Hematological Diseases and Therapies
Maloisel F, et al. Hem Disease Therapies 8: 133.
www.doi.org/10.29011/2577-1418.000133
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Research Article

Biosimilar Filgrastim (Nivestim®) in the Treatment and Prevention of Chemotherapy-Induced Neutropenia: Results of the NEXT Observational Study

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Citation: Maloisel F, Lepretre S, Kamioner D, Berthou C, Cals L (2024) Biosimilar filgrastim (Nivestim®) in the treatment and prevention of chemotherapy-induced neutropenia: results of the NEXT observational study. Hem Disease Therapies 8: 133. DOI:https://doi.org/10.29011/2577-1418.000133

Received Date: 19 January 2024; **Accepted Date:** 29 January 2024; **Published Date:** 02 February, 2024

Abstract

Background: This study was a prospective, non-interventional, multicentre study to evaluate the safety and efficacy of Nivestim® (biosimilar of filgrastim) in chemotherapy-induced febrile neutropenia in real-life setting. **Methods:** Adult patients undergoing chemotherapy for solid tumor or hematological malignancy treated with prophylactic or curative Nivestim were included. Patients were followed for 1–6 chemotherapy cycles following study inclusion. The primary objective was the assessment of the safety of Nivestim. **Results:** 2102 patients (mean age, 63.5 years) were analyzed (1579 with solid tumor and 532 with hematological malignancy); 2065 (98.2%) received Nivestim as prophylaxis administered with a median time of two days after onset of chemotherapy. Chemotherapy regimens were associated with a high risk of febrile neutropenia for 19.4%, intermediate risk for 55.6% and low risk for 25.0%. Adverse events were reported for 20.4% (414/2034) of patients: the most common adverse event was muscle and/or bone pain (12.1%). In prophylactic patients, febrile neutropenia was reported in 98 patients (4.9%; 95% CI, 4.06–5.98), occurring at a median time of 14.0 days after the first chemotherapy cycle. Infection occurred in 61 patients (3.1%; 95% CI, 2.39–3.93) after a median time of 23.5 days following onset of chemotherapy. A total of 98 prophylactic patients (4.9%) who presented with febrile neutropenia and/or infection were hospitalized. **Conclusions:** The safety and efficacy of Nivestim in cancer patients in real-world clinical practice were consistent with the registration studies and in line with reference filgrastim in both the prophylactic and curative settings.

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Keywords: Biosimilars; Filgrastim; G-CSF; Febrile neutropenia; Chemotherapy.

Introduction

Febrile neutropenia is a common but serious consequence of myelosuppressive cytotoxic chemotherapy, which can delay or reduce doses of chemotherapy regimens and thereby compromise the anticancer treatment [1–3]. Febrile neutropenia can lead to potentially fatal infections that require antibiotic treatment and usually necessitate hospitalization [4], with a mortality rate of approximately 8% in the inpatient setting [5].

Granulocyte-colony stimulating factor (G-CSF) is a cytokine that acts upon hematopoietic progenitor cells to stimulate the formation and function of mature neutrophils [6]. G-CSF reduces the incidence and duration of febrile neutropenia, thereby decreasing the need to delay the chemotherapy cycles or to reduce the doses [7–9]. US [10] and European [11] guidelines recommend prophylactic G-CSF for chemotherapy regimens associated with a high risk of febrile neutropenia (≥ 20%) and consideration in patients at intermediate risk (10–20%). However, a number of studies have shown that G-CSF is underused in patients undergoing chemotherapy treatments associated with a high risk of febrile neutropenia [12].

Filgrastim (G-CSF) was first approved in 1991 in Europe [13] and US [14], under the trade name Neupogen® (Amgen). Additionally, a pegylated recombinant human filgrastim with a longer half-life, pegfilgrastim (Neulasta®, Amgen) [15], has been developed [16]. Another recombinant human G-CSF, lenograstim (Granocyte®, Chugai Pharma), is also available [17]. In addition, several biosimilars of filgrastim have been developed [18]. One of them is Nivestim® (Hospira Inc) which was subsequently approved for use in Europe in 2010. Nivestim demonstrated equivalent efficacy and a similar safety profile as the reference product Neupogen® in a phase-III double-blind clinical trial that included patients with breast cancer undergoing myelosuppressive chemotherapy [19].

The aim of the present article is to describe the results of the non-interventional NEXT study which assessed the safety and efficacy of the biosimilar filgrastim Nivestim in real-life in patients undergoing chemotherapy for solid tumor or hematological malignancies.

Methods:

Study design

The NEXT ("Tolérance de Nivestim chez les patiEnts traités par une chimiothérapie anticancéreuse cytotoXique en praTique courante") study was a prospective, non-interventional, longitudinal, national, multicentre study conducted across 160 sites in France by oncologists and hematologists. The study design has been previously published [20]. This study has the ClinicalTrials.gov identifier NCT01574235.

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.

The primary objective was to evaluate the safety of Nivestim, administered either as prophylactic or curative treatment. The secondary objectives included information on patient characteristics, efficacy of Nivestim therapy, use of Nivestim, physician knowledge regarding filgrastim prescription and reasons for choosing Nivestim.

Patient data were recorded for 1–6 chemotherapy cycles following study inclusion, with three study visits; at inclusion (Visit 1), at one-month follow-up (Visit 2) and at the end of the last chemotherapy cycle (Visit 3).

Patient demographics, clinical characteristics and Nivestim treatment-related data on efficacy and safety, such as febrile neutropenia and adverse events, were recorded on case report forms. Physicians who took part in the survey completed a questionnaire concerning the treatment and prevention of chemotherapy-induced febrile neutropenia.

Patients

Patients who met the following criteria were included: patients with an age ≥ 18 years presenting with a solid tumor or a hematological malignancy; on-going or starting treatment with neutropenia-inducing chemotherapy (regardless of the cycle); treatment with Nivestim instituted for the purpose of reducing the duration of neutropenia and the incidence of chemotherapy-induced febrile neutropenia. Patients were not included if they presented with a chronic myeloproliferative syndrome or a myelodysplastic syndrome, had hypersensitivity to any of the ingredients of Nivestim or were not receiving chemotherapy.

Patients were classified for the risk of febrile neutropenia according to the European Organization for Research and Treatment of Cancer (EORTC) recommendations [11]: chemotherapy regimen with a low risk (<10%), medium risk (10–20%) or high risk (>20%) of febrile neutropenia.

Statistical methodology

The primary endpoint was the description of all treatment-emergent adverse events. The secondary endpoints were the occurrence of febrile neutropenia and infections, their impact on chemotherapy treatment, the hospitalizations due to any febrile neutropenia or infection, the characteristics of patients treated with Nivestim in real-life practice, the methods of treatment with

Nivestim (curative or prophylactic) in routine practice and the assessment of the general practice of study physicians for G-CSF prescription.

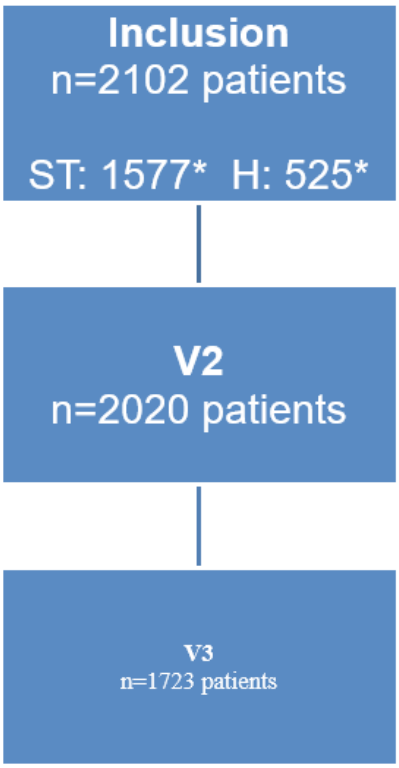
The percentages of prophylactic patients who experienced febrile neutropenia and/or infection were calculated according to the modified Wald method.

Analyses were performed with SAS software version 9.2 (SAS Institute; Cary, NC, USA). Missing data were not replaced for the analyses.

Results

Study population

A total of 2114 patients were enrolled and 12 patients were excluded due to protocol deviations; 2102 patients were included in the analysis population (**Figure 1**). During the study, 516 patients prematurely withdrew from the study: 86 patients prior to V2, 297 patients prior to V3 and 133 patients at V3. The most frequent reasons of patient withdrawals were cessation of chemotherapy (52.2%), switch from Nivestim to another G-CSF (23.5%) and patient death (16.5%) (**Table 1**). In patients with premature withdrawal due to chemotherapy discontinuation, recurrent febrile neutropenia was reported for 4 patients (1.5%) and persistent febrile neutropenia for 3 patients (1.1%).



Patients included in NEXT: 2114

Patients analysed: 2102

24.4% of patients discontinued before the study end

Reason for early discontinuation	%
Withdrawal of CT	52.2
Withdrawal of Nivestim® for another G-CSF	23.5
Lost to follow-up	4.5
Death	16.5
Patient decision	8.4
Other	13.6

Figure 1: Study population.

*12 patients were excluded from the analysis due to no information, missing age, patient with a disorder outside of the protocol, patient already included and no biosimilar filgrastim prescription upon inclusion.

	N=515*
Withdrawal of the chemotherapy	269 (52.2)
Switch from biosimilar filgrastim to another G-CSF	121 (23.5)
Death	85 (16.5)
Decision of the patient	43 (8.4)
Patient lost to follow-up	23 (4.5)
Other reason	70 (13.6)

Table 1: Reasons for premature withdrawal from the observational NEXT study.

Results are given as n (%) G-CSF: granulocyte-colony stimulating factor. * Premature withdrawal could be due to more than one reason.

Patient demographics and clinical characteristics

Patient characteristics are summarized in (**Table 2)**. Their mean age was 63.5 years and 50.2% were male. A total of 75.1% (n = 1579) of patients had a solid tumor and the most common were gynecological (37.2%), digestive (26.2%) and lung tumors (18.8%). Patients with hematological malignancies were 25.3% (n = 532), the most frequent being lymphoma (19.5%; n=410).

In the entire population, 34.4% of patients had received prior chemotherapy, 19.6% prior radiotherapy and 20.2% prior G-CSF therapy. In patients with available data, first-line chemotherapy was predominantly administered: 74.8% (n = 1082) of patients with solid tumors and 70.7% (n = 378) of patients with hematological malignancies.

The indication for Nivestim was mainly for prophylaxis (98.2%, n = 2065) rather than for curative treatment (1.8%, n = 37).

In the prophylactic population, Nivestim was prescribed as primary prophylaxis in 92.6% (n = 1912) of patients and as secondary prophylaxis in 7.4% (n = 153). The 2065 patients with prophylactic Nivestim received chemotherapy regimens with a high risk of febrile neutropenia for 19.4% (n=975), intermediate risk for 55.6% (n=752) and low risk for 25.0% (n=338). Among patients receiving chemotherapy regimens with an intermediary or low risk of febrile neutropenia, 95.4% and 96.5% had at least one patient risk factor for febrile neutropenia, respectively.

Among patients who received curative treatment, 32.4% (n = 12) had grade 3 neutropenia (500–1000 neutrophils/mm^3) and 29.7% (n = 11) grade 4 neutropenia (<500 neutrophils/mm^3). Five patients who were prescribed curative treatment presented with an infection at the inclusion visit (three cases were bacterial and one viral; missing data for one patient).

Characteristics	Patients (n=2102)*
Age (years), mean (SD)	63.5 (12.7)
Male gender, n (%)	1056 (50.2)
Malignancies†, n (%)	
Solid tumor	1579 (75.1)
Gynecological	588 (37.2)
Digestive	413 (26.2)
Lung	297 (18.8)
Urological	152 (9.6)
ENT	101 (6.4)
Bone/muscle (sarcoma)	27 (1.7)
Neurological	9 (0.6)
Skin	6 (0.4)
Other	6 (0.4)
Hematological malignancies	532 (25.3)
Lymphoma	410 (19.5)
CLL	66 (3.1)
Myeloma	48 (2.3)
Acute leukemia	5 (0.2)
Other	3 (0.1)
BMI (kg/m^2), mean (SD)	24.9 (4.7)
ECOG performance score, n (%)	
Grade 0	990 (48.1)
Grade 1	875 (42.5)
Grade 2	187 (9.1)
Grade 3	7 (0.3)
Grade 4	1 (0.1)

Table 2: Patient characteristics at inclusion in NEXT study.

* Some patients had missing data Patients could present with more than one type of malignancy

BMI, body mass index; CLL, chronic lymphoid leukemia; ECOG, Eastern Cooperative Oncology Group; ENT, ear, nose or throat.

Safety

During the study, treatment-emergent adverse events were reported in 20.4% (414/2034) of patients. Muscle and/or bone pain was the most commonly reported adverse event (12.1%), followed by nausea (3.0%). Allergic reactions to Nivestim occurred in 0.4% of patients (**Table 3**).

The percentages of patients who experienced adverse events were comparable in patients with solid tumors (21.1%, n = 321) or with hematological malignancies (18.5%, n = 97). Regarding adverse events of particular interest for G-CSF, one patient presented with cutaneous vasculitis, two patients with hypersensitivity and two patients with inefficacy during the course of the study (all received Nivestim as prophylactic treatment).

Adverse events, n (%)	n=2102
Muscle and/or bone pain	245/2034 (12.1)
Nausea	61/2035 (3.0)
Diarrhea	47/2033 (2.3)
Headache	36/2033 (1.8)
Chest pain	25/2033 (1.2)

Table 3: Patients with at least one treatment-emergent adverse events experienced by >1% of patients during the study.

Prophylaxis with Nivestim

Treatment administration

In patients who received Nivestim as prophylactic treatment, the median time to initiation after onset of chemotherapy was 2 days (**Table 4**). The dose of Nivestim was 30 MIU for 79.9% (n = 1646) of patients and was administered subcutaneously in 99.4% (n = 2049) of patients; the mean (SD) treatment duration was 6.0 (3.8) days.

Anti-infective prophylaxis was also prescribed to 47.9% (n = 251) of patients with a hematological malignancy and 2.6% (n = 41) of patients with solid tumor. Among patients who were administered at least one treatment for anti-infective prophylaxis, 93.6% (n = 235) and 58.5% (n = 24) with hematological malignancies and solid tumors received an antibiotic, 9.2% (n = 23) and 43.9% (n = 18) received an antifungal, 94.8% (n = 238) and 14.6% (n = 6) received an antiviral and 1.6% (n = 4) and 7.3% (n = 3) received other anti-infective agents, respectively.

Febrile neutropenia and infections. Febrile neutropenia was reported in 98 patients (4.9%; 95% CI, 4.06–5.98) in the prophylactic group, occurring at a median time of 14.0 days after chemotherapy cycle. Among patients who were chemotherapy-naïve at study inclusion, febrile neutropenia occurred in 4.3% (n = 42) and 6.4% (n = 62) after the first chemotherapy cycle and throughout the study, respectively (**Figure 2**). Overall, prophylactic patients with hematological malignancies experienced more frequently febrile neutropenia (7.5%, n = 38) compared with patients with solid tumors (4.1%; n = 60).

Infections were reported in 61 patients (3.1%; 95% CI, 2.39–3.93) on prophylaxis during the study and occurred after a median time of 23.5 days following the first chemotherapy cycle. Among prophylactic patients who had been chemotherapy-naïve, 2.2% (n = 21) and 4.1% (n = 40) experienced infections after their first chemotherapy cycle and throughout the rest of the study, respectively (**Figure 3**).

Characteristics	Prophylactic treatment (n = 2065)	Curative treatment (n = 37)
Time (days) to initiation of Nivestim after onset of chemotherapy		
N	2053	NA
Median (range)	2 (0–45)	NA
Time (days) to febrile neutropenia since last chemotherapy cycle		
N	NA	27
Mean (SD)	NA	14.7 (8.1)
Dose, n (%)		
N	2061	37
30 MIU	1646 (79.9)	31 (83.8)
48 MIU	415 (20.1)	6 (16.2)
Route of administration, n (%)		
N	2062	37
Subcutaneous	2049 (99.4)	37 (100)
Intravenous	13 (0.6)	0

Duration of treatment (days)		
N	1306	30
Mean (SD)	6.0 (3.8)	5.3 (1.5)

Table 4: Characteristics of Nivestim treatment during the study.

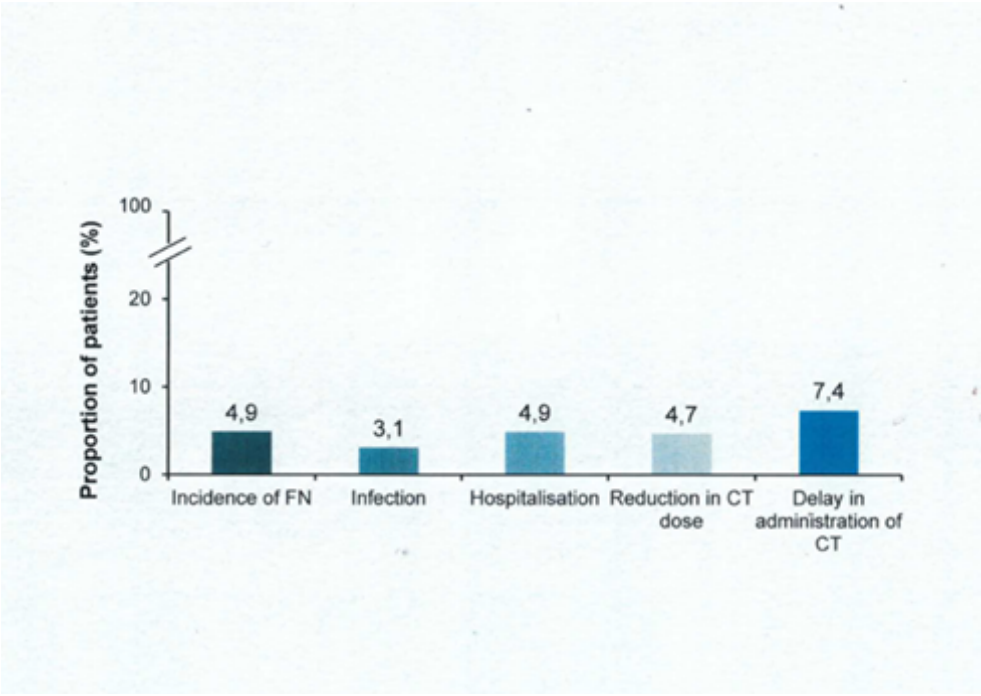


Figure 2: Incidence of febrile neutropenia in patients receiving prophylactic treatment with Nivestim*. Overall, 4,9% (7,2% primary prophylaxis, 4,7% secondary prophylaxis) of patients presented with FN during study (CLL: chonic lymphocytic leukemia; FN: febrile neutropenia).

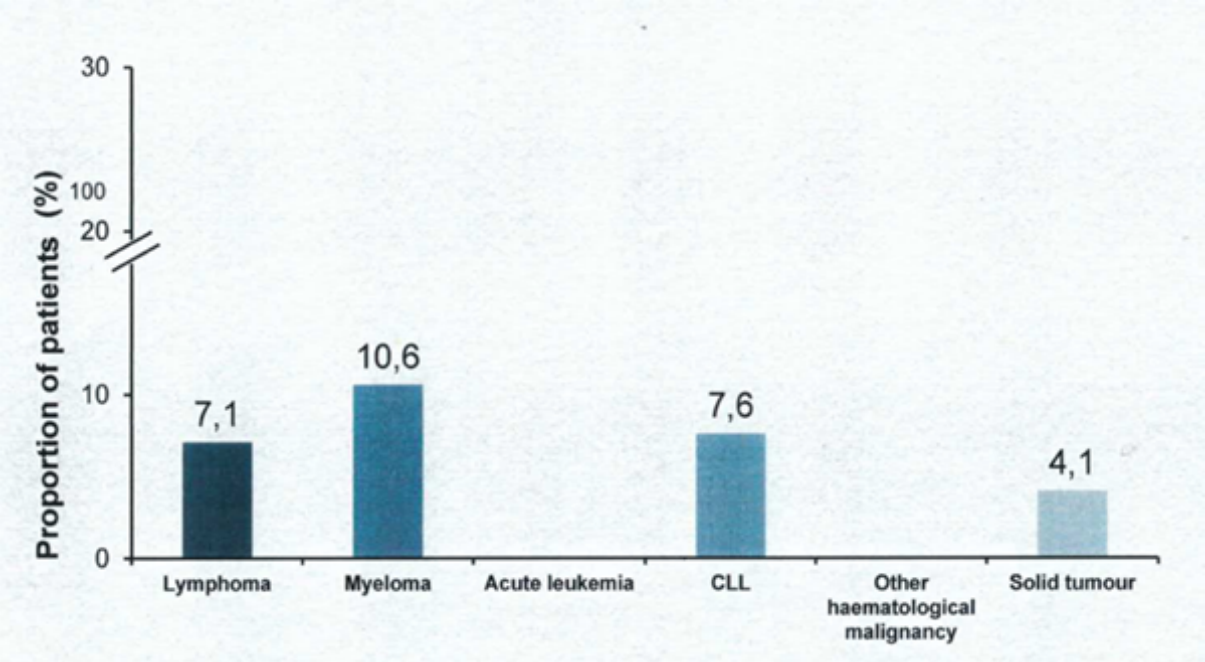


Figure 3: Efficacy of prophylactic Nivestim* at the first CT cycle. Mean duration of hospitalization for FN and/or infection after the first cycle was 8,7+/-10,9 days. (CT: chemotherapy; FN febrile neutropenia)

Hospitalizations. A total of 98 patients (4.9%) in the prophylaxis group who presented with febrile neutropenia and/or infection were hospitalized within a median of 14.0 days after initiating Nivestim. Among the patients who had been chemotherapy-naïve, 4.5% (n = 44) were hospitalized for febrile neutropenia and/or infection after the first chemotherapy cycle, with 1.2% (n = 10) of patients hospitalized after the second cycle and ≤ 1% hospitalized for febrile neutropenia and/or infection throughout subsequent cycles.

Impact on chemotherapy. Reductions in the chemotherapy dose due to febrile neutropenia and/or infection occurred in 4.7% (n = 92) of patients receiving prophylaxis. Among patients who had been chemotherapy-naïve, the percentages of reduction in chemotherapy doses due to febrile neutropenia and/or infection decreased with the number of cycles: 1.5% (n=14) for cycle 1, 1.3% (n=11) for cycle 2, 1.2% (n = 9) for cycle 3 and <1% in subsequent cycles.

Chemotherapy administration was delayed because of febrile neutropenia and/or infection in 7.4% (n = 146) of patients receiving prophylaxis. Among patients who had been chemotherapy-naïve, the greatest percentage of delays in chemotherapy administrations occurred during the third cycle of chemotherapy: 2.3% (n = 22), 1.6% (n = 14), 3.2% (n =23), 2.6% (n = 15), 1.2% (n = 6) and 1.0% (n = 1) for the cycles 1 to 6, respectively.

Overall, 71.4% (n = 352) of patients treated with Nivestim achieved a neutrophil count within normal limits at the end of the first course of prophylaxis. The mean (SD) neutrophil count at the end of the first course of prophylaxis was 6,393 (11,063) cells/ mm^3.

Curative treatment with Nivestim

The mean (SD) time from the last chemotherapy cycle to the onset of febrile neutropenia for patients who received Nivestim as curative treatment was 14.7 (8.1) days. Nivestim was administered at16.4 (11.9) days following the last chemotherapy cycle with a duration of 5.3 (1.5) days.

All patients (n = 37) who received curative Nivestim had the therapy administered subcutaneously and 83.8% (n = 31) received a dose of 30 MIU, as described in (**Table 4)**. In patients who received curative Nivestim, a concomitant antibiotic was prescribed to 9.7% (n = 3) with a solid tumor and 66.7% (n = 4) with a hematological malignancy. Antifungal and antiviral

treatments were prescribed to one patient (3.2%) and zero patient with solid tumors compared to zero patient and 3 patients (50%) with hematological malignancies, respectively.

The mean (SD) neutrophil count upon prescription of curative Nivestim was 1573 (2738) cells/mm^3. Subsequently, 76.5% (n = 13) of patients achieved a neutrophil count within normal limits (≥ 2000/mm^3) upon cessation of treatment.

Characteristics	**Prophylactic treatment (n = 2065)**	**Curative treatment (n = 37)**
Time (days) to initiation of Nivestim after onset of chemotherapy		
N	2053	NA
Median (range)	2 (0–45)	NA
Time (days) to febrile neutropenia since last chemotherapy cycle		
N	NA	27
Mean (SD)	NA	14.7 (8.1)
Dose, n (%)		
N	2061	37
30 MIU	1646 (79.9)	31 (83.8)
48 MIU	415 (20.1)	6 (16.2)
Route of administration, n (%)		
N	2062	37
Subcutaneous	2049 (99.4)	37 (100)
Intravenous	13 (0.6)	0
Duration of treatment (days)		
N	1306	30
Mean (SD)	6.0 (3.8)	5.3 (1.5)

Table 4. Characteristics of Nivestim treatment during the study.

Characteristics of physicians and physicians' prescribing patterns

Among the 232 study physicians, 205 (88.4%) completed the physician questionnaire concerning treatment and prevention of chemotherapy-induced febrile neutropenia (183 out of 205 included at least one patient; 89.3%). Among these 205 physicians, 86.8% were practicing in an oncology department and 13.2% in a hematology department.

Most physicians (73.1%, n = 147) stated that they prescribed G-CSF both as prophylactic and curative treatment, however, 25.9% (n = 52) prescribed G-CSF as prophylaxis only and 1.0% (n = 2) prescribed G-CSF as a curative treatment only.

For prophylaxis, the treatment is started the day after the last dose of chemotherapy for 24.3% (n=70) of physicians, after 2-3 days for 32.8% (n=67) and after 4-7 days for 28.4% (n=58); 95.6% (n=195) of the physicians do not combine filgrastim with antibiotic treatment for prophylaxis. The median duration of G-CSF treatment is 5 days (interquartile range, 5–6). The rise of neutrophils count is not verified before the discontinuation of filgrastim. Filgrastim is considered to be effective for a median neutrophil count of 1500/mm^3 (interquartile range, 1000–1500).

For curative treatment of chemotherapy-induced febrile neutropenia, 75.4% of physicians consider other factors before initiating treatment: general condition (83.9%), expected duration of neutropenia (79.2%), presence of a confirmed infection (85.2%) and type of infection (45.0%).

Most physicians cited cost savings (87.3%), comparable efficacy (81.4%) and comparable safety (66.2%) as main reasons for prescribing Nivestim.

Discussion

In this observational study, safety and efficacy associated with Nivestim were consistent with registration studies [19] and were in line with reference G-CSF [13], both in prophylactic and curative settings. To our knowledge, the NEXT study conducted on more than 2000 patients is the largest observational post-approval study of a biosimilar of filgrastim for neutropenia-induced chemotherapy [18, 20–23]. This study is in agreement with the 2006 European Medicines Agency recommendations for the clinical development of biosimilars of filgrastim [24] and provides real-life data on the use of Nivestim in patients undergoing neutropenia-inducing chemotherapy [18, 22, 23].

The patient characteristics of this study encompassed a range of cancer types including 75.1% of patients with solid tumors and 25.3% with hematological malignancies. The study patient cohort reflects the known demographics for these diseases and is in agreement with previous studies in similar populations [18].

The percentage of patients who reported at least one adverse event (20.4%) was lower than the proportion of patients who experienced adverse events of any grade during the phase-III study that evaluated Nivestim in patients with breast cancer (86.9%) [19]. Differences in the incidence of adverse events could be due to the close monitoring of patients during clinical trials in contrast with real-life practice, as well as the strict criteria used for the phase-III clinical trials [25]. Muscular and/or bone pain, which are common side effects across all G-CSF treatments, were the most frequent adverse events reported in the study [26–28]. These adverse events could explain the switches from Nivestim to another G-CSF (23.5% of patients). No unexpected adverse event was reported from the 2102 patients who were included in the analysis.

The rate of febrile neutropenia reported in the study was higher than the rate reported in the registration trial that compared Nivestim to Neupogen [19]. The older age of patients in the NEXT post-approval study may have been a contributing factor for this higher rate. Indeed, patients who participated in this observational study had a mean age of 63.5 years vs. 49.3 years in the registration trial. Indeed, an older age (> 65 years) is a risk factor for febrile neutropenia [10,11].

G-CSF use for patients undergoing chemotherapy-induced neutropenia has been shown to reduce risk, duration and severity of febrile neutropenia, but has so far been limited to high-risk patients [7, 9, 10]. According to the EORTC guidelines, G-CSF treatment should be prescribed as prophylactic treatment in patients with a high risk of febrile neutropenia and should be considered in patients with an intermediate risk [11]. Among the 752 patients associated with an intermediate risk of febrile neutropenia, 95.4% (n = 717) of them had one or more patient risk factors for febrile neutropenia and were prescribed G-CSF in agreement with EORTC guidelines. The 338 patients (25.0%) with a low risk of febrile neutropenia received nevertheless G-CSF although they were not eligible according to EORTC guidelines.

This study has the limitations of observational studies. Nevertheless, post-approval observational studies are an appropriate way to evaluate efficacy and safety of pharmaceutical products in real-life practice. As such they can complement randomized controlled trials by offering real-life data such as conditions of treatment administration and profiles of patient treatment. Observational studies generate valuable data for the risk management plan and the periodic safety update reports as required by regulatory authorities.

In conclusion, the biosimilar filgrastim Nivestim was well tolerated as prophylactic or curative treatment in a large cohort of patients undergoing cytotoxic chemotherapy for solid tumors and hematological malignancies in a real-world setting. Efficacy in routine clinical practice was also consistent with previous reports. The large cohort evaluated through the NEXT study provides data on the characteristics of more than 2000 patients treated according to real-world practices. The adverse event profile observed was consistent with the expected profile in this patient population.

Competing interests

All authors received funding from Hospira for the conduct of the studies in their institutions. Additionally, FM has received research funding from Amgen, Hospira, Pfizer and Novartis. DK has participated in an advisory board for Hospira. LC has acted as a consultant for Hospira. SL and CB have no further conflicts of interest to declare.

Author contributions

All authors contributed to the study's conception and design and had full access to the data for its analysis and interpretation. All authors had final responsibility for the decision to submit the manuscript and have read and approved the final draft of the manuscript.

Acknowledgements

The authors gratefully acknowledge the patients and clinical investigators who participated in this trial. This study was sponsored by Hospira SAS. Medical writing assistance, provided by Dr Juliet Bell of ApotheCom ScopeMedical Ltd, was funded by Hospira SAS. Statistical analyses were performed by CLINACT, funded by Hospira SAS.

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