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ORIGINAL ARTICLE

Zarzio®, biosimilar of filgrastim, in prophylaxis of chemotherapy-induced neutropenia in routine practice: a French prospective multicentric study

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Abstract
Purpose Chemotherapy-induced neutropenia is a serious and potentially life-threatening consequence of cancer treatment. Prophylactic treatment with granulocyte-colony stimulating factor (G-CSF) decreases the incidence of febrile neutropenia, the rate of hospitalization, and the use of antibiotics in patients at risk. The aim of this study was to assess efficacy, safety, and use of Zarzio®—biosimilar of Neupogen® (G-CSF; filgrastim)—in prophylaxis of chemotherapy-induced neutropenia in current practice in cancer patients.
Methods We conducted an observational, prospective, longitudinal, and multicentric study in France. The incidence of neutropenia was evaluated at each cycle of chemotherapy.
Results One hundred eighty-four patients (women, 64.7 %; mean age, 61.7 years) with solid tumor (89.7 %; breast cancer, 50.5 %) or non-Hodgkin lymphoma (10.3 %) were included. The risk of febrile neutropenia based on chemotherapy regimen was >20 % for 32.1 % of patients. No case of febrile neutropenia was reported. Neutropenia was the cause of hospitalization and/or antibiotic therapy in 10 patients. The most frequent adverse events related to Zarzio® were pain, in particular bone pain. No serious adverse event related to Zarzio® was reported.
Conclusion The results obtained in real-life conditions confirm that Zarzio® is efficient and well tolerated in cancer patients.

Keywords Chemotherapy-induced neutropenia · Filgrastim · Biosimilar · Observational study · Zarzio®

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Introduction

Chemotherapy-induced neutropenia is a serious and potentially life-threatening consequence of cancer treatment because sepsis or severe infections are possible complications; neutropenia is generally observed during the first cycles of chemotherapy [1–6]. Moreover, delays and dose reductions of chemotherapy due to neutropenia in subsequent treatment cycles compromise efficacy [7–11].

Prophylactic administration of antibiotics significantly reduces the incidence of febrile neutropenia and mortality related to infections [12]. Antibiotic prophylaxis to prevent infection and infection-related complications in cancer patients at risk of febrile neutropenia is however controversial due to possible emergence of antibiotic resistance. The guidelines of the European Organization for Research and Treatment of Cancer (EORTC) do not recommend systematic administration of prophylactic administration of antibiotics [13]. An alternative approach is the prophylactic treatment with granulocyte-colony stimulating factor (G-CSF; filgrastim, lenograstim, pegfilgrastim) which decreases the incidence of febrile neutropenia, the rate of hospitalization, and the use of antibiotics in patients at risk [14].

The use of G-CSF in the prevention of chemotherapy-induced febrile neutropenia has been defined in different international guidelines. The guidelines of the American Society of Oncology (ASCO) in 2006 and those of the

National Comprehensive Cancer Network (NCCN) in 2014 recommend the use of G-CSF in primary prophylaxis for chemotherapy associated with a risk of febrile neutropenia ≥20 % [15, 16]. The 2006 guidelines of EORTC updated in 2010 recommend the systematic use of G-CSF in primary prophylaxis to prevent febrile neutropenia if the risk of febrile neutropenia associated with the cytotoxic chemotherapy is ≥20 %, but also on a case-by-case basis if the cytotoxic chemotherapy induces a risk from 10 to 20 % [13]. In this case, the recommendations take into account patient-related risk factors that may increase the overall risk of febrile neutropenia such as age above 65 years.

Zarzio® is a biosimilar of filgrastim (Neupogen®). This biosimilarity has been demonstrated in analytical tests that assessed the physicochemical and biological characteristics of Zarzio® [17], in four phase I studies in 146 healthy volunteers and in a confirmatory phase III study for clinical efficacy in 176 patients with breast cancer [18]. Moreover, a retrospective study comparing the efficacy of Zarzio® to a historical cohort treated with Neupogen® [19] and an observational study [20] in patients with solid tumor or hematological cancer demonstrated that Zarzio® prevented chemotherapy-induced febrile neutropenia in ambulatory care, without unexpected adverse events. Few data were however available on the use of this biosimilar of filgrastim outside the controlled experimental environment of clinical trials. The objective of the present study was (1) to improve knowledge on Zarzio® for efficacy and safety in real-world conditions and (2) to understand how clinicians use Zarzio® in their clinical practice for the prophylaxis of chemotherapy-induced neutropenia.

Patients and methods

Study design

The Zarzio® Observational Study (ZOS) was an observational, prospective, longitudinal, and multicenter study, performed in French cancer centers. The objective of the study was to describe the prophylactic effect of Zarzio® on the incidence of severe neutropenia (<500 neutrophils/mm^3) and to collect data on safety and conditions of use in current clinical practice. The prescription of Zarzio® to a patient was independent of the inclusion of this patient in the study. The follow-up of each patient was a maximum of 6 cycles.

Inclusion criteria

Patients of both genders included in the study were aged of 18 years and older, received first-line chemotherapy for solid tumor or non-Hodgkin lymphoma with a performance index ≤ 3, and were treated with Zarzio® with either a risk of febrile neutropenia>20 % or between 10 and 20 % with patient-related risks of febrile neutropenia as described by EORTC. Female patients must be postmenopausal for at least 1 year, sterile, or used efficient contraception. The main exclusion criteria were as follows: patient with grade 3 or 4 neutropenia (neutrophils $<1\times10^9$/L or 1000/mm^3), myeloid leukemia, hypersensitivity to Zarzio® or to any other G-CSF, hypersensitivity to *Escherichia coli*-derived proteins or treatment by chemotherapy at high doses.

The patients were informed both orally and in writing on the objectives of the study. This study was conducted according to the current revision of the 1964 Helsinki declaration and with the French laws and regulations.

Data collected

Data of each patient were collected in an electronic case report form by the study physicians: sociodemographic data of investigator and patient, characteristics of cancer disease, number of chemotherapy treatments, type of chemotherapy, total scheduled dose and total administered dose, scheduled interval between chemotherapy cycles, risk factors of chemotherapy-induced neutropenia, number of neutrophils during follow-up, adverse events, clinical and biological data, treatment with Zarzio® (date of onset, duration of treatment, and dosage), episodes of febrile neutropenia, and use of antibiotics. Data were collected at each cycle of chemotherapy.

Statistical analysis

The primary endpoint of the study was the comparison of the incidence of severe neutropenia at nadir between the 1st and the 4th cycle under treatment with Zarzio®. The expected incidence of severe neutropenia (grade 4: < 500 neutrophils/mm^3) at nadir was approximately 40 % for the 1st cycle of chemotherapy and 25 % for the 4th cycle [12]. In order to detect a decrease of 15 % of the incidence of severe neutropenia with an alpha-risk at 5 % and a statistical power at 80 %, 150 patients were needed. With a rate of 20 % of non evaluable patients, 200 patients must be included. This analysis could not be performed due to the lack of data on neutrophil rates at nadir. This study allowed nevertheless collecting data on efficacy, safety and conditions of use of Zarzio®. Clinical and hematological parameters during the follow-up were analyzed in the population of patients treated with Zarzio®.

The relative dose intensity (RDI) was calculated at each cycle (total dose of chemotherapy administered during a cycle divided by the total dose scheduled for the same cycle).

Results

Characteristics of study physicians

Among the 14 study physicians, 9 were male and they had a median of 18 years of practice (from 3 to 36 years). Nine practiced in general/university hospitals, 3 in specialized cancer centers, and 2 in private clinics. About the use of G-CSF in chemotherapy-induced neutropenia, 11 out 14 reported to refer to the guidelines of EORTC, and the 3 other physicians referred to ASCO recommendations.

Disposition of patients

Figure 1 summarizes the disposition of the 184 patients included in the study during the chemotherapy cycles and, among them, those who received Zarzio®. The median duration of follow-up of patients was 110 days (range from 28 to 243 days). A total of 32 patients (17.4 %) discontinued the study, most frequently due to disease progression.

Characteristics of patients

The characteristics of the 184 patients at inclusion are described in Table 1. The study population had a median age of 64 years, and two-third were women. Chemotherapy was administered for solid tumor for 89.7 % of patients, mainly breast cancer (50.5 %); 10.3 % of patients (19/184) had non-Hodgkin lymphoma. The median time interval between diagnosis and inclusion was 1.7 months, and mean was 10.2 months.

Among patients with solid tumor, tumoral stage was T3 for 20.1 % and T4 for 11.0 %; there was stage N1 or more of lymph node involvement for 52.1 % (85/163), and 20.2 % (33/163) had metastases (stage M1). Nineteen patients among the 33 stage M1 patients had a metastatic relapse that was diagnosed with a median of 2.1 months before inclusion. Among patients with non-Hodgkin lymphoma, 42.1 % (8/19) achieved stage IV (classification of Ann Arbor).

Risk factors of neutropenia

The risk factors of febrile neutropenia were assessed before the first cycle of chemotherapy: 32.1 % (59/184) of patients had a risk of febrile neutropenia >20 %; 55.4 % (102/184) of patients had a risk between 10 and 20 %, and for 12.5 % (23/184), the risk was <10 % (Table 2). The patient-related risk factors increasing the overall risk of febrile neutropenia were as follows: age>65 years for 45 % (82/184) of patients, concomitant at-risk diseases for 20 % (36/184), and hemoglobin< 12 g/dL for 25 % (46/184). Among the patients with a risk of febrile neutropenia<10 %, 9/23 had an age above 65 years, 6/23 had a concomitant at-risk disease, and 8/23 had hemoglobin<12 g/dL (Table 2).

Cycles of chemotherapy

For most patients, the scheduled number of cycles was between 3 and 6 (96.2 %; 177/184) and, for the majority, 6 cycles were scheduled (70.1 %; 129/184) (Table 1). Most frequently, the scheduled time interval between 2 cycles was 3 weeks (78.3 %; 144/184).

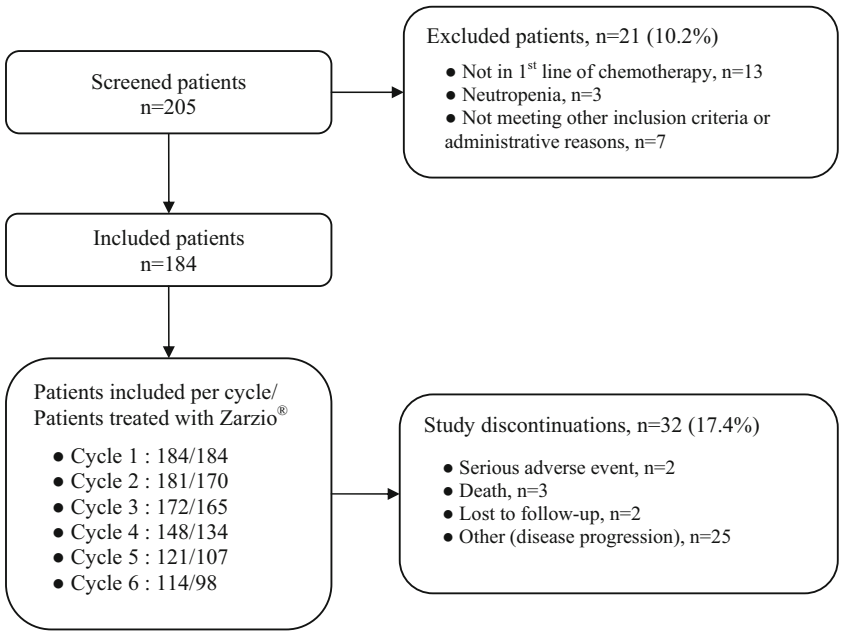

Fig. 1 Disposition of patients

Table 1 Characteristics of patients at inclusion

Characteristics	*N*=184
Female gender, *n* (%)	119 (64.7)
Age, years	
Mean (SD)	61.7 (11.6)
Median (min–max)	64.0 (26–88)
Body mass index, kg/m^2	
Mean (SD)	26.7 (6.0)
Median (min–max)	25.8 (16.5–50.6)
Time interval since diagnosis, months	
Mean (SD)	10.2 (30.0)
Median (min–max)	1.7 (0–228)
Type of primary tumor, *n* (%)	
Non-Hodgkin lymphoma	19 (10.3)
Solid tumor	165 (89.7)
Breast cancer	93 (50.5)
Lung cancer	13 (7.1)
Other solid tumor	59 (32.1)
Patients with metastases (stage M1)	33 (20.2)*
Metastatic relapse, *n*	19
1 site	12
≥2 sites	7
Metastatic sites, n	
Liver	6
Lung	5
Bone marrow	2
Other	14
Previous treatments, *n* (%)	
Radiotherapy	27 (14.7)
Surgery	98 (53.3)
Hormone therapy	13 (7.1)
Number of planned chemotherapy cycles, *n* (%)	
6	129 (70.1)
4	21 (11.4)
3	24 (13.0)
Other (1, 2, 5, 8)	10 (5.4)

*Two patients with missing data

The RDI administered for the included population varied from 96 to 99 % between cycle 1 and cycle 6; the rate of patients with RDI≥85 % varied from 89 to 99 % between cycle 1 and cycle 6.

A modification of chemotherapy protocol occurred for 47.8 % of patients (88/184): decrease>15 % of scheduled dose (29.5 %; 26/88), increase of the scheduled duration between 2 cycles (70.5 %; 62/88), or change of the number of scheduled cycles (35.2 %; 31/88).

Overall, chemotherapy began according to the initial schedule in 85.9 % of cases. When it was not the case, neutropenia was responsible for this administration delay in 19.8 % of cases.

Surgery of tumor was scheduled during chemotherapy for four patients (2.2 %) (during cycle 3 for the four patients). Radiotherapy was scheduled during at least one cycle for three patients (cycle 1; cycles 1 and 2; cycle 3).

Treatment with Zarzio®

Table 3 describes the conditions of administration and exposition to Zarzio® during the 6 chemotherapy cycles. The mean dose was stable during the 6 cycles (approximately 33 MIU per day; median, 30 MIU per day) with a median number of 5 injections per cycle. The mean duration between the onset of chemotherapy cycle and the onset of Zarzio® administration varied from 3.6 to 4.5 days according to cycles (median, 3 days for each cycle); the mean duration of exposition to Zarzio® varied from 4.6 to 4.8 days (median, 5 days for each cycle). All injections were done by a nurse (and not by a physician or by the patient him/herself).

Rates of neutrophils during the follow-up and chemotherapy-induced neutropenia

The mean rates of neutrophils between cycle 1 and cycle 6 progressively decreased from 4584 to 3601/mm^3 in patients treated with Zarzio (Table 4). This decrease mainly occurred after the first chemotherapy cycle and remained nearly stable for the next cycles. Accordingly, the rate of grade 1–2 neutropenia (1000–2000 neutrophils/mm^3) mostly increased after the first cycle: 5.6, 20.5, 16.1, 24.4, 23.4, and 31.6 % for each of the 6 successive cycles. Only one grade 4 neutropenia was observed (after cycle 1).

No case of febrile neutropenia was reported during the study. Neutropenia led to hospitalization and/or antibiotic treatment in 10 patients (hospitalization with antibiotic treatment, *n*=2; hospitalization without antibiotic treatment, *n*=4; antibiotic treatment without hospitalization, *n*=4).

Other hematological and clinical parameters

The clinical parameters (body mass index, temperature, performance status) remained stable during the study in the population of patients treated with Zarzio (Table 5).

As for neutrophils, the means of the other hematological parameters decreased between cycle 1 and cycle 6 in the population of patients treated with Zarzio: leucocytes from 7479 to 6137/mm^3; lymphocytes from 1733 to 1330/mm^3; and Hb from 12.8 to 11.2 g/dL (Table 5). The rates of platelets remained relatively stable, from 279 to 266×10^9/L.

Table 2 Assessment of the risk of chemotherapy-induced febrile neutropenia and patient-related factors increasing this risk

Patient-related factors increasing the risk of febrile neutropenia	Risk of febrile neutropenia, *n* (%)			Total (*n*=184)
	<10 % (*n*=23)	10–20 % (*n*=102)	>20 % (*n*=59)	
Age>65 years, *n* (%)	9 (39)	43 (42)	30 (51)	82 (45)
Concomitant disease, *n* (%)	6 (26)	17 (17)	13 (22)	36 (20)
Hepatic, *n*	0	5	3	8
Renal, *n*	0	1	0	1
Cardiovascular, *n*	1	9	1	11
Other, *n*	6	10	10	26
Hemoglobin<12 g/dL, *n* (%)	8 (35)	22 (22)	16 (27)	46 (25)
No patient-related factors, *n* (%)	0	20 (20)	0	20 (11)

Safety

Overall, 15.8 % (29/184) of patients had at least one adverse event related to Zarzio® according to the investigator's judgment. An analysis of each cycle showed that this rate progressively decreased throughout the 6 cycles: from 7.7 % (14/181) during cycle 2 to 2.6 % (3/114) during cycle 6. The most frequent adverse event related to Zarzio® was pain, in particular bone pain (*n*=15 patients).

There were three deaths due to cancer disease. Serious adverse events were reported for 2 patients (1.1 %); none of them was considered to be related to Zarzio® (one adverse event was related to chemotherapy and the other one was due to the general condition requiring chemotherapy discontinuation). The study was discontinued for these two patients. One case of intolerance to Zarzio® (lingual edema) led to study discontinuation. Most of the other study discontinuations were related to disease progression (Fig. 1).

Discussion

The strength of this non-interventional study rests on the following points: a relatively large number of patients (*n*=184) followed in the usual conditions of administration of Zarzio®; a high percentage of patients with a risk of febrile neutropenia>20 % (32.1 %) or between 10 and 20 % (55.4 %); a high percentage of elderly patients (44.6 % of patients>65 years); a low number of patients lost to follow-up (6.3 %); data on hematological parameters between each cycle with very few

Table 3 Administration of Zarzio®

	Cycle 1 *N*=184	Cycle 2 *N*=170	Cycle 3 *N*=165	Cycle 4 *N*=134	Cycle 5 *N*=107	Cycle 6 *N*=98
Time interval between onset of chemotherapy and onset of Zarzio®, days						
Mean (SD)	3.8 (2.2)	3.9 (2.3)	4.5 (4.8)	3.7 (2.3)	3.9 (2.2)	3.6 (2.0)
Median	3.0	3.0	3.0	3.0	3.0	3.0
Range	1–9	1–9	1–33	1–9	1–10	0–8
Dosage of Zarzio®, MIU/day						
Mean (SD)	33.1 (6.8)	32.9 (6.6)	32.6 (6.5)	32.7 (6.4)	33.1 (6.8)	33.5 (7.1)
Median	30.0	30.0	30.0	30.0	30.0	30.0
Range	30–48	30–48	30–60	30–48	30–48	30–48
Number of injections of Zarzio®						
Mean (SD)	4.7 (1.2)	4.8 (1.2)	4.7 (1.2)	4.6 (1.4)	4.5 (1.3)	4.5 (1.3)
Median	5.0	5.0	5.0	5.0	5.0	5.0
Range	2–7	2–7	2–7	2–10	2–8	2–8
Exposition to Zarzio®, days						
Mean (SD)	4.8 (1.3)	4.8 (1.3)	4.8 (1.2)	4.6 (1.4)	4.6 (1.4)	4.6 (1.3)
Median	5.0	5.0	5.0	5.0	5.0	5.0
Range	2–9	2–9	2–9	2–10	2–9	2–9

Table 4 Rates of neutrophils and rates of neutropenia before each cycle (population of patients treated with Zarzio®)

	Cycle 1 *N*=184	Cycle 2 *N*=170	Cycle 3 *N*=165	Cycle 4 *N*=134	Cycle 5 *N*=107	Cycle 6 *N*=98
Neutrophils/mm^3						
Mean (SD)	4584 (3492)	3665 (1897)	3980 (2868)	3239 (1777)	3389 (1918)	3601 (3494)
Median	3969	3354	3360	2890	3028	3169
Range	1000–38,219	460–9996	530–27,770	951–12,270	611–11,377	1037–33,830
Neutropenia[a], *n* (%)						
Grade 1	5 (2.8)	18 (10.8)	14 (8.7)	20 (15.3)	14 (13.1)	17 (17.3)
Grade 2	5 (2.8)	16 (9.6)	12 (7.5)	12 (9.2)	11 (10.3)	14 (14.3)
Grade 3	0	1 (0.6)	1 (0.6)	2 (1.5)	4 (3.7)	0
Grade 4	0	1 (0.6)	0	0	0	0
MD	*3*	*4*	*4*	*3*	*0*	*1*

MD missing data

[a] Grades of neutropenia: Grade 1, [1500–2000[; Grade 2, [1000–1500[; Grade 3, [500–1000[; Grade 4, < 500/mm^3

Table 5 Clinical and hematological parameters during the follow-up (population of patients treated with Zarzio®)

	Cycle 1 *N*=184	Cycle 2 *N*=170	Cycle 3 *N*=165	Cycle 4 *N*=134	Cycle 5 *N*=107	Cycle 6 *N*=98
Body mass index, kg/m^2						
Mean (SD)	26.7 (6.0)	26.8 (6.2)	26.7 (6.1)	27.3 (5.9)	27.1 (5.5)	26.8 (5.0)
Median	25.8	25.8	25.7	26.3	26.3	26.7
MD	*1*	*0*	*2*	*0*	*0*	*3*
Performance status (OMS), *n* (%)						
0	108 (63.9)	87 (61.7)	82 (60.7)	71 (65.7)	59 (69.4)	49 (66.2)
1	55 (32.5)	50 (35.5)	48 (35.6)	34 (31.5)	23 (27.1)	25 (33.8)
2	6 (3.6)	4 (2.8)	4 (3.0)	3 (2.8)	3 (3.5)	0
3	0	0	1 (0.7)	0	0	0
MD	*15*	*29*	*30*	*26*	*22*	*24*
Temperature, °C						
Mean (SD)	37.0 (0.2)	37.0 (0.1)	37.0 (0.2)	37.0 (0.1)	37.0 (0.2)	37.0 (0.1)
Median	37.0	37.0	37.0	37.0	37.0	37.0
MD	*37*	*37*	*36*	*31*	*23*	*25*
Leucocytes/mm^3						
Mean (SD)	7479 (5151)	6705 (4835)	6755 (4514)	5960 (6128)	6186 (4158)	6137 (5087)
Median	6520	5700	5800	4810	5300	5100
MD	*1*	*3*	*4*	*4*	*0*	*0*
Lymphocytes/mm^3						
Mean (SD)	1733 (760)	1665 (788)	1493 (691)	1322 (549)	1402 (709)	1330 (871)
Median	1586	1539	1354	1271	1280	1109
MD	*2*	*5*	*7*	*6*	*1*	*0*
Platelets × 10^9/L						
Mean (SD)	279 (84)	312 (128)	280 (110)	279 (105)	276 (113)	266 (80)
Median	273	284	270	267	259	260
MD	*3*	*3*	*5*	*3*	*0*	*1*
Hemoglobin, g/dL						
Mean (SD)	12.8 (1.6)	12.0 (1.3)	11.7 (1.2)	11.6 (1.2)	11.4 (1.2)	11.2 (1.2)
Median	12.9	12.1	11.8	11.7	11.3	11.1
MD	*2*	*4*	*5*	*4*	*1*	*3*

MD missing data

missing data and high RDI (>95 % for 83.2 % of patients, all cycles). There are nevertheless some limitations due precisely to the observational and non-stringent conditions of the study. Thus, the primary endpoint (comparison of the incidence of severe neutropenia between cycle 1 and cycle 4) could not be assessed.

Most of the study physicians referred to the EORTC recommendations for primary prophylaxis of febrile neutropenia [13]. According to these recommendations, G-CSF administration is based on an expected risk of febrile neutropenia≥20 % related to the type of chemotherapy. Patient-related risk factors such as age>65 years, history of febrile neutropenia, female gender, Hb<12 g/dL or concomitant hepatic, renal or cardiovascular disease are taken into account for the decision to treat patients with a risk of febrile neutropenia between 10 and 20 %.

Half of the study patients were women with breast cancer. Almost half of patients had an age >65 years and about one third had a risk of febrile neutropenia>20 %. In this high-risk population, no case of febrile neutropenia was reported. Neutropenia led to hospitalization and/or antibiotic treatment in 10 patients. Even in the absence of control group, these results confirm the efficacy of the prophylactic treatment in patients consecutively included without selection criteria, apart for the indication of prophylaxis with G-CSF.

Analysis of hematological parameters evidences that the rates of neutrophils decreased between cycle 1 and cycle 2 and remained then relatively stable in normal ranges (>2000 neutrophils/mm^3). These data validate in usual clinical conditions the results of a phase III study that assessed Zarzio® in 170 women with breast cancer; the most important decrease of the rates of neutrophils was also observed after the first cycle of chemotherapy. In the retrospective study of Verpoort and Möhler in 77 patients treated with Zarzio®, the efficacy of Zarzio® was comparable to Neupogen®; one patient in each treatment group had an episode of febrile neutropenia [19].

The most frequent adverse event related to Zarzio® in our study was pain, more particularly bone pain. These adverse events were expected, and they are considered as very frequent (≥10 %) in the Summary of Product Characteristics of Zarzio® in cancer patients treated with G-CSF [21]. No serious adverse event related to Zarzio® was reported in the 184 study patients. The study discontinuations were most often related to disease progression.

Compared to original filgrastim, Zarzio® has a greater affordability that should encourage the use of G-CSF as recommended by guidelines. Indeed, with the financial constraints on healthcare cost systems, biosimilars offer clinically effective alternative, and Zarzio® should improve access to expensive biological treatments for patients [22]. Moreover, the use and handling of the pre-filled syringes of Zarzio® is easy [23].

In conclusion, this non-interventional study allowed improving knowledge on Zarzio®, biosimilar of Neupogen®, in current clinical practice. The results obtained in real-life conditions confirm that Zarzio® is efficient and well tolerated in cancer patients.

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Compliance with Ethical Standards

Conflict of interest SN has received honoraria from Amgen, Teva, Roche, Sandoz and Boehringer; MR has received honoraria from Sandoz; MBA has been consultant for Sanofi; RFS and IG are employed by Sandoz Biopharmaceuticals; JLB has received honoraria from Sandoz, Hospira, Teva and Novartis.

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