Filgrastim prophylaxis in elderly cancer patients in the real-life setting: a French multicenter observational study, the TULIP study

Kamel Laribi1,2 · Delphine Badinand3 · Philippe Janoray4 · Khaled Benabed5,6 · Jean-Loup Mouyssset7 · Elizabeth Fabre8 · Françoise Monchecourt9 · Rafik Diab10

Received: 19 September 2018 / Accepted: 1 March 2019 / Published online: 14 March 2019
© The Author(s) 2019

Abstract
Purpose Few studies are currently available among elderly patients, justifying the need for better understanding of daily medical practices in terms of use of growth factors to prevent chemotherapy (CT)-induced neutropenia. The primary objective of this study was to describe the use of filgrastim in the elderly.

Methods Cancer patients aged 65 years and above, undergoing CT and initiating a prophylactic treatment with filgrastim, were enrolled. Patients were followed according to routine medical practice from filgrastim initiation until the end of the CT or after a maximum of 6 cycles.

Results One thousand one hundred nineteen evaluable patients were documented in the study (mean age 73.9 ± 6.2 years, 52.1% men). The majority were suffering from solid tumor (73%) with ECOG 0–1 for 80% of them. Approximately two-third had a global risk for FN ≥ 20%, and one third < 20%. Through all CT cycles, no differences were observed between age classes ([65–74], [75–85], or > 85) in dose, duration, and time to first injection from CT start. Most patients (84%) received primary prophylaxis (PP) and 70% were administered during the first CT cycle. The median time from CT start until filgrastim was 4 days. The median duration of filgrastim treatment was 5 days. Dose reductions and CT delays were less frequent in patients receiving PP (4.8% and 7.1% respectively) than secondary prophylaxis (9.2% and 13.3% respectively).

Conclusions Filgrastim use was consistent with French Market Authorization terms. No difference was shown compared with younger patients. Safety data were consistent with the known safety profile.

Keywords Chemotherapy-induced neutropenia · Elderly patients · Filgrastim · Primary prophylaxis · Secondary prophylaxis

Introduction
Neutropenia is one of the most frequent limiting dose toxicities in cancer patients [1, 2]. It mainly depends on the chemotherapy (CT) regimen and can generate serious life-threatening complications. The incidence of febrile neutropenia (FN) varies from 10 to 57% depending on the chemotherapy protocols [1, 3].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00520-019-04725-0) contains supplementary material, which is available to authorized users.

Kamel Laribi klaribi@ch-lemans.fr

1 Department of Hematology, Le Mans Hospital, Le Mans, France
2 Department of Medical Onco-Hematology, Le Mans Hospital, 194 Avenue Rubillard, 72037 Le Mans Cedex 9, France
3 Department of Radiotherapy Oncology, Hospital La Timone, Marseille, France
4 Oncology Institute of Bourgogne, Dijon, France
5 Department of Clinical Hematology, Hospital Côte de Nacre, Caen, France
6 Public Hospital Center of Cotentin, Cherbourg-en-Cotentin, France
7 Department of Chemotherapy, Outpatient Unit, Polyclinic Parc Rambot Provence, Aix-en-Provence, France
8 Department of Medical Oncology, European Hospital Georges Pompidou, Paris, France
9 Teva Santé, La Défense, France
10 Specialized Medical Center of Praz-Coutant, Passy, France
Age is an independent risk factor regarding the development of chemotherapy-induced neutropenia (CIN) in solid and hematologic tumors [4]. According to EORTC’s [3, 5] and ASCO’s [6] guidelines, an age higher than or equal to 65 is an aggravating factor related to FN and must be taken into account when deciding on granulocyte colony-stimulating factors (G-CSF) treatment. In France, median age at the time of diagnosis is 68 years old for men and 65 years old for women and approximately 30% of patients are followed by oncogeriatrics [7]. The general condition associated with age is also a significant risk factor, the physiological age being more relevant than the chronological age to predict the risk of chemotherapy-induced neutropenia [8]. Neutropenic complications are not only more frequent among older patients but also more severe, entailing more numerous and longer hospitalizations as well as a higher mortality rate [9].

In order to prevent these complications, elderly patients are often treated with less aggressive CT protocols or with lower doses whereas (i) age is not a contraindication to the use of standard CT protocols; patients over 65 can profit from the same treatments as younger patients with comparable effectiveness [10]; (ii) controlled clinical trials have shown that the use of low-dose or shorter duration CT decreases the patients’ overall survival [11, 12]; (iii) G-CSF proved to be effective in reducing the incidence of FN, namely with elderly patients [13, 14].

Since elderly patients are excluded from most clinical trials [15], few studies are currently available concerning the management of CIN among this specific population of patients [16, 17]. No study under real conditions of medical practice evaluating the use of filgrastim has been conducted on cancer patients aged 65 or over. The optimum treatment duration with filgrastim and the optimum time for treatment initiation are also not clearly determined.

The aim of this national, observational, and multicenter study is to describe the modalities of use of filgrastim in the prevention of CIN in elderly patients in a real-life setting. Primary endpoint was administration modalities of filgrastim (e.g., time to treatment start, administration doses and patterns, number of injections per cycle, duration of treatment). Secondary endpoints included incidence of CT delays and CT dose reductions, description of patient’s characteristics, and description of cancer management strategies.

After the patient had given an oral consent, the patient’s data were collected by the participating physicians in a prospective manner in an electronic case report form (eCRF) during an inclusion visit when filgrastim was initiated and during a non-compulsory follow-up visit performed at the end of the chemotherapy or after a maximum of six chemotherapy cycles. This non-interventional study was performed under real conditions of medical practice and standard care and did not entail any additional visit or specific exam for the patient.

**Statistical analysis**

The statistical analysis was performed using SAS statistical package version 9.2.

All variables collected in the eCRF and all derived parameters were used in the descriptive statistical analysis. Quantitative variables were analyzed in terms of mean, standard deviation, median, first quartile, third quartile, and extreme values. Binary, categorical, and ordinal parameters were analyzed in terms of number and frequency within the various categories. Conditions of use of filgrastim were described according to the following subgroups: type of prophylaxis (PP vs. SP), age (65–75 years old vs. 75–85 years old vs. > 85 years old), type of tumor (solid vs. hematologic), risk for FN associated with CT protocol (high vs. interim vs. low), and global risk for FN (≥ 20% vs. < 20%). The FN risk categories were those defined by the EORTC guidelines [3].
Results

Patient characteristics

A total of 1176 cancer patients were enrolled in the study, 1119 (95.2%) of whom were included in the statistical analysis (Fig. 1). A total of 57 patients were thus excluded from the analysis. The main reason for being excluded from the analysis was an insufficient number of CT cycles to be run (at least 3 cycles were required). Patient main characteristics at inclusion according to the type of prophylaxis (i.e., PP or SP) are summarized in Table 1. Overall mean age was 73.9 ± 6.2 years, 40.9% of patients were at least 75 years old, and 4.4% of patients were at least 85 years old. The majority of patients had a solid tumor (72.9%). Common primary sites for the malignancies included digestive cancer (18.1%), non-Hodgkin lymphoma (18.0%), lung cancer (16.3%), and breast cancer (15.0%). Most patients (79.7%) had a good performance status (i.e., ECOG score 0–1). More than one-third of the patients (35.4%) had received previous chemotherapy, the proportion being slightly higher for secondary prophylaxis patients (43.8% vs. 33.7%). The mean neutrophil count was 3755 ± 1984 cells/mm$^3$ at the onset of filgrastim treatment and 89.7% of patients had neutrophil count > 1500 cells/mm$^3$. Lower counts were recorded when filgrastim was used as SP rather than PP (2505 ± 1672 cells/mm$^3$ vs. 4010 ± 1946 cells/mm$^3$). Thirty-four patients (3.2%) presented grade 3 or 4 neutropenia at the onset of filgrastim treatment (11.2% of the secondary prophylaxis patients vs. 1.6% of the primary prophylaxis patients). Overall, each patient presented 1 to 7 risk factors for FN in addition to age (median number of 3): no prophylactic antibiotic treatment (84.5%), advanced stage (51.8%), female gender (47.9%), Hb level < 12 g/dL (41.5%), heart disease (19.7%), malnutrition (13.5%), renal failure (5.7%), history of febrile neutropenia (5.5%). A similar number of risk factors was reported for the patients who received PP or SP although history of severe or febrile neutropenia was more frequent in SP patients (respectively 49.7% and 12.4%).

Condition of use of filgrastim

Filgrastim was mainly administered as primary prophylaxis (934 patients, 83.5%) regardless of the ECOG scores. Patients with hematologic malignancies were more likely to receive primary prophylaxis (89.4% vs. 81.3% for solid tumors) while patients presenting with an overall risk of FN < 20% were more likely to receive secondary prophylaxis (21.6% vs. 15.6%). Condition of use of filgrastim according to the type of prophylaxis is detailed in Table 2. In PP patients, filgrastim was initiated within the first CT cycle (79.1%). Approximately 10% of the patients started using filgrastim during or after the third CT cycle.

The median time before treatment initiation was 4 days after the onset of chemotherapy. In SP patients, filgrastim was mainly initiated after the first CT cycle (75.5%) with more than 40% of the patients who started to receive filgrastim during or after the third CT cycle. In SP patients, the median time before treatment initiation was 3 days after the onset of chemotherapy.

Fig. 1 Flow diagram of patient enrollment
The preferred dosage, posology, and administration route throughout treatment initiation were identical, regardless of the type of prophylaxis: the median dose was 0.5 MIU/kg/day administered by subcutaneous injections for 99.7% of the patients, and the most commonly used dosage was 30 MIU/0.5 mL. The median treatment duration was 5 days. Throughout all CT cycles, the median time to first injection (from start of CT cycle) was 3 to 4 days for PP patients and 2 to 3 days for SP patients (Online Resource 1) and treatment duration was slightly longer in PP patients compared with SP patients (Table 2 and Fig. 2). Daily dose across CT cycles was not affected by the type of prophylaxis. No main difference was shown regarding treatment modalities according to type of tumor, except the median time to filgrastim injection (from start of CT cycle) that was 6 days for patients with hematologic malignancy and 3 days for patients with solid tumor (Table 3). No difference in condition of use of filgrastim was shown according to age (Online Resource 2). As regards condition of use of filgrastim according to overall FN risk, patients presenting with a high risk level (i.e., ≥20%) initiated

Table 1 Main baseline patient characteristics according to the type of prophylaxis

|                                | Primary prophylaxis (N=934) | Secondary prophylaxis (N=185) | Total (N=1119) |
|--------------------------------|-----------------------------|-------------------------------|----------------|
| Age (years)                    |                             |                               |                |
| Mean ± SD                      | 73.9 ± 6.2                  | 73.7 ± 6.1                    | 73.9 ± 6.2     |
| Median (min–max)               | 73.2 (65–93)                | 73.3 (65–90)                  | 73.2 (65–93)   |
| ≤85, n (%)                     | 894 (95.7)                  | 176 (95.1)                    | 1070 (95.6)    |
| >85, n (%)                     | 40 (4.3)                    | 9 (4.9)                       | 49 (4.4)       |
| Sex                            |                             |                               |                |
| Female, n (%)                  | 443 (47.4)                  | 93 (50.3)                     | 536 (47.9)     |
| Male, n (%)                    | 491 (52.6)                  | 92 (49.7)                     | 583 (52.1)     |
| ECOG score                     |                             |                               |                |
| 0–1, n (%)                     | 727 (79.8)                  | 143 (79.0)                    | 870 (79.7)     |
| 2, n (%)                       | 168 (18.4)                  | 37 (20.4)                     | 205 (18.8)     |
| 3, n (%)                       | 15 (1.6)                    | 1 (0.6)                       | 16 (1.5)       |
| 4, n (%)                       | 1 (0.1)                     | 0 (0.0)                       | 1 (0.1)        |
| Tumor site                     |                             |                               |                |
| Digestive tract, n (%)         | 147 (15.7)                  | 55 (29.7)                     | 202 (18.1)     |
| Non-Hodgkin lymphoma, n (%)    | 182 (19.5)                  | 19 (10.3)                     | 201 (18.0)     |
| Lung or chest, n (%)           | 147 (15.7)                  | 35 (18.9)                     | 182 (16.3)     |
| Breast, n (%)                  | 146 (15.6)                  | 22 (11.9)                     | 168 (15.0)     |
| Uterus or ovary, n (%)         | 79 (8.4)                    | 21 (11.3)                     | 100 (8.9)      |
| Prostate, kidney, bladder, n (%) | 78 (8.3)                  | 13 (7.0)                      | 91 (8.1)       |
| Other site, n (%)              | 155 (16.6)                  | 20 (10.8)                     | 175 (15.6)     |
| Advanced stagea                | 454 (70.2)                  | 126 (85.1)                    | 580 (73.0)     |
| Current chemotherapy           |                             |                               |                |
| First line, n (%)              | 662 (71.6)                  | 117 (63.9)                    | 779 (70.3)     |
| Second line, n (%)             | 152 (16.4)                  | 40 (21.9)                     | 192 (17.3)     |
| Third line or higher, n (%)    | 111 (12.0)                  | 26 (14.2)                     | 137 (12.4)     |
| Hb level (g/dL)                |                             |                               |                |
| <12, n (%)                     | 370 (40.5)                  | 86 (46.5)                     | 456 (41.5)     |
| ≥12, n (%)                     | 544 (59.5)                  | 99 (53.5)                     | 643 (58.5)     |
| Neutrophil count (cells/mm³)   |                             |                               |                |
| ≥1500, n (%)                   | 821 (93.6)                  | 126 (70.4)                    | 947 (89.7)     |
| 500–1500, n (%)                | 54 (6.2)                    | 52 (29.0)                     | 106 (10.0)     |
| <500, n (%)                    | 2 (0.2)                     | 1 (0.6)                       | 3 (0.3)        |
| Antibiotic prophylaxis         | 149 (16.0)                  | 24 (13.0)                     | 173 (15.5)     |
| Comorbidities                  |                             |                               |                |
| Malnutrition, n (%)            | 121 (13.0)                  | 30 (16.2)                     | 151 (13.5)     |
| Immune deficiency, n (%)       | 88 (9.4)                    | 17 (9.2)                      | 105 (9.4)      |
| COPD, n (%)                    | 102 (10.9)                  | 25 (13.5)                     | 127 (11.3)     |
| Cardiopathy, n (%)             | 175 (18.7)                  | 45 (24.3)                     | 220 (19.7)     |
| Renal failure, n (%)           | 54 (5.8)                    | 10 (5.4)                      | 64 (5.7)       |
| Hepatic dysfunction, n (%)     | 14 (1.5)                    | 6 (3.2)                       | 20 (1.8%)      |
| Medical history                |                             |                               |                |
| History of febrile neutropenia, n (%) | 39 (4.2)                  | 23 (12.4)                     | 62 (5.5)       |
| History of severe neutropeniab | 78 (8.4)                    | 92 (49.7)                     | 170 (15.2)     |
| History of fungal infection, n (%) | 6 (0.6)                     | 4 (2.2)                       | 10 (0.9)       |
| Global risk for FN             |                             |                               |                |
| ≥20%, n (%)                    | 286 (68.1)                  | 53 (58.9)                     | 339 (66.5)     |
| <20%, n (%)                    | 134 (31.9)                  | 37 (41.1)                     | 171 (33.5)     |

aFor solid tumors only. b Grade 3 or 4. c Among patients with identified risk for FN
Filgrastim prophylaxis more frequently during the first CT cycle (71.3% vs. 59.1%; \( p = 0.003 \)) (Fig. 3) but mean time to injection, daily dose, and duration of treatment were similar regardless of the risk for FN.

**Impact of filgrastim on CT management**

CT dose reduction related to neutropenic event was necessary for 58 (5.5%) patients, and on average, each of these patients was subjected to one dose reduction during their study follow-up period. CT delay due to neutropenic event was reported for 85 patients (8.1%). Median duration of CT delay was 7 days. CT dose reductions and CT delays were less frequent in PP patients (4.8% and 7.1%, respectively) than in SP patients (9.2% and 13.3%, respectively). There was no significant difference in the impact of filgrastim treatment on CT management with respect to the age group and the risk level of FN.

**Safety data**

A total of 1160 patients received at least one dose of Tevagrastim®. Eighteen patients (1.6%) experienced at least one adverse event (AE) possibly related to Tevagrastim®, and 9 of these patients (0.8%) had at least one serious AE (SAE). Overall, 34 AEs possibly related to Tevagrastim® were reported during the study, primarily general disorders and administration site conditions (7 patients [0.6%]; 9 AEs) and musculoskeletal and connective tissue disorders (6 patients [0.5%]; 10 AEs, mainly bone and back pain). The only AE of particular interest (with respect to the risk management plan for Tevagrastim®) was a lack of efficacy reported in a 65-year-old patient who discontinued treatment due to febrile leukopenia after 8 days of treatment. No immunogenicity assay was performed.

**Discussion**

The TULIP study shows that filgrastim is mostly prescribed to elderly patients as primary prophylaxis (PP, 80%). These results are consistent with those of a French study (NEXT study), which reported the use of primary prophylaxis in 91.7% of the patients aged 70 years and older [18]. In contrast, primary prophylaxis was less common in a German study (HEXAFIL) conducted on a younger population (mean age, 59.4 ± 12.7 years), as 59.1% of the patients received secondary prophylaxis [19]. When filgrastim was used as PP, the treatment was predominantly initiated during the first CT cycle (79.1%); only 6.2% of the patients started to receive filgrastim during or after the fourth CT cycle; more particularly, 71.3% of patients with a high risk for CIN (≥20%) have initiated filgrastim during the first CT cycle. These results clearly highlight the implementation in common practice of the recommendations of the EORTC (original version written
in 2006 and updated in 2010), namely the initiation of G-CSF primary prophylaxis within the first CT cycle for all patients presenting a risk of FN ≥ 20%. A Spanish retrospective study (LEARN study) conducted in 2003 reported a significantly lower proportion of patients treated with primary prophylaxis (45%) [20]. In contrast, a European study (MONITOR-GCSF study), recently conducted on 1447 patients in 12 countries [21], reported a proportion of primary prophylaxis (72.3%) comparable with that of the TULIP study (83.5%). For the patients who received filgrastim as secondary prophylaxis (SP), the treatment was generally initiated after the first CT cycle (75.5% of the cases), likely to address a neutropenic event which occurred during the previous close CT cycles. The median time to treatment initiation was 1 day longer for PP patients compared with SP patients (4 days after the onset of CT cycle vs. 3 days), and 3 days longer for hematologic malignancy compared with solid tumor (6 days vs. 3 days).

In nearly all cases, filgrastim was administered by subcutaneous injections at a daily dose of 0.5 MIU/kg. The treatment was considerably shorter than those usually adopted in randomized trials [22–27]. Mean duration was 5.2 ± 1.9 days for patients with solid tumor and 5.5 ± 1.7 days for patients with hematologic malignancy. According to SmPC of Tevagrastim®, filgrastim treatment must continue after the expected date of the nadir and until the neutrophil counts have returned to normal to induce a lasting response. It is not recommended to discontinue the treatment prematurely before the expected date of the nadir [28]. After a chemotherapy for solid tumors, lymphoma, and lymphocytic leukemia, filgrastim treatment can last up to 14 days [28]. After induction and consolidation treatments for acute myeloid leukemia, the treatment may be significantly longer (up to 38 days) depending on the type, dose, and regimen of the cytotoxic chemotherapy [28]. Nonetheless, clinical studies showed that
patients are often treated for shorter periods of time [19, 27, 29, 30]. In a retrospective study conducted from 1998 to 2002 in USA, the mean duration of filgrastim treatment was 6.5 ± 3.1 days for NHL, 6.1 ± 2.9 days for breast cancer, and 4.3 ± 3.1 days for lung cancer [27]. Another American retrospective study conducted from 2004 to 2008 reported treatment durations shorter than 6 days in 74% of patients [31]. In the HEXAFIL study, the median treatment duration was 4 to 5 days depending on the cycles, and the patients treated with PP received longer treatments than those treated with SP.

### Table 3: Condition of use of filgrastim according to tumor type

|                      | Solid tumor (N = 816) | Hematologic malignancy (N = 303) | p value | Total (N = 1119) |
|----------------------|-----------------------|---------------------------------|---------|------------------|
| **Type of prophylaxis** |                       |                                 |         |                  |
| Primary, n (%)       | 663 (81.3)            | 271 (89.4)                      | 0.001a  | 934 (83.5)       |
| Secondary, n (%)     | 153 (18.8)            | 32 (10.6)                       |         | 185 (16.5)       |
| **Treatment initiation** |                       |                                 |         |                  |
| First CT cycle, n (%) | 563 (69.4)            | 218 (71.9)                      | 0.412a  | 781 (70.1)       |
| Second CT cycle, n (%) | 116 (14.3)         | 44 (14.5)                       |         | 160 (14.4)       |
| Third CT cycle or after, n (%) | 132 (16.3) | 41 (13.5)                      |         | 173 (15.5)       |
| **Time to first injection** |                   |                                 |         |                  |
| Mean ± SD            | 4.00 ± 4.15           | 5.81 ± 2.38                     | < 0.001c | 4.49 ± 3.84      |
| 95% CI               | 3.71; 4.29            | 5.54; 6.08                      |         | 4.27; 4.72       |
| Median (min–max)     | 3 (0–39)              | 6 (0–24)                        |         | 4 (0–39)         |
| **Daily dose within the first CT cycle (MIU/kg)** |             |                                 |         |                  |
| Mean ± SD            | 0.49 ± 0.09           | 0.49 ± 0.11                     | 0.443c  | 0.49 ± 0.09      |
| 95% CI               | 0.49; 0.50            | 0.48; 0.51                      |         | 0.49; 0.50       |
| Median (min–max)     | 0.5 (0.2–1.0)         | 0.5 (0.3–0.9)                   |         | 0.5 (0.2–1.0)    |
| **Route of administration** |                   |                                 |         |                  |
| Intravenous, n (%)   | 3 (0.4)               | 0 (0.0)                         |         | 3 (0.3)          |
| Subcutaneous, n (%)  | 809 (99.6)            | 303 (100.0)                     | 0.567d  | 1112 (99.7)      |
| **Treatment duration per CT cycle (days)** |               |                                 |         |                  |
| Mean ± SD            | 5.21 ± 1.95           | 5.56 ± 1.84                     | < 0.001c | 5.30 ± 1.93      |
| 95% CI               | 5.07; 5.34            | 5.35; 5.77                      |         | 5.19; 5.42       |
| Median (min–max)     | 5.0 (1.0–20.3)        | 5.0 (3.0–19.0)                  |         | 5.0 (1.0–20.3)   |

a Chi-square test. b From onset of CT cycle. c Wilcoxon-Mann-Whitney test. d Fisher exact test
(5 days vs. 3 days for the first CT cycle) [19]. On the other hand, identical treatment durations (5 days) were reported in the MONITOR-GCSF study and the TULIP study [21], thus indicating a well-established practice for the prevention of CIN. It should be noted that treatment duration was reported in an overwhelming majority of the patients (less than 0.5% of missing data) in the TULIP study, which contributed to the establishment of reliable conclusions for this parameter.

CT dose reduction and CT delay are main concerns in patients presenting with high-risk neutropenia, especially in elderly patients. When patients develop severe neutropenia (grade 3 or 4) or febrile neutropenia, most of the time, CT dose is reduced or treatments are delayed [32, 33]. These practices have a significant impact on the success rate of the treatments, especially for curative chemotherapies aiming to extend survival or maintain the quality of life. Primary prophylaxis using G-CSF was clearly demonstrated to prevent the development of neutropenia and to reduce the rate of infection and infection-related mortality in adult cancer patients receiving chemotherapy [34, 35]. However, little data is currently available with respect to elderly patients because they are often excluded from randomized trials. Furthermore, randomized trials conducted on Tevagrastim® did not address directly the effects on modifications of the chemotherapy [36–38]. In practice, the rates of CT dose reductions and CT delays due to neutropenic events in patients treated with short-acting G-CSF (filgrastim, lenograstim) vary considerably between studies (ranging from 1 to 46%) [18, 20, 39–43]. In our study, less than 10% of the patients required CT dose reduction or CT delay due to a neutropenic event (5.5% and 8.1%, respectively). These rates were lower for the patients who received PP (4.8% and 7.1%) than for those treated with SP (9.2% and 13.3%). These findings confirm the efficacy of Tevagrastim® for the prevention of CIN in elderly patients in a real-life setting.

There are several limitations to our study. First, the enrolled patients included those with various cancer diagnoses, disease stages, and chemotherapy regimen. Our results therefore cannot necessarily be extrapolated to specific patient populations. Second, we could only determine the risk of CT-induced febrile neutropenia for less than half of the patients included in the analysis, in accordance with the risks defined by the EORTC. Although the risk of developing FN from chemotherapy is a key element in the decision algorithm developed for the prevention of CIN, there is currently no classification system comparing the risk levels of all different protocols of chemotherapy. Whereas the 2010 EORTC guidelines offers a classification for the most common protocols [3], many are not included yet in this classification, therefore leading to a large number of missing data as regards the subgroups analysis for the risk of CIN. Consequently, the description of this parameter remains unclear and the impact of filgrastim treatment modalities on the risk of FN may be difficult to interpret. Although less robust than clinical trials from the methodological point of view, observational studies have the advantage of enabling “real-life” data collection, and thus to reflect the current clinical practice when a sufficiently large number of patients is included. The TULIP study was conducted on more than 1000 elderly cancer patients (aged 65 years or older). These patients are often excluded from clinical trials and, thus, seldom described in the literature [14]. Therefore, the TULIP study was able to establish the profile of an expanding category of patients as a result of the aging population. In France, more than 700,000 patients each year receive cancer treatments in hospital settings [7]. As of today, the incidence of malignancies after the age of 65 years has increased 11-fold compared with younger adults [44, 45] and nearly 30% of cancer patients are onco-geriatric patients [7]. Hence, it is essential to gain a better understanding of the conditions of use of filgrastim prophylaxis in these patients, which was the goal of the TULIP study.

As a conclusion, the French TULIP study is taking place in a broadly international reflection on cancer management of the elderly patients [44, 45]. Results provide a snapshot of real-life conditions of use of Tevagrastim® in elderly patients who receive prophylactic G-CSF medication: treatment is mainly initiated in primary prophylaxis during the first CT cycle (66%) and mean treatment duration per cycle is 5.3 ± 1.9 days. No difference was observed with regard to age or overall FN risk. Treatment duration was slightly longer when filgrastim was used in primary compared with secondary prophylaxis. The rates of CT delays and CT dose reductions were in the range of those reported previously for younger adult populations. These results highlight the efficacy and safety of prophylaxis with Tevagrastim® as common practice for elderly patients and support the data obtained from previous randomized trials on younger patient populations. Safety data were consistent with the known safety profile.

Acknowledgments The authors acknowledge all investigators for the conduct of the study and also all enrolled patients for their participation. This manuscript was prepared with the assistance of Lise Bosquet (on behalf of ICTA PM) in accordance with the European Medical Writers Association guidelines and Good Publication Practice.

Funding information The study was funded by Teva Santé.

Compliance with ethical standards Oral consent was obtained from each patient included. The study was conducted according to the ethical principles of the Declaration of Helsinki and in accordance with Good Epidemiological Practices. Approvals from the French review boards (Advisory Committee for data processing in Health Research [CCTIRS] and French data protection authority [CNIL]) were obtained.

Conflict of interest K.L. has received grants and personal fees from Novartis and Takeda; grants from Roche, Mundipharma, Hospira, and Teva Santé; and personal fees from Amgen. F.M. is an employee of Teva Santé. All remaining authors have declared no conflicts of interest.
Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

1. Crawford J, Caserta C, Rolla F, Group EGW (2010) Hematopoietic growth factors: ESMO Clinical Practice Guidelines for the applications. Ann Oncol 21(Suppl 5):v248–v251

2. Viret F, Goncalves A, Tarpin C, Chabannon C, Viens P (2006) G-CSF in oncology. Bull Cancer 93:463–471

3. Aapro MS, Bohlius J, Cameron DA, Dal Lago L, Donnelly JP, Kearney N, Lyman GH, Pettengell R, Tjan-Heijnen VC, Walewski J, Weber DC, Zielinski C, European Organisation for Research and Treatment of Cancer (2011) 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer 47:78–82

4. Repetto L (2003) Greater risks of chemotherapy toxicity in elderly patients with cancer. J Support Oncol 1:18–24

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

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

7. Institut National du cancer (2015) Les cancers en France. L’essentiel des faits et des chiffres. In: http://www.e-cancer.fr/Professionnels-de-sante/Les-chiffres-du-cancer-en-France/Epidemiologie-des-cancers

8. Lyman GH, Kuderer N, Agboola O, Balducci L (2003) Evidence-based use of colony-stimulating factors in elderly cancer patients. Cancer Control 10:487–499

9. Morrison VA, Picoci Z, Scott S, Pohlman B, Dickman E, Lee M, Lawless G, Kerr R, Caviglione V, Delgado D, Friedman M, Ford J, Carter WB, Oncology Practice Pattern Study Working Group (2001) The impact of age on delivered dose intensity and hospitalizations for febrile neutropenia in patients with intermediate-grade non-Hodgkin’s lymphoma receiving initial CHOP chemotherapy: a risk factor analysis. Clin Lymphoma 2:47–56

10. Balducci L (2003) Myelosuppression and its consequences in elderly patients with cancer. Oncology 17:27–32

11. Budman DR, Berry DA, Ciricione CT, Henderson IC, Wood WC, Weiss RB, Ferrer CR, Muss HB, Green MR, Norton L, Frei E (1998) Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. The Cancer and Leukemia Group B. J Natl Cancer Inst 90:1205–1211

12. Lepage E, Gisselbrecht C, Haioun C, Sebban C, Tilly H, Bosly A, Morel P, Herbrecht R, Reyes F, Coiffier B (1993) Prognostic significance of received relative dose intensity in non-Hodgkin’s lymphoma patients: application to LNH-87 protocol. The GELA (Groupe d’Etude des Lymphomes de l’Adulte). Ann Oncol 4: 651–656

13. Balducci L, Lyman GH (2001) Patients aged > or = 70 are at high risk for neutropenic infection and should receive hematopoietic growth factors when treated with moderately toxic chemotherapy. J Clin Oncol 19:1583–1585

14. Repetto L, Bignozzi L, Koehne CH, Luebbe AS, Soubeyran P, Tjan-Heijnen VCG, Aapro MS (2003) EORTC Cancer in the Elderly Task Force guidelines for the use of colony-stimulating factors in elderly patients with cancer. Eur J Cancer 39:2264–2272

15. Aapro MS, Koneh CH, Cohen HJ, Extermann M (2005) Never too old? Age should not be a barrier to enrollment in cancer clinical trials. Oncologist 10:198–204

16. Balducci L, Al-Halawani H, Charu V et al (2007) Elderly cancer patients receiving chemotherapy benefit from first-cycle pegfilgrastim. Oncologist 12:1416–1424

17. Romieu G, Clemens M, Mahlberg R, Fargeot P, Constena M, Schütte M, Easton V, Skacel T, Bacon P, Brugger W (2007) Pegfilgrastim supports delivery of FEC-100 chemotherapy in elderly patients with high risk breast cancer: a randomized phase 2 trial. Crit Rev Oncol Hematol 64:64–72

18. Kamioner D, Maloisel F, Leprêtre S, Berthou C, Abtrand H (2015) Safety of biosimilar filgrastim in elderly patients undergoing neutropenia-inducing chemotherapy: a subanalysis of the NEXT study. ASCO Annual Meeting 33:9541

19. Tesch H, Ulshofer T, Vehling-Kaiser U et al (2015) Prevention and treatment of chemotherapy-induced neutropenia with the biosimilar filgrastim: a non-interventional observational study of clinical practice patterns. Oncol Res Treat 38:146–152

20. Almenar D, Mayans J, Juan O et al (2009) Pegfilgrastim and daily granulocyte-colony-stimulating factor: patterns of use and neutropenia-related outcomes in cancer patients in Spain-results of the LEARN Study. Eur J Cancer Care 18:280–286

21. Gascon P, Aapro M, Ludwig H et al (2016) Treatment patterns and outcomes in the prophylaxis of chemotherapy-induced (febrile) neutropenia with biosimilar filgrastim (the MONITOR-GCSF study). Support Care Cancer 24:911–925

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

23. Gabrilove JL, Jakubowski A, Scher H, Stemberg C, Wong G, Grous J, Yagoda A, Fain K, Moore MAS, Clarkson B, Oettgen HF, Alton K, Welte K, Souza L (1988) Effect of granulocyte colony-stimulating factor on neutropenia and associated morbidity due to chemotherapy for transitional-cell carcinoma of the urothelium. N Engl J Med 325:1414–1422

24. Heil G, Hoelzer D, Sanz MA et al (1997) A randomized, double-blind, placebo-controlled, phase III study of filgrastim in remission induction and consolidation therapy for adults with de novo acute myeloid leukaemia. The International Acute Myeloid Leukemia Study Group. Blood 90:4710–4718

25. Morstyn G, Campbell L, Souza LM, Alton NK, Keech J, Green M, Sheridan W, Metcalf D, Fox R (1988) Effect of granulocyte colony stimulating factor on neutropenia induced by cytotoxic chemotherapy. Lancet 1:667–672

26. Trillet-Lenoir V, Green J, Manegold C, von Pawel J, Gatzemeier U, Lebeau B, Depierre A, Johnson P, Decoster G, Tomita D (1993) Pegfilgrastim supports delivery of FEC-100 chemotherapy in elderly patients with high risk breast cancer: a subanalysis of the NEXT study. Support Care Cancer 2:319–324
27. Weycker D, Hackett J, Edelsberg JS, Oster G, Glass AG (2006) Are shorter courses of filgrastim prophylaxis associated with increased risk of hospitalization? Ann Pharmacother 40:402–407

28. Tevagrasim. Résumé des Caractéristiques du Produit. In: http://www.ema.europa.eu/docsf

29. Scott SD, Chrischilles EA, Link BK et al (2003) Days of prophylactic filgrastim use to reduce febrile neutropenia in patients with non-Hodgkin’s lymphoma treated with chemotherapy. J Manag Care Pharm 9:15–21

30. Chrischilles EA, Link BK, Scott SD, Delgado DJ, Fridman M (2003) Factors associated with early termination of CHOP therapy and the impact on survival among patients with chemosensitive intermediate-grade non-Hodgkin’s lymphoma. Cancer Control 10:396–403

31. Tan H, Tomic K, Hurley D, Daniel G, Barron R, Malin J (2011) Comparative effectiveness of colony-stimulating factors for febrile neutropenia: a retrospective study. Curr Med Res Opin 27:79–86

32. Lyman GH, Lyman CH, Agboola O (2005) Risk models for predicting chemotherapy-induced neutropenia. Oncologist 10:427–437

33. Ray-Coquard I, Borg C, Bachelot T, Fayette J, Zufferey L, Guastalla JP, Ghesquière H, Blay JY, Sebban C, Marec-Bérard P, Biron P (2006) Prognostic factors for febrile neutropenia. Bull Cancer 93:501–506

34. Kuderer NM, Dale DC, Crawford J, Lyman GH (2007) Impact of primary prophylaxis with granulocyte colony-stimulating factor on febrile neutropenia and mortality in adult cancer patients receiving chemotherapy: a systematic review. J Clin Oncol 25:3158–3167

35. Rajan SS, Lyman GH, Steams SC, Carpenter WR (2011) Effect of primary prophylactic granulocyte-colony stimulating factor use on incidence of neutropenia hospitalizations for elderly early-stage breast cancer patients receiving chemotherapy. Med Care 49:649–657

36. del Giglio A (2008) XM02 is superior to placebo and equivalent to Neupogen in reducing the duration of severe neutropenia and the incidence of febrile neutropenia in cycle 1 in breast cancer patients receiving docetaxel/doxorubicin chemotherapy. BMC Cancer 8:332

37. Gatzemeier U, Ciuleanu T, Dediu M, Ganea-Motan E, Lubenau H, del Giglio A (2009) XM02, the first biosimilar G-CSF, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with small cell or non-small cell lung cancer receiving platinum-based chemotherapy. J Thorac Oncol 4:736–740

38. Engert A, Griskevicius L, Zyuzgin Y, Lubenau H, del Giglio A (2009) XM02, the first granulocyte colony-stimulating factor biosimilar, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with non-Hodgkin lymphoma receiving chemotherapy. Leuk Lymphoma 50:374–379

39. Mitchell S, Li X, Woods M, Garcia J, Hebard-Massey K, Barron R, Samuel M (2016) Comparative effectiveness of granulocyte colony-stimulating factors to prevent febrile neutropenia and related complications in cancer patients in clinical practice: a systematic review. J Oncol Pharm Pract 22:702–716

40. Barni S, Lorusso V, Giordano M, Sogno G, Gamucci T, Santoro A, Passalaqua R, Iaffaioli V, Zilembo N, Mencoboni M, Roselli M, Pappagallo G, Pronzato P (2014) A prospective observational study to evaluate G-CSF usage in patients with solid tumors receiving myelosuppressive chemotherapy in Italian clinical oncology practice. Med Oncol 31:797

41. Chan A, Leng XZ, Chiang JY et al (2011) Comparison of daily filgrastim and pegfilgrastim to prevent febrile neutropenia in Asian lymphoma patients. Asia Pac J Clin Oncol 7:75–81

42. Lane SW, Crawford J, Kenealy M, Cull G, Seymour JF, Prince HM, Marlton P, Gill D, Molle P (2006) Safety and efficacy of pegfilgrastim compared to granulocyte colony stimulating factor (G-CSF) supporting a dose-intensive, rapidly cycling anti-metabolite containing chemotherapy regimen (Hyper-CVAD) for lymphoid malignancy. Leuk Lymphoma 47:1813–1817

43. Schippingen W, Holab R, Dandachi N, Bauerahofer T, Samonigg H (2006) Frequency of febrile neutropenia in breast cancer patients receiving epirubicin and docetaxel/paclitaxel with colony-stimulating growth factors: a comparison of filgrastim or lenograstim with pegfilgrastim. Oncology 70:290–293

44. Pallis AG, Fortpied C, Wedding U, van Nes MC, Penninckx B, Ring A, Lacombe D, Monfardini S, Scalliet P, Wildiers H (2010) EORTC elderly task force position paper: approach to the older cancer patient. Eur J Cancer 46:1502–1513

45. Marosi C, Koller M (2016) Challenge of cancer in the elderly. ESMO Open 1:e000020

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.