Granulocyte-Colony-Stimulating Factor in Elderly Patients Receiving Chemotherapy for Breast and Gynaecological Cancers: Results of a French Survey

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Abstract. *Background: Age is a risk factor for chemo-induced febrile neutropenia (FN). According to ASCO guidelines, granulocyte colony-stimulating factor (G-CSF) use should be considered for regimens leading to a 10- to 20-percent risk of FN. Patients and Methods: A survey was undertaken describing the prescription of G-CSF in routine practices by 101 French physicians for 791 patients ≥70 years, having breast or gynaecological cancers, and receiving chemotherapy. Results: G-CSF was prescribed in 51% of the cases. A primary prophylaxis was prescribed in 90%, 59% and 36% of patients receiving regimens presenting a FN-risk of ≥20%, 10-20% and <10%, respectively. Covariates associated with the use of G-CSF were adjuvant chemotherapy, 3- or 4-weekly regimens, and geriatric assessment. Validated risk factors of FN were rarely considered. Conclusion: The prescription of G-CSF was multi-factorial. The estimation of FN risk was mainly based on physician's experience, explaining differences between guidelines and routine practice.*

Chemotherapy-induced neutropenia is often a dose-limiting toxicity of numerous chemotherapy regimens, knowing that the incidence of this side-effect varies according to the regimen. Febrile neutropenia (FN) is associated with substantial morbidity, mortality and costs (1-3). Chemotherapy-induced neutropenia may also result in a decrease of the dose intensity, with a potential detrimental consequence on the treatment outcome (4). All of these events could be grouped together under a unique entity named neutropenic events defined as either hospital admission due to FN, dose delay of at least 7 days due to neutropenia or dose reduction of ≥15% due to neutropenia (5).

The use of human recombinant granulocyte colony-stimulating factor (G-CSF) represents the only prophylaxis of chemotherapy-induced neutropenia. The prescription of G-CSF can be implemented either as primary prophylaxis for chemotherapy regimens inducing a high risk of chemotherapy-related FN, or as secondary prophylaxis, if a neutropenic event occurs within previous chemotherapy cycles. The role of G-CSF on the decrease of FN rates and duration of severe neutropenia has been well-documented (6, 7). The impact on early mortality and infection-related mortality remains controversial (7-9), although a recent meta-analysis focusing on breast cancer patients showed a decrease in all-cause mortality during treatment, and a reduced need for hospital care (10).

Appropriate use of G-CSF use has been standardized by international guidelines updated in 2006 by American Society of Clinical Oncology (ASCO), in 2012 by the National Comprehensive Cancer Network (NCCN) and in 2010 by European Society of Medical Oncology (ESMO) and European Organization for Research and Treatment of Cancer (EORTC) (4, 11-13). Overall, the G-CSF use must be tailored to the FN-risk of a given chemotherapy regimen (CT-FN-risk). Regimens associated with FN-risk ≥20% should be considered as high-risk, and a primary prophylaxis with G-CSF is recommended. When the risk ranges between 10 and 20%, the individual predisposing factors for increased incidence of FN and its

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complications should be assessed. The patient-related risk factors identified by ASCO, NCCN and EORTC guidelines are: age ≥65 years, advanced disease, history of prior FN, poor performance status (PS), poor nutritional status, and comorbidities. In elderly patients, it is now recognized that the G-CSF may be used in order to maintain chemotherapy and reduce the incidence of neutropenic events that are more frequent during the two first cycles of chemotherapy (14).

This multi-centre survey, based on anonymous data, involved French physicians. The purpose of this survey was to describe the current management of women ≥70 years presenting breast and gynaecological cancers. In this article, we focused on the results of G-CSF prescription in patients who received chemotherapy.

Patients and Methods

Selection of physicians and sample size. A representative sample of physicians was selected upon the following criteria: specialization (oncologist, radiotherapist), type of healthcare institutions (private hospitals, university hospitals, comprehensive cancer centres, and general hospitals), distribution among French regions, and sex. Each practitioner had to have at least three patients ≥70 years with ongoing chemotherapy regimens for breast and gynaecological cancers. One-hundred oncologists and radiotherapists were requested for a good representativeness according to the quota method. Each had to collect two patient cases of each following settings: adjuvant or neoadjuvant chemotherapy for breast cancer, first-line chemotherapy for metastatic breast cancer (MBC), second-line (or more) chemotherapy for MBC, and any line of chemotherapy for ovarian or endometrial cancer. Taking into account the medical specialization of each physician, the calculated sample size was estimated at 813 patients.

The format of collected/registered data did not allow the identification of patients.

Data collection and statistics. The data collection was performed either during a face-to-face interview, or through a file completed by the physician. The interview lasted about 60 minutes. The data collection was performed from October 4th to November 18th 2011. The questionnaire was made of three parts: • Physician's attitude - Impact of geriatric parameters on decision-making, criteria for chemotherapy prescription, criteria for G-CSF use; • Simplified collection - Description of currently treated breast and gynaecological cancer patients, regardless of the treatment; • Detailed collection - Description of currently treated breast and gynaecological cancer patients receiving chemotherapy.

Qualitative data were presented as a percentage, and quantitative data were described using mean, median, standard deviation and range. The chi-square test was used to compare baseline categorical variables. Continuous variables were compared using analysis of variance. Differences were considered statistically significant when the *p*-value was 0.05 or less.

Results

Patient and treatment characteristics. Among the 101 physicians recruited, 62 were oncologists and 39 radiotherapists; 65 were men and 36 women. They practised in private hospitals for 23, in university hospitals for 32, in comprehensive cancer centres for 15, and in general hospitals for 3 years. The mean number of years of practising was 13 years.

The sampled physicians declared to treat at least ninety patients ≥70 years per year for breast or gynaecological cancer (76 for oncologists, 112 for radiotherapists). A total number of 928 patients were entered in the simplified collection; 654 patients (70%) received chemotherapy; 791 patients were entered in the detailed collection. In the current analysis, the use of G-CSF was analyzed in these patients.

The distribution of patients according to primary tumor and treatment is presented in Table I. The CT-FN-risk was estimated according to the classification of chemotherapy regimen from EORTC guidelines (4). Among patients receiving chemotherapy, the CT-FN-risk was <10% in 657 patients (83%), between 10 and 20% in 124 patients (16%), and ≥20% in 10 patients (1%) (Table I). The great majority of patients have a CT-FN-risk <10% and, among the intermediate risk (*i.e.* 10 to 20%), breast cancer patients were the more numerous. Nearly 80% of the patients had a 0-1 PS, 69% of them presented a comorbidity and 33% presented with at least two comorbidities having a potential impact on safety.

The type of chemotherapy regimen is described in Table II. In 131 out of 584 breast cancer patients (22%), chemotherapy was combined with a targeted-therapy consisting of trastuzumab for 45 (8%), lapatinib for 9 (2%), and bevacizumab for 77 (13%). A significant lower rate of poly-chemotherapy was prescribed for breast cancer patients compared to ovarian and endometrial cancer patients (33% *vs*. 72% and 69%; $p<0.0001$). The cycle duration was also different since more than half of breast cancer patients received a weekly/divided schedule when nearly three-quarters of ovarian and endometrial cancer patients received a 3-4 weekly regimens ($p<0.0001$). With regard to cytotoxic, 20% of patients had received an anthracycline, especially in breast cancer; more than half of patients had received a taxane of whom more than 70% for ovarian and endometrial cancers; capecitabine and vinorelbine were prescribed exclusively for breast cancer; and platinum salts were mainly used for ovarian and endometrial cancers within the frame of paclitaxel-carboplatin regimen.

G-CSF use. A G-CSF was prescribed in 401 patients (51%). The prescription of G-CSF was significantly higher in ovarian cancer than in breast and endometrial cancers (61% *vs*. 48% and 52%; $p=0.01$). The profile of G-CSF prescription according to indication, setting, group of age, and chemotherapy-related risk is summarized in Table III. In 80% of the cases, a G-CSF was prescribed as primary prophylaxis. In 75% of the cases, a G-CSF was prescribed in patients presenting a CT-FN-risk <10%. In this latter group, breast cancer patients were less likely to receive a G-CSF (68% *vs*. 93% and 86%; $p<0.0001$). Overall, 46% of

Table I. *Distribution of patients according to primary tumor and treatment*.

Nr. of patients (%)	Breast	Ovary	Endometrium	Total
Overall	584	165	42	791
Age, median (range)	74 (70-91)	74 (70-89)	73 (70-84)	74 (70-91)
Group of age				
70-72 years	202 (35)	51 (31)	18 (43)	271 (34)
73-75 years	178 (30)	51 (31)	16 (38)	245 (31)
>75 years	204 (35)	63 (38)	8 (19)	275 (35)
Performance status				
0-1	462 (79)	126 (76)	31 (74)	619 (78)
≥2	108 (19)	26 (16)	9 (21)	143 (18)
Not reported	14 (2)	13 (8)	2 (5)	29 (4)
Comorbidities	407 (70)	111 (67)	29 (69)	547 (69)
Metastatic disease	391 (67)	97 (59)	28 (67)	516 (65)
Line of treatment				
Adjuvant/neoadjuvant	193 (33)	68 (41)	14 (33)	275 (35)
1st-line	194 (33)	67 (41)	24 (57)	285 (36)
≥2nd-line	197 (34)	30 (18)	4 (10)	231 (29)
Chemotherapy-related risk of FN				
<10%	465 (80)	154 (94)	38 (91)	657 (83)
10-20%	116 (20)	7 (4)	1 (2)	124 (16)
≥20%	3 (<1)	4 (2)	3 (7)	10 (1)

FN, Febrile neutropenia.

Table II. *Type of chemotherapy regimen*.

Regimen, n (%)	Breast[b]	Ovary	Endometrium	Total
Nr. of patients	584	165	42	791
Polychemotherapy	190 (33)	119 (72)	29 (69)	338 (43)
Rhythm of administration				
Every 21-28 days	289 (49)	120 (73)	31 (74)	440 (56)
Weekly/divided dose	295 (51)	45 (27)	11 (26)	351 (44)
Anthracycline[a]	134 (22)	20 (12)	3 (7)	157 (20)
Epirubicin	101 (17)	-	-	101 (13)
Doxorubicin	14 (2)	1 (<1)	2 (5)	17 (2)
Liposomal doxorubicin	19 (3)	19 (12)	1 (2)	39 (5)
Taxane[a]	280 (48)	118 (71)	30 (71)	428 (54)
Docetaxel	128 (22)	2 (1)	2 (4)	132 (17)
Paclitaxel	151 (26)	116 (70)	28 (67)	295 (37)
Ixabepilone	1 (<1)	-	-	1 (<1)
CMF	3 (<1)	-	-	3 (<1)
Capecitabine[a]	108 (18)	-	-	108 (14)
Vinorelbine[a]	59 (10)	-	1 (2)	60 (8)
Gemcitabine[a]	21 (4)	5 (3)	-	26 (3)
Platinum salt[a]	12 (2)	132 (80)	33 (78)	179 (23)
Cisplatin	-	4 (2)	9 (21)	13 (2)
Carboplatin	10 (2)	128 (78)	24 (57)	164 (21)
Oxaliplatin	2 (<1)	-	-	2 (<1)
Topotecan	-	6 (4)	-	6 (<1)

CMF, Cyclophosphamide, methotrexate, 5-fluorouracil. [a]As patients can have received polychemotherapy, the total number of each drugs prescribed exceeds 100%. Of note, in ovarian cancer, one patient received cyclophosphamide as single-agent and one patient received 5-fluorouracil as single-agent. In the other cases, cyclophosphamide and 5-fluorouracil were prescribed in combination with other cytotoxics among all gynecologic cancers. [b]In 131 of 584 breast cancer patients (22%), chemotherapy was combined with a targeted therapy consisting of trastuzumab for 45 (8%), lapatinib for 9 (2%), and bevacizumab for 77 (13%).

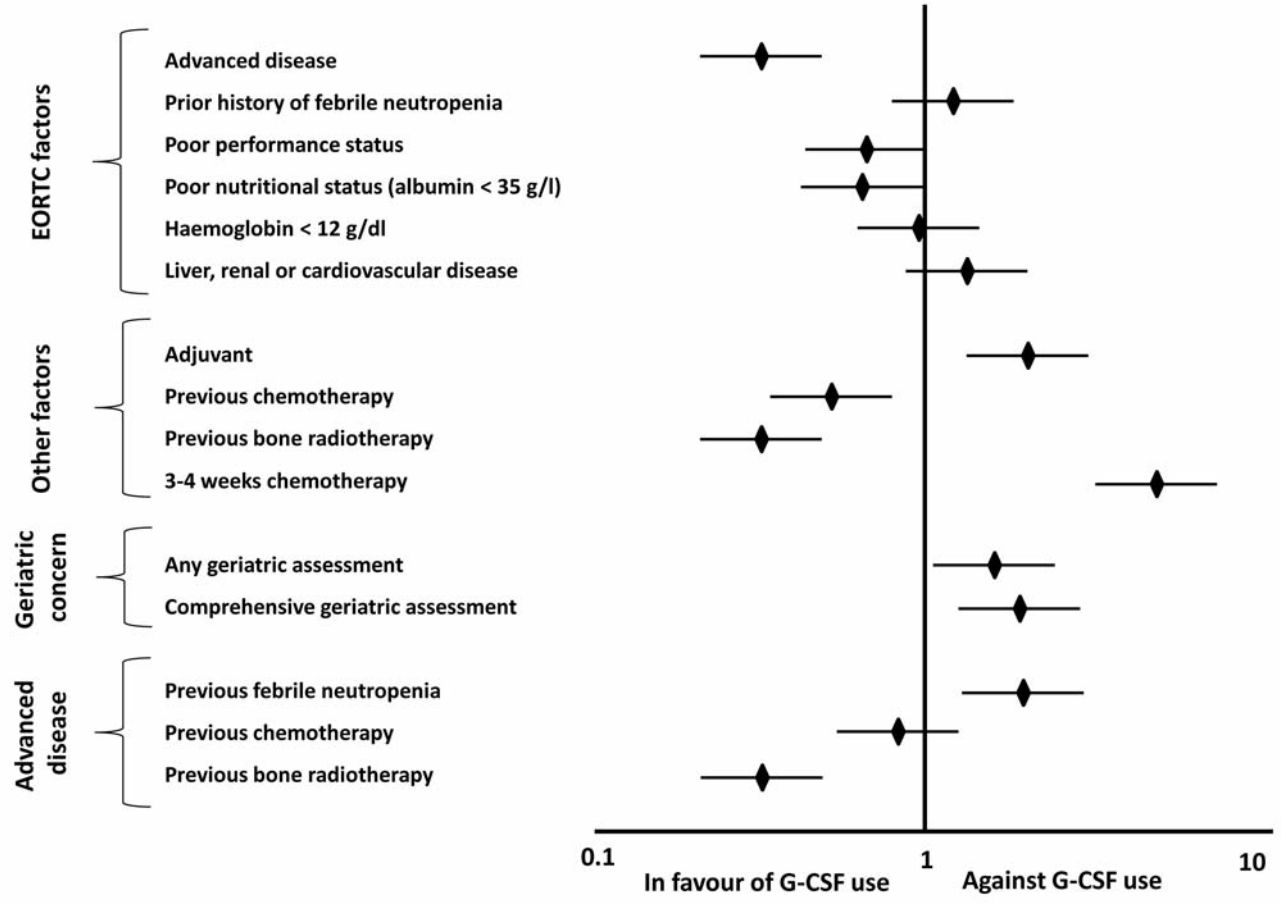

Figure 1. *Factors associated with G-CSF use in the whole population.*

patients having a CT-FN-risk <10% received a G-CSF compared with 73% of those having a risk between 10% and 20%, and 100% of those having a risk ≥20%.

The significant factors associated with G-CSF use in the whole population were advanced disease, previous chemotherapy and bone radiotherapy (Figure 1). Adjuvant setting, chemotherapy delivered 3-4 weekly and geriatric assessments favoured the use of G-CSF. The factors associated with G-CSF primary prophylaxis in the subset of patients with a CT-FN-risk lower than 10% were similar to those declared in the whole population, whereas no significant factors were associated in patients with a 10- to 20% CT-FN-risk (Figure 2).

The type of G-CSF prescribed was lenograstim in 159 patients (40%), pegfilgrastim in 171 (43%), filgrastim-reference in 31 (8%), and filgrastim-biosimilars in 39 (9%). In patients receiving weekly/divided regimens, pegfilgrastim was significantly less delivered than other G-CSFs (18% *vs.* 82%, respectively) compared to patients receiving q3w-q4w regimens (49% *vs.* 51%, respectively) ($p<0.0001$).

The cycle of initiation was the first cycle in more than 80% of the cases, irrespective of the G-CSF prescribed (Figure 3a). The median day of G-CSF initiation was day 3 although the day of initiation varied among G-CSFs: pegfilgrastim was preferentially delivered between day 2 and 4 (92%) comparatively to the other G-CSFs (about 60%); only filgrastim and pegfilgrastim were prescribed during chemotherapy in less than 5% of the cases (Figure 3b). The onset day of G-CSF was significantly later in patients receiving weekly/divided regimens compared to those receiving q3w-q4w regimens, as the onset was at least day 5 in 39% *vs.* 18% of patients, respectively ($p<0.0001$).

The median duration of daily G-CSF (lenograstim or filgrastim) therapy was 5 days. Only 7 patients of 229 (3%) received more than 7 days of daily G-CSF. There was no significant difference in terms of G-CSF duration (1 to 3 days *vs.* ≥4 days) between weekly/divided regimens and q3w-q4w regimens (1 to 3 days: 47% *vs.* 57%, respectively; ≥4 days: 53% *vs.* 43%, respectively; $p=0.07$).

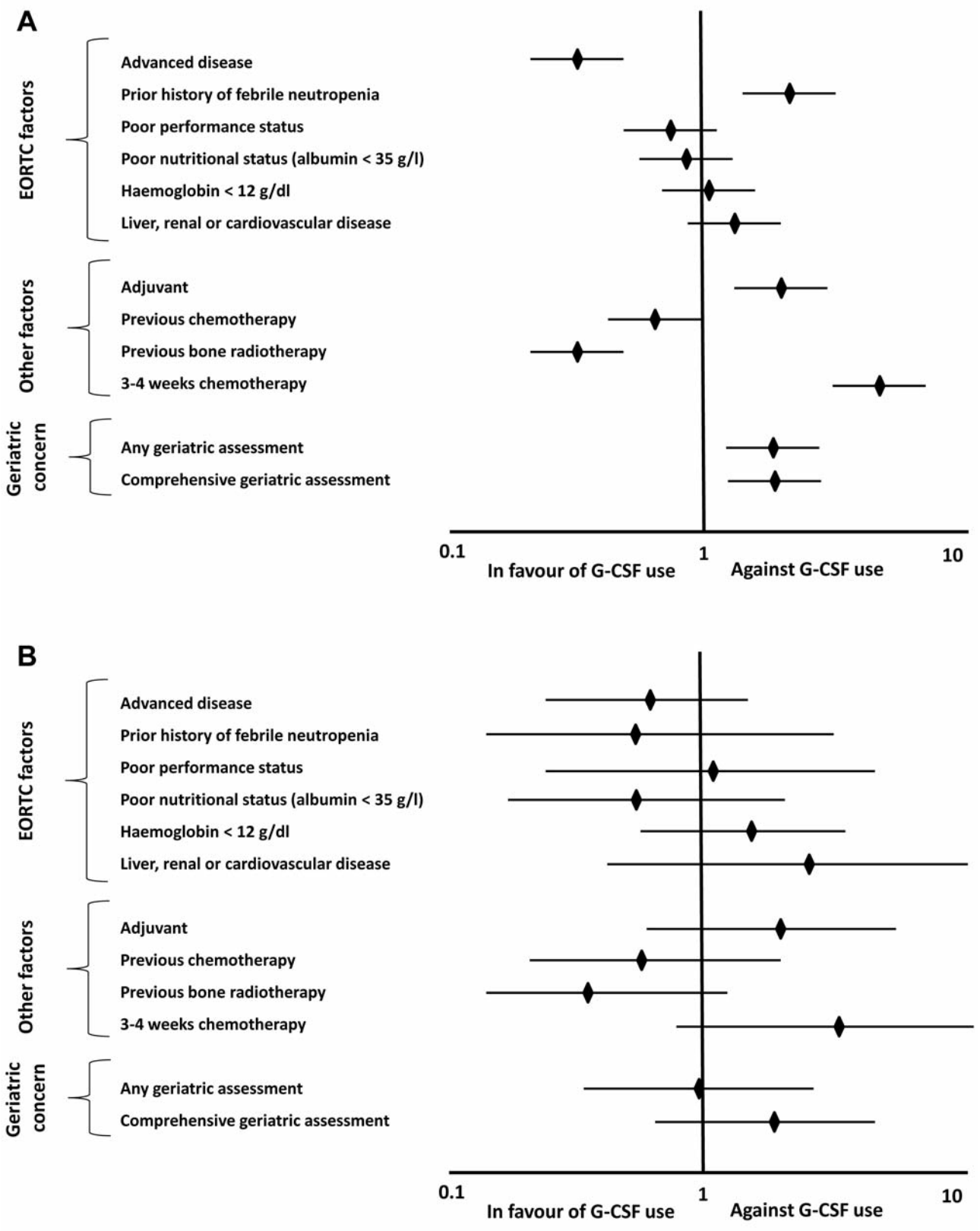

Figure 2. *Factors associated with G-CSF primary prophylaxis in patients with a chemotherapy-related risk of FN <10% (a) and 10-20% (b). Secondary and curative settings were excluded.*

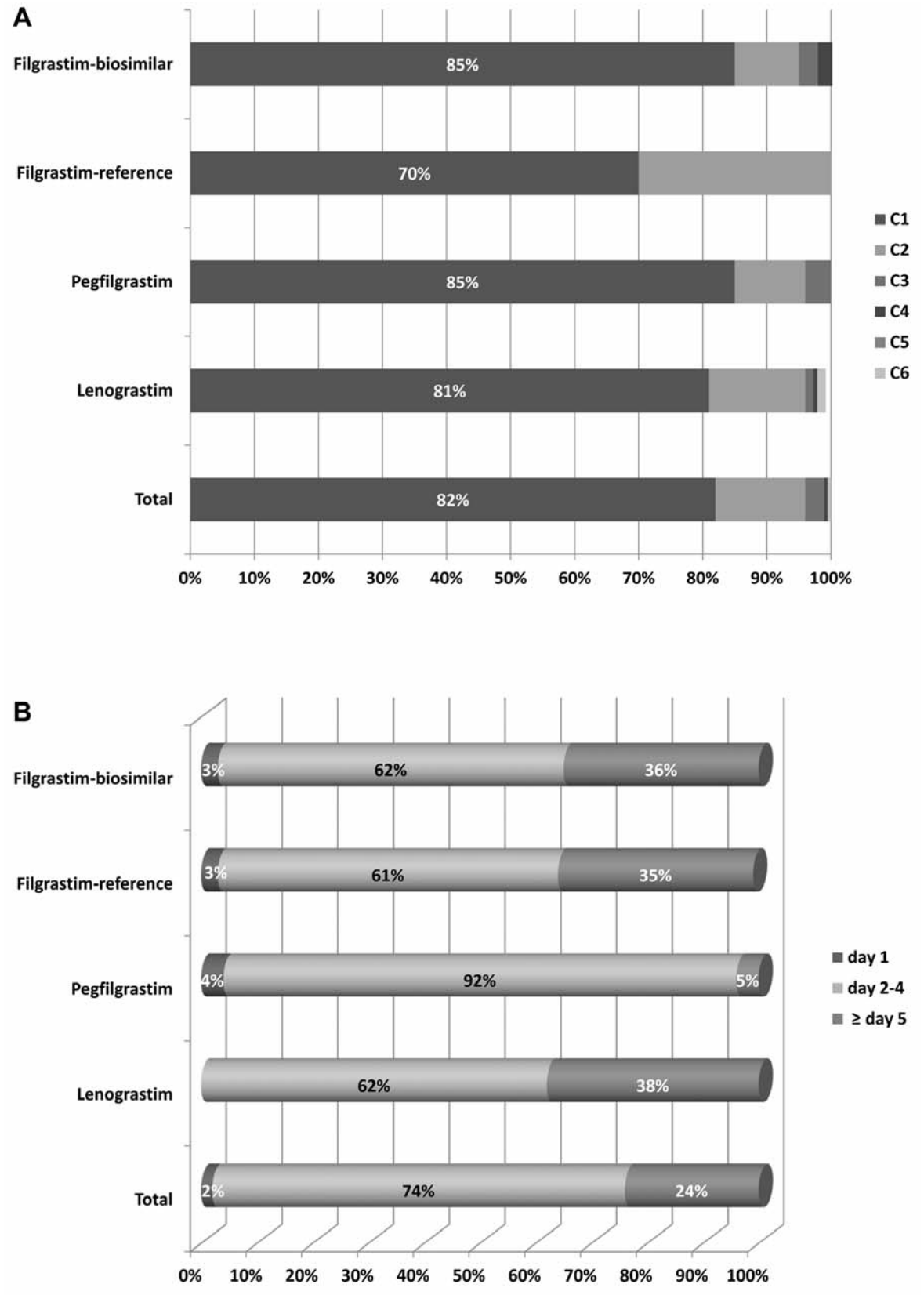

Figure 3. *G-CSF treatment modalities: cycle of initiation (a) and day of initiation (b).*

Table III. *G-CSF use: profile of prescription.*

Profile, n (%)	Breast (n=584)	Ovary (n=165)	Endometrium (n=42)	Total (n=791)
G-CSF use	279 (48)	100 (61)	22 (52)	401 (51)
Indication				
Primary prophylaxis	218 (78)	81 (81)	21 (95)	320 (80)
Secondary prophylaxis	57 (20)	19 (19)	1 (5)	77 (19)
Not reported	4 (2)	-	-	4 (1)
Setting				
Adjuvant/Neoadjuvant	129 (46)	42 (42)	6 (27)	177 (44)
Metastatic	150 (54)	58 (58)	16 (73)	224 (56)
Age				
70-72 years	106 (38)	31 (31)	9 (41)	146 (36)
73-75 years	98 (35)	32 (32)	9 (41)	139 (35)
>75 years	75 (27)	37 (37)	4 (18)	116 (29)
Chemotherapy-related risk of FN				
<=10% (n=657)	189 (68)	93 (93)	19 (86)	301 (75)
10-20% (n=124)	87 (31)	3 (3)	-	90 (22)
≥20% (n=10)	3 (1)	4 (4)	3 (14)	10 (3)

FN, Febrile neutropenia.

Discussion

Cancer is a disease of the elderly, with more than 60% of cancer cases diagnosed in patients over the age of 65 years (15). Despite these demographics, elderly patients are infrequently included in clinical trials, resulting in a paucity of data regarding the effectiveness of standard treatments for many common cancers in the elderly, notably in breast cancer (16, 17). There is evidence that in clinical practice, older women with early-stage breast cancer receive adjuvant chemotherapy less frequently than do their younger counterparts (18, 19). However, the majority of comparative trials demonstrate that chemotherapy is tolerated equally well by healthy elderly women with breast cancer as by younger women (20, 21). Even if our findings present the limitation of an observational study, the interest of this survey is to address, for the first time, the issue of G-CSF prescription in elderly breast and gynaecological cancer patients.

In the present survey, among patients who were sent to physicians specialised in oncology, 70% of them have received chemotherapy. In 2006, a French survey involving MBC patients over 75 years showed that only 31% received chemotherapy, and that, in 75% of cases, cytotoxics doses were lower than those usually recommended (22). The present findings show a trend in a better management of elderly cancer patients. However, we have to keep in mind that few cancer patients were referred to these Institutions.

In more than 80% of cases, chemotherapy regimens presented a CT-FN-risk lower than 10% according to the EORTC classification (4). The frequency of low-risk regimens is dramatically higher than in the general population where this rate is about 20% (23). Overall, 46% of patients receiving a chemotherapy with a FN-risk <10% were treated with a G-CSF compared with 73% of those having a risk between 10% and 20%, and 100% of those having a risk ≥20%. The prescription of G-CSF was partially in compliance with guidelines for patients receiving a chemotherapy regimen with a CT-FN-risk ≥20% as 10% of them were treated with a G-CSF in secondary prophylaxis (4, 11-14). Noteworthy, the use of G-CSF was also extensive in patients with low and intermediate CT-FN-risk. An epidemiologic survey was reported performed in order to better define the prescription of G-CSF according to EORTC guidelines (23). Contrary to the EORTC guidelines, about 25% of patients with a high CT-FN-risk and 25% of those with a risk between 10 and 20% plus associated risk factor did not receive G-CSF, whereas a prescription of G-CSF was not rare in patients with a risk <10%. The authors concluded that the trend to initiate G-CSF in low CT-FN-risk population may be indicative of changing practice in order to optimize patient well-being and minimize the risk of FN. Moreover, the estimation of the FN incidence for a given chemotherapy regimen is based on clinical trials, which could underestimate this risk. Several reports showed that hematologic toxicity, as well the use of G-CSF or antibioprophylaxis were often underreported in clinical trials (24-28). For instance, the docetaxel-cyclophosphamide (TC) regimen in adjuvant setting of breast cancer exhibited an 8%-rate of FN in patients older than 65 years in spite of a systematic antibioprophylaxis (27). In routine clinical practice, TC and FEC-D without G-CSF are associated with FN rates exceeding the 20% threshold for which primary G-CSF prophylaxis is commonly recommended, and are considerably higher than those reported in pivotal clinical trials (28).

In 80% of the cases, a G-CSF was prescribed as primary prophylaxis. In a French survey conducted from 2010 to 2011, describing the routine use of G-CSF in patients of all age (26% ≥70 years), the rate of primary prophylaxis was 66% (29). Another survey evaluating the neutropenia prophylaxis in patients receiving myelosuppressive chemotherapy with moderate or high CT-FN-risk showed that the rate of primary prophylaxis exceeded 80%, irrespective of primary tumour and age (30). These results highlight that a primary prophylaxis is more frequent in elderly patients and in high-risk patients.

In the present survey, the mean duration of G-CSF was 5 days. These findings were similar to those previously described in a survey conducted in 2006 for patients receiving chemotherapy in the frame of solid tumours or lymphomas (31). The duration of G-CSF therapy remains controversial as no standard duration has been clearly defined. The international guidelines recommend continuing G-CSF until a stable/sufficient, post-nadir neutrophil count (4, 12, 13). The

ASCO guidelines mention a target value of 2-3×10^9/L (11). Thereby, the treatment duration should be guided by blood count that is not commonly prescribed for outpatient in routine practices. The first trials evaluating G-CSF efficacy were designed for 2-week G-CSF regimens, correlating with a target value of 10×10^9/L (32,33). The ESMO guidelines state that this target value is not mandatory, knowing that this goal does not match with routine practices and is not cost-effective (12). A G-CSF duration of 5 days has been studied, showing the efficacy of such schedule for the prophylaxis of FN in patients with sarcoma (34). Some authors faced with alternative schedules with reduced number of injections to decrease the incidence of bone pains (35). The ASCO guidelines mention that these schedules have to be evaluated (11). In spite of routine practices, the 5-day regimen is not validated and will be probably never confirmed with a high level of evidence because of the number of trials to initiate, establishing the proof of concept.

With regard to the onset day of G-CSF, the prescription was in agreement with the guidelines that recommend initiating G-CSF 24 to 72 hours after the end of chemotherapy (11-13).

The use of G-CSF was based on multifactorial conditions. Probably, the estimate of chemotherapy-induced risk of FN was mainly based on physician's experience more than on the EORTC classification, explaining the differences between this classification and routine practices. Moreover, this classification is not fully adapted to elderly patients as no clinical trial has been designed for this subset of patients. A review of ASCO stated that approximately half of the patients receiving a chemotherapy with a theoretical CT-FN-risk <10% or between 10 and 20% have individual risk factors increasing the risk to 20% (36). When use in an appropriate way, the authors concluded that G-CSF represents one of the top five key opportunities to improve care and reduce costs.

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