (64–1,455)	€1,154; 440 (63–1,427)	€1,124; 443 (51–1,429)	0.0093
Miscellaneous (dentist fees, etc.)	€15; 0 (0–0)	€11; 0 (0–0)	€12; 0 (0–0)	€15; 0 (0–0)	€10; 0 (0–0)	€12; 0 (0–0)	0.0003
1. Total cost of ambulatory care	€7,645; 6,542 (4,147–9,028)	€10,558; 6,440 (3,703–10,504)	€9,624; 8,399 (4,152–12,541)	€9,410; 7,474 (4,468–12,961)	€9,783; 7,290 (3,835–12,303)	€9,416; 6,918 (3,983–10,889)	0.0190
2. Total cost of hospital care (including day care hospital)	€9,176; 6,717 (4,440–10,888)	€24,080; 16,364 (8,312–28,304)	€14,582; 12,001 (7,190–19,898)	€15,834; 13,785 (7,754–19,482)	€15,199; 11,203 (5,607–20,296)	€15,730; 10,839 (5,569–19,993)	<.0001
(1 + 2) Total cost	€16,821; 13,826 (10,088–19,058)	€34,638; 24,977 (14,906–43,552)	€24,206; 22,242 (14,504–30,789)	€25,244; 22,256 (15,564–30,765)	€24,981; 20,918 (13,104–33,450)	€25,147; 19,384 (12,135–31,693)	<.0001

<sup>a</sup>Pharmacy expenses excluded G-CSF and oral chemotherapy.<sup>b</sup>The part of G-CSF in the total cost of ambulatory care was 39% for breast cancer, 27% for hematological malignancies, 26% for lung cancer, and 28% for colorectal cancer.

Q1 = 25% quartile/Q3 = 75% quartile.

breast cancer (€3,017, SD = €1,843), 27% for hematological malignancies (€2,904, SD = €2,474), 26% for lung cancer (€2,487, SD = €2,054), and 28% for colorectal cancer (€2,654, SD = €2,795).

The total annual reimbursed costs (in-hospital and ambulatory care) were €27,001 (SD = €22,843) for patients treated with filgrastim, €24,511 (SD = €21,824) for patients treated with lenograstim, and €20,802 (SD = €15,366) for patients treated with pegfilgrastim. The respective costs of ambulatory care (% of total) were €9,512 (SD = €13,758) (35%), €9,344 (SD = €11,740) (38%) and €8,534 (SD = €6,655) (41%) (Table 3).

### Patients with breast cancer

Patients with breast cancer (n = 375) represented 23% of the study population (Table 4). They were younger than the other patients (mean age = 57 years).

The breast cancer patients who received more than one G-CSF product were younger, probably had a poorer prognosis, as shown by the higher death rate (21.7%) during the study period, were more frequently hospitalized in the public sector, and received more hospital daycare. Patients treated with pegfilgrastim seemed to have a better prognosis (2% of deaths), were more frequently treated in the private sector, required less hospital daycare, and had fewer hospital admissions.

The total costs of ambulatory care in this sub-population were €7,915 (SD = €8,478) with filgrastim, €7,750

(SD = €7,775) with lenograstim, €6,989 (SD = €3,798) with pegfilgrastim, and €9,814 (SD = €7,629) with G-CSF combination therapy. G-CSF was the more expensive item of ambulatory care, representing 22% of the total cost of ambulatory care among patients treated with filgrastim (€1,733, SD = €1,341), 20% (€1,559, SD = €1,280) among patients treated with lenograstim, and 52% (€3,668, SD = €1,665) among patients treated with pegfilgrastim. Patients who received G-CSF combination therapy had higher pharmacy and laboratory costs. Patients treated with pegfilgrastim had higher G-CSF costs and lower ambulatory costs (pharmacy, nursing care, tests, medical devices, and transport) than other patients.

### Discussion

Three G-CSF products (lenograstim, filgrastim, and pegfilgrastim) are available in France and are used to prevent chemotherapy-induced febrile neutropenia, which still has a considerable clinical and economic burden, since it was recently reported that 7.4% of newly-diagnosed patients receiving chemotherapy were hospitalized for febrile neutropenia, with a mortality rate of 7%<sup>27</sup>. In our sample of patients treated with G-CSF, the hospitalization rate for neutropenia or infection was extremely low, but these complications could have been treated during other hospitalizations or at home. The annual total costs reimbursed by the French Sickness Funds varied with the type of cancer: hematological malignancies incurred the highest costs and breast cancer



**Table 3.** Treatment costs reimbursed by the French national healthcare insurance for cancer patients according to the type of G-CSF (€).

Mean; Median (Q1–Q3)	Filgrastim (n = 288)	%	Lenograstim (n = 431)	%	Pegfilgrastim (n = 550)	%	Combined G-CSF (n = 343)	%	p
Medical fees	€640; 285 (96–739)	6.7%	€762; 353 (113–801)	8.2%	€694; 313 (133–742)	8.1%	€655; 348 (147–727)	6.0%	.6833
Pharmacy and derived products <sup>a</sup>	€3,556; 1,041 (388–2,782)	37.4%	€2,588; 653 (194–2,099)	27.7%	€1,295; 465 (171–1,307)	15.2%	€2,815; 1,005 (359–2,626)	26.0%	<.0001
G-CSF <sup>b</sup>	€1,801; 1,336 (610–2,434)	18.9%	€1,591; 1,189 (531–2,081)	17.0%	€3,723; 2,947 (1,964–4,911)	43.7%	€3,441; 3,016 (1,801–4,527)	31.7%	<.0001
Ambulatory cancer treatment	€836; 0 (0–26)	8.8%	€1,501; 0 (0–235)	16.1%	€835; 0 (0–226)	9.8%	€990; 0 (0–104)	9.1%	.0537
Nursing care	€671; 256 (96–702)	7.1%	€740; 271 (95–627)	7.9%	€447; 114 (40–346)	5.2%	€791; 270 (110–646)	7.3%	<.0001
Laboratory tests	€277; 191 (68–380)	2.9%	€275; 194 (62–393)	2.9%	€170; 86 (17–215)	2.0%	€312; 258 (98–453)	2.9%	<.0001
Medical devices, dressings, etc.	€601; 115 (0–474)	6.3%	€647; 125 (5–422)	6.9%	€376; 88 (0–275)	4.4%	€596; 118 (7–431)	5.5%	.0956
Transport	€1,121; 518 (69–1,401)	11.8%	€1,228; 433 (28–1,513)	13.1%	€983; 352 (50–1,216)	11.5%	€1,219; 534 (76–1,492)	11.3%	.3415
Miscellaneous (dentist fees, etc.)	€9; 0 (0–0)	0.1%	€12; 0 (0–0)	0.2%	€11; 0 (0–0)	0.1%	€17; 0 (0–0)	0.2%	.0210
1. Total cost of ambulatory care	€9,512; 6,230 (3,389–10,718)	35.2%	€9,344; 6,089 (3,162–10,463)	38.1%	€8,534; 7,151 (4,450–10,504)	41.0%	€10,836; 7,827 (4,862–13,185)	38.1%	<.0001
2. Total cost of hospital care (including day care hospital)	€17,489; 12,070 (6,497–23,149)	64.8%	€15,167; 10,696 (5,721–18,751)	61.9%	€12,268; 8,560 (4,650–16,108)	59.0%	€20,514; 14,957 (7,910–27,936)	61.9%	<.0001
(1 + 2) Total cost	€27,002; 20,926 (12,406–35,308)	100%	€24,511; 18,564 (11,568–29,083)	100%	€20,802; 16,991 (11,133–26,347)	100%	€31,350; 24,741 (15,988–39,470)	100%	<.0001

<sup>a</sup>Pharmacy expenses excluding G-CSF and ambulatory cancer treatment; the part of pharmacy in total ambulatory costs was 37% for filgrastim, 28% for lenograstim, and 15% for pegfilgrastim.

<sup>b</sup>The part of G-CSF in the total cost of ambulatory care was 19% for filgrastim, 17% for lenograstim, and 44% for pegfilgrastim. Q1 = 25% quartile/Q3 = 75% quartile.

the lowest costs. Thus, the overall annual cost of ambulatory care was similar, regardless of the G-CSF product: €9,512 (SD = €13,758) with filgrastim, €9,344 (SD = €11,740) with lenograstim, and €8,534 (SD = €6,555) with pegfilgrastim. Surprisingly, the cost of the G-CSF itself represented a larger part of the total ambulatory cost with pegfilgrastim (43.7%; €3,723, SD = €2,628), than with filgrastim (18.9%; €1,801, SD = €1,643) and lenograstim (17%; €1,591, SD = €1,442).

The analysis restricted to patients with breast cancer showed that the choice of the G-CSF product seemed to be related to the patient's prognosis, the prescriber's specialty, and care consumption. Patients treated with G-CSF combinations appeared to be more severely ill than those who received filgrastim or lenograstim, and especially pegfilgrastim, based on the mortality rate, the total number of hospital days, and the level of costs of different resources. It is also interesting to note that patients treated in the private sector were prescribed pegfilgrastim more frequently than those treated in the public sector. The cost consequences of these differences in the use of G-CSF are that total costs are not so different, especially for ambulatory care. Ambulatory care consumption was lower with pegfilgrastim than with filgrastim or lenograstim, but this was offset by the higher cost of pegfilgrastim itself.

Few recent economic analyses have been published on the real-life use of G-CSF, even though guidelines now take the cost dimension into account. A recent German study compared the costs of G-CSF prescription (filgrastim, filgrastim biosimilar, lenograstim, and pegfilgrastim) based on a

statutory health insurance database containing prescription data for more than 28,000 patients<sup>28</sup>. After adjustment for age, gender, the number of injections, and prescriber specialties, a regression model showed statistically significant cost-reducing effects per cycle with lenograstim compared with the other G-CSF products. However, the authors did not analyze total costs and restricted their analysis to G-CSF treatment costs without taking into account the type of cancer. Therefore, our results highlight large differences in the prescription of the G-CSF according to the type of cancer and characteristics of patients. This could be completely different in other countries, applying more or less restricted national or regional guidelines and, consequently, these results are difficult to apply in other contexts.

One limitation of our cohort study is that some patient's categories, such as students and civil servants, have specific healthcare insurers and are not included in the EGB cohort. However, the impact of this difference among populations should be limited and should not change the conclusions of the study. In addition, the database contains no information on G-CSF dispensing in hospitals, but it should be noted that G-CSF is mainly dispensed in retail pharmacies (90%)<sup>25</sup>. Another limitation is the absence of medical details on the management of cancer patients and on whether or not G-CSF was used according to international guidelines. Particularly, it was not planned to assess simultaneous use of G-CSF and chemotherapy/radiotherapy, which is a contraindication since it was clearly identified to increase myelosuppression<sup>29,30</sup>. One of the limits of the EGB database is

**Table 4.** Patient characteristics, G-CSF, and reimbursements (€) by the French national healthcare insurance for patients with breast cancer (*n* = 375).

	Filgrastim ( <i>n</i> = 33)	Lenograstim ( <i>n</i> = 82)	Pegfilgrastim ( <i>n</i> = 200)	Combined G-CSF ( <i>n</i> = 60)	<i>p</i>
Age (years), mean (SD)	60.6 (11.9)	56.7 (12.7)	56.4 (11.5)	54.3 (14.8)	.14
Died during the study period, <i>n</i> (%)	5 (15.2%)	9 (11.0%)	4 (2.0%)	13 (21.7%)	<.0001
Hospital care (all): <i>n</i> (%)					.0829
private sector	8 (25.0%)	21 (25.9%)	76 (38.0%)	12 (20.0%)	
public sector	14 (43.8%)	36 (44.4%)	80 (40.0%)	26 (43.3%)	
both sectors	10 (31.3%)	24 (29.6%)	44 (22.0%)	22 (36.7%)	
At least one hospital admission, <i>n</i> (%)	31 (93.4%)	78 (95.1%)	189 (94.5%)	57 (95.0%)	.9927
Number of day-care hospitalizations during the year, mean (SD)	17.7 (14.4)	19.1 (14.4)	15.9 (14.9)	19.8 (14.1)	.1998
Total hospital stay (days) during the year, mean (SD)	4.6 (6.8)	3.3 (3.6)	2.3 (2.2)	3.6 (5.3)	.0737
Total number of G-CSF units at each dispensing date, mean (SD)	4.4 (1.6)	4.4 (1.4)	1.0 (0.2)	3.0 (1.4)	<.0001
Estimated duration of G-CSF treatment (days), mean (SD)	18.5 (13.6)	19.3 (23.1)	43.9 (19.2)	46.0 (33.2)	<.0001
Medical fees, mean; median (Q1–Q3)	€963; 685 (349–999)	€1,002; 574 (217–1,145)	€725; 339 (183–804)	€745; 534 (294–1,074)	.0219
Pharmacy and derivatives, mean; median (Q1–Q3) <sup>a</sup>	€913; 479 (222–778)	€887; 431 (168–1,022)	€532; 282 (123–562)	€1,452; 621 (236–2,093)	<.0001
G-CSF, mean; median (Q1–Q3)	€1,733; 2,004 (573–2,542)	€1,559; 1,387 (595–1,982)	€3,668; 3,929 (2,456–4,911)	€3,549; 3,396 (2,047–4,847)	<.0001
Oral chemotherapy, mean; median (Q1–Q3)	€1,681; 121 (0–535)	€1,870; 151 (13–1,096)	€572; 52 (0–596)	€1,758; 111 (0–774)	.0646
Nursing care, mean; median (Q1–Q3)	€453; 255 (84–421)	€502; 261 (106–568)	€246; 82 (33–216)	€479; 205 (132–537)	<.0001
Laboratory tests, mean; median (Q1–Q3)	€193; 135 (31–242)	€204; 97 (17–291)	€91; 29 (0–115)	€272; 225 (36–414)	<.0001
Medical devices, dressings, mean; median (Q1–Q3)	€383; 105 (6–159)	€194; 125 (1–175)	€186; 80 (0–166)	€318; 70 (20–151)	.8995
Transport, mean; median (Q1–Q3)	€1,585; 1,247 (387–2,345)	€1,309; 711 (84–1,756)	€957; 367 (52–1,225)	€1,225; 446 (64–1,207)	.032
Others (dentist fees, etc.), mean; median (Q1–Q3)	€11; 0 (0–0)	€23; 0 (0–0)	€12; 0 (0–0)	€16; 0 (0–18)	.1196
(1) Total cost of ambulatory care, mean; median (Q1–Q3)	€7,915; 5,729 (4,514–7,258)	€7,550; 5,990 (3,316–9,214)	€6,990; 6,427 (4,501–8,835)	€9,814; 7,765 (4,714–12,051)	.022
(2) Total cost of hospital care, (including day care hospital) mean; median (Q1–Q3)	€12,106; 8,801 (5,197–15,798)	€10,748; 7,963 (5,021–12,478)	€7,673; 5,936 (3,960–9,485)	€10,425; 7,625 (4,826–11,791)	.0006
(1 + 2) Total cost, mean; median (Q1–Q3)	€20,021; 13,800 (11,299–21,396)	€18,298; 14,726 (10,958–21,804)	€14,663; 12,737 (9,584–17,486)	€20,238; 16,187 (10,745–25,852)	.0143
Interval between chemotherapy cures <18 days, <i>n</i> (%)	7 (22.6%)	16 (20.5%)	23 (12.1%)	16 (27.1%)	.0333

<sup>a</sup>Pharmacy expenses excluding G-CSF and oral chemotherapy.<sup>b</sup>G-CSF represented 22% of total ambulatory care costs with filgrastim, 20% with lenograstim, 52% with pegfilgrastim, and 36% with combined G-CSF. Q1 = 25% quartile/Q3 = 75% quartile.

represented by the lack of details concerning chemotherapies administered in hospitals. However, a recent French survey involving 990 patients showed that G-CSF prescription largely complied with international guidelines<sup>31</sup>.

## Conclusion

Our cost comparison of the different G-CSF products used to treat cancer patients in France raises some interesting observations. First, the different products are used by the French physicians in various medical situations and through different ways that could be driven by the results of particular clinical trials or by the habits. In particular, we found that care costs relating to chemotherapy-induced neutropenia, including G-CSF and nursing care, are higher with pegylated G-CSF, even though these patients did not appear to need a longer duration of G-CSF treatment. (The total cost of cancer management of this sub-group of patients receiving pegfilgrastim is not higher, suggesting, out of neutropenia prevention, less costly management of the cancer disease and so less advanced form of the disease). In order to analyze other

parameters that might influence the choice of G-CSF, such as patient, cancer or chemotherapy characteristics and social factors, an in-depth analysis of the EGB database may be performed with a completely different design that allow adjusted comparisons. Nevertheless, our findings show that the choice of G-CSF can have a significant impact on the total cost of ambulatory care for cancer patients.

## Transparency

### Declaration of funding

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### Declaration of financial/other interests

PT acts as a Consultant/Advisor for Astellas, Chugai, Chiesi, and Biogen, and is on a speakers' bureau for MSD and Roche. AL and CE declare sponsorship from Chugai. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Peer reviewers on

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