MONITOR-GCSF DLBCL subanalysis: Treatment patterns/ outcomes with biosimilar filgrastim for chemotherapy-induced/ febrile neutropenia prophylaxis

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Abstract

Objective: Prospective data on the use of granulocyte-colony-stimulating factor (G-CSF) in non-Hodgkin’s lymphoma and its aggressive subtypes, including diffuse large B-cell lymphoma (DLBCL), are limited. MONITOR-GCSF is a pan-European, multicenter, prospective, observational study aiming to describe treatment patterns and clinical outcomes in patients receiving biosimilar filgrastim in the prophylaxis of chemotherapy-induced neutropenia (CIN) and febrile neutropenia (FN).

Methods: This analysis describes patient characteristics, treatment patterns, and outcomes for 245 patients with stage 3 or 4 DLBCL receiving ≤6 chemotherapy cycles as part of MONITOR-GCSF study, including patients aged ≥65 years and ≥70 years. Outcomes of interest included the incidence of CIN and FN, antibiotic prophylaxis, biosimilar filgrastim prophylaxis, and adverse events (AEs).

Results: MONITOR-GCSF included 245 patients with DLBCL. Of these patients, 87 (35.5%) experienced one or more CIN (any grade) episode and 24 (9.8%) experienced FN (any grade). The most frequent AE reported was bone pain (n = 7, 2.9%), followed by arthralgia (n = 2, 0.8%) and back pain (n = 2, 0.8%).

Conclusion: In real-life practice, biosimilar filgrastim demonstrated clinical effectiveness and safety in patients with DLBCL. The large percentage of patients aged ≥65 years adds to the evidence on how to best treat older patients with DLBCL receiving myelosuppressive chemotherapy.

KEYWORDS
non-Hodgkin’s lymphoma, socio-economics and ethics, supportive care

1 | INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma (NHL), with a crude incidence rate of 3.8 per 100,000 people each year in Europe.1

The current standard of care for DLBCL comprises combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, prednisone plus immunotherapy with the humanised monoclonal antibody directed at CD20, rituximab (R-CHOP).2 This regimen yields 5- and 10-year survival rates of 51% and 45%, respectively,2,4 but is associated with a significant risk of chemotherapy-induced neutropenia (CIN)/febrile neutropenia (FN), a complication of myelotoxic chemotherapy that can markedly decrease quality of life and increase healthcare costs.5 Clinical trials have shown that up to 50% of patients who receive R-CHOP experience CIN/FN, which can result in dose delays or reductions that can adversely impact patient outcomes.5
Prophylactic prevention of CIN/FN is therefore warranted to ensure cytotoxic chemotherapy is delivered on time and at doses that have been shown in clinical trials to be effective. International guidelines recommend primary prophylaxis with granulocyte-colony-stimulating factors (G-CSFs), such as filgrastim or pegfilgrastim, for patients with a 20% or greater risk of CIN/FN. Filgrastims have well established efficacy in terms of decreasing the risk of CIN/FN, the severity and duration of CIN/FN episodes, and chemotherapy disturbances.

With regard to DLBCL, European Society of Clinical Oncology guidelines state that prophylactic use of hematopoietic growth factors is justified in patients treated with curative intent and in patients older than 60 years of age. Similarly, the American Society of Clinical Oncology specifically recommends G-CSF support for all NHL patients aged greater than 65 years who are receiving CHOP-based chemotherapy because the risk of neutropenia increases with age. In the IMPACT observational study of 1113 patients with DLBCL treated with R-CHOP, rates of CIN/FN and unplanned hospitalisation were higher in patients aged 65 years and older, and delivery of chemotherapy was poorer. However, limited data exist on how best to treat older patients since comorbidities, poor functional status, and enhanced sensitivity to chemotherapy toxicities often mean they are ineligible for inclusion in clinical trials.

While patients treated in a clinical trial are dosed according to strict guidelines and are closely monitored, the same cannot be said for patients treated in a real-life setting. In the IMPACT study, substantial proportions of patients, irrespective of age, failed to receive G-CSF prophylaxis in accordance with international guidelines. Further data on the effectiveness and safety of G-CSF prophylaxis outside of a clinical trial setting are therefore required.

MONITOR-GCSF was an observational study of cancer patients treated with myelosuppressive chemotherapy regimens whose treating physicians prescribed CIN/FN prophylaxis with Sandoz biosimilar filgrastim (Zarzio®/Zarzio®/EP2006/filgrastim-sndz, Hexal AG, Holzkirchen, Germany). Treatment patterns and associated outcomes of CIN/FN prophylaxis with biosimilar filgrastim in 1447 patients with solid or haematologic malignancies have already been reported. Here, we describe patient characteristics, treatment patterns and outcomes for the cohort of patients with DLBCL who received primary or secondary prophylaxis with biosimilar filgrastim as part of routine clinical practice. We also present results for patients aged ≥65 years and ≥70 years.

2 | METHODS

2.1 | Design

The background and methodology of MONITOR-GCSF have previously been described elsewhere. Briefly, MONITOR-GCSF was a pan-European, prospective, observational, multilevel, pharmacoepidemiological study of chemotherapy-treated cancer patients who started treatment with biosimilar filgrastim for the prophylaxis of CIN/FN as per their prescribing physician’s best clinical judgement. Male or female adults (age ≥18 years) diagnosed with stage III or IV breast cancer, bladder cancer, or non-small cell lung cancer; metastatic prostate cancer; or stage III or IV DLBCL were eligible for inclusion if they were scheduled to receive their first cycle of ≥4 cycles of chemotherapy and received treatment with biosimilar filgrastim as indicated. The study was approved by the ethical review committees of participating centres in accordance with national laws and regulations. Patients provided written informed consent.

2.2 | Data collection

Patients were observed for up to six cycles of chemotherapy. All data were recorded as available. Descriptive data on demographics, clinical status, medical history, concomitant comorbid conditions and current status of disease, and prior and concomitant medications were collected at enrolment. Data on chemotherapy regimen, including any changes, were collected at every visit. Outcomes of interest included the incidence of CIN/FN, antibiotic prophylaxis, biosimilar filgrastim prophylaxis and adverse events (AEs). Data were summarised overall and according to categorical subgroups of age (≥65 years and ≥70 years at baseline). Here, we present results for patients with DLBCL only.

3 | RESULTS

3.1 | Patients

In total, 245 patients with DLBCL were included in MONITOR-GCSF, of whom 103 patients (42%) had stage III disease, and 135 (55.1%) had stage IV disease. Most patients (n = 144, 58.8%) were male. Mean body weight was 73.4 kg (range: 40-155 kg). Mean age was 62.7 years (range: 21-87 years), and overall, 125 patients (51%) were aged ≥65 years and 96 patients (39.2%) were aged ≥70 years. Patient demographics and baseline characteristics are shown in Table 1.

CHOP-based chemotherapy was used in most patients (n = 159; 64.8%), comprising R-CHOP-21 (R-CHOP given every 21 days) in 113 (46.1%) patients, CHOP-21 in 29 (11.8%) patients and R-CHOP-14 (R-CHOP every 14 days) in 17 (6.9%) patients (Table 2). Other frequent combination chemotherapy regimens included dexamethasone, high-dose cytarabine plus cisplatin (DHAP) in seven patients (2.9%); rituximab, prednisolone, mitoxantrone, cyclophosphamide, etoposide, bleomycin plus vincristine (R-PmitCEBO) in seven patients (2.9%); and busulfan plus melphalan (BuMel) in five

**TABLE 1** Patient demographics and baseline characteristics

| Characteristics       | All patients (n = 245) |
|-----------------------|-----------------------|
| Age yrs, mean (range)| 62.7 (21-87)          |
| Gender, % (n)         |                       |
| Male                  | 58.8% (144)           |
| Female                | 41.2% (101)           |
| Weight kg, mean (range)| 73.4 (40-155)        |
| Cancer stage, % (n)   |                       |
| 3                     | 42% (103)             |
| 4                     | 55.1% (135)           |
patients (2%). R-CHOP-21 was the most commonly prescribed chemotherapy regimen in patients aged ≥65 and ≥70 years, followed by CHOP-21 and R-PMitCEBO. Of the seven patients treated with R-PMitCEBO, all but one were aged ≥70 years.

3.2 | Prophylaxis

Data on biosimilar filgrastim prophylaxis were available for 239 patients with DLBCL, including 123 aged ≥65 years and 94 aged ≥70 years (Table 3). Reasons for discontinuation of prophylaxis with biosimilar filgrastim and for switching to other G-CSF included “change of G-CSF,” “unavailability of drug in the hospital,” “stopping chemotherapy” and “cancellation of the chemotherapy protocol.”

3.3 | Clinical outcomes

In total, 87 (35.5%) patients experienced one or more CIN (any grade) episode and 24 (9.8%) patients had FN (any grade) throughout the duration of the study. In Cycle 1, CIN (any grade) occurred in 41 (16.7%) patients and FN occurred in 6 (2.4%) patients. Grade 3 or 4 FN occurred in 5 patients (2%) in Cycle 1 and in 23 patients (9.4%) in all cycles. Changes to the chemotherapy regimen are detailed in Table 4.

3.4 | Safety

The most frequent AE reported in patients with DLBCL was bone pain, followed by arthralgia and back pain (Table 5).

4 | DISCUSSION

This analysis described patient characteristics, treatment patterns and clinical outcomes for patients with DLBCL who received primary or secondary prophylaxis with biosimilar filgrastim as part of routine clinical practice in the MONITOR-GCSF observational study.

4.1 | Prevention of chemotherapy-induced neutropenia

Of the patients with DLBCL included in MONITOR-GCSF, patients had a mean age of 62.7 years, with 51% of patients aged ≥65 years and 39.2% of patients aged ≥70 years. In line with guideline recommendations for the treatment of DLBCL, R-CHOP-21 was the most common chemotherapy regimen in DLBCL patients in MONITOR-GCSF, including in patients aged ≥65 and ≥70 years. Clinical outcomes for patients with DLBCL were generally consistent with those reported for the overall population of 1447 patients. For example, 35.5% of DLBCL patients experienced one or more CIN episode of any grade throughout the study, compared with 34.8% in the overall study population. Studies assessing real-world use of filgrastim in patients with NHL are limited; however, randomised controlled studies performed in patients with NHL have shown that G-CSF support is efficacious in preventing CIN. A study in patients with NHL treated with VAPEC-B (vincristine, doxorubicin, prednisone, etoposide, cyclophosphamide, bleomycin) chemotherapy reported that neutropenia occurred in 37% of patients receiving G-CSF. This result is comparable with the findings from the current study. Another study in patients with NHL reported that neutropenia occurred in 23% of patients treated with VNCOP-B (cyclophosphamide, mitoxantrone, vincristine, etoposide, bleomycin and prednisone) and receiving G-CSF. This lower incidence in a clinical trial compared with our observational study may reflect differences in how G-CSF between is used in everyday practice compared with clinical trials. However, even comparing results between clinical studies also has serious limitations due to differences in chemotherapy regimens, clinical settings and patient populations. Indeed, patients had a median age of 51 years (range 16-67) in the G-CSF group of the Pettengell study, compared with 69 years in patients receiving G-CSF in the Zinzani study where all patients were aged ≥60 years (range 60-82).

4.2 | Prevention of febrile neutropenia

In MONITOR-GCSF, the percentage of patients experiencing FN (any grade) was higher in patients with DLBCL (9.8%) compared with the overall population (5.9%). In Cycle 1, FN was reported in 2.4% patients

| TABLE 2 | Frequent chemotherapy regimens (>3 patients) in patients with DLBCL in the MONITOR-GCSF study |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Chemotherapy regimen            | All patients (n = 245), n (%) | ≥65 yrs of age (n = 125), n (%) | ≥70 yrs of age (n = 96), n (%) |
| R-CHOP-21                        | 113 (46.1)       | 65 (52)         | 50 (52.1)       |
| CHOP-21                          | 29 (11.8)        | 16 (12.8)       | 12 (12.5)       |
| R-CHOP-14                        | 17 (6.9)         |                  |                 |
| DHAP                             | 7 (2.9)          |                  |                 |
| R-PMITCEBO                       | 7 (2.9)          | 7 (5.6)         | 6 (6.3)         |
| BuMel                            | 5 (2)            |                  |                 |

BuMel, busulfan plus melphalan; DHAP, dexamethasone, high-dose cytarabine plus cisplatin; R-PMITCEBO, rituximab, prednisolone, mitoxantrone, cyclophosphamide, etoposide, bleomycin plus vincristine.

Percentages do not equal 100 since only frequent chemotherapy regimens (>3 patients) are presented.

| TABLE 3 | G-CSF prophylaxis in patients with DLBCL included in the MONITOR-GCSF study |
|---------------------------------|-----------------|-----------------|-----------------|
| Patient group                  | Mean (SD) dose (µg) | Median dose (min, max) | Discontinued prophylaxis, n (%) | Used another G-CSF |
| All patients (n = 239)          | 8242.6 (4987.9)  | 7500 (300, 31500)  | 14 (5.9)        | 4 (1.7)          |
| ≥65 yrs of age (n = 123)        | 8422.9 (4945.3)  | 9000 (300, 31500)  | 7 (5.7)         | 2 (1.6)          |
| ≥70 yrs of age (n = 94)         | 8642.5 (4861.8)  | 9000 (600, 31500)  | 7 (7.4)         | 2 (2.1)          |

SD, standard deviation.
4.3 | Real-world data

A US retrospective observational study described the incidence of grade 3/4 neutropenia, patterns of G-CSF use and incidence of chemotherapy dose delays, dose reductions and reduced relative dose intensity (RDI) among 1,579 patients <65 and ≥65 years who received CHOP-based chemotherapy for NHL. Most patients (86.9%) received G-CSF; however, compared to the MONITOR-GCSF study, a substantial proportion (57.4%) had documented grade 3/4 neutropenia. Dose delays and reduced RDI were common across all ages of patients with NHL receiving CHOP-based chemotherapy, but patients ≥65 years had a 24.9% incidence of dose reductions, which was higher than that reported in patients <65 years (9.6%), and also higher than in patients ≥65 years in MONITOR-GCSF (10.4%-12.5%). All patients who were indicated for G-CSF support received it in MONITOR-GCSF; however, both younger and older patients often fail to receive any or optimum G-CSF prophylaxis in clinical practice, despite guideline recommendations. Maintaining a CHOP RDI of >90% has been shown to improve overall survival in DLBCL. As such, better adherence to guidelines for the use of prophylactic G-CSF during chemotherapy could improve the outcome and care of patients with DLBCL.

4.4 | Safety profile

The most frequent AE reported in patients with DLBCL was bone pain; however, this AE was experienced at lower levels compared with the overall study population (2.9% vs 24.7%). The reasons for this difference are unclear, although a low reported incidence may reflect the fact that bone pain is a widely recognised AE associated with use of G-CSF and, therefore, less likely to be reported in long-term observational studies. Indeed, bone pain was reported in 5.6% of patients in the HEXAFIL study and in 8.2% of a French observational study. Regarding randomised controlled studies with DLBCL, musculoskeletal pain was reported in 2.6% and 7.1% of patients. These incidences are lower than those reported in other studies of filgrastim; for example, incidences of 26%-42% have been reported in patients with breast cancer. It should be noted that differences may be due to different types of cancer and the chemotherapy regimen used, as well as variations in the recording of AEs and how bone/musculoskeletal pain was defined.

5 | CONCLUSION

This analysis reports the effectiveness and safety of Sandoz biosimilar filgrastim in real-life practice in patients with DLBCL. This supports the use of filgrastim in patients with NHL in a real-world setting and extends the efficacy and safety from its clinical development programme. The large percentage of patients aged ≥65 years included in the study adds to the body of evidence on how to best treat older patients with DLBCL receiving myelosuppressive chemotherapy.

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CONFLICT OF INTEREST

PG has no conflicts of interest. AK is an employee of Hexal AG. NH is a former employee of Hexal AG. MA has the following disclosures:

### TABLE 4 Change to chemotherapy regimen in patients with DLBCL included in the MONITOR-GCSF study

| Change to chemotherapy regimen, n (%) | All patients (n = 245), n (%) | ≥65 yrs of age (n = 125), n (%) | ≥70 yrs of age (n = 96), n (%) |
|----------------------------------------|-----------------------------|--------------------------------|-----------------------------|
| Any change                             | 130 (53.1)                  | 70 (56)                        | 53 (55.2)                   |
| Received <6 cycles                     | 89 (36.3)                   | 46 (36.8)                      | 34 (35.4)                   |
| Dose reduction                         | 22 (9)                      | 13 (10.4)                      | 12 (12.5)                   |
| Dose delay                             | 39 (15.9)                   | 23 (18.4)                      | 19 (19.8)                   |
| Cycle cancelled                        | 9 (3.7)                     | 6 (4.8)                        | 3 (3.1)                     |

### TABLE 5 AEs reported in patients with DLBCL included in the MONITOR-GCSF study

| AE                                          | All patients (n = 245), n (%) | ≥65 yrs of age (n = 125), n (%) | ≥70 yrs of age (n = 96), n (%) |
|---------------------------------------------|-----------------------------|--------------------------------|-----------------------------|
| Bone pain                                  | 7 (2.9)                     | 2 (1.6)                        | 2 (2.1)                     |
| Arthralgia                                  | 2 (0.8)                     | 1 (0.8)                        | 1 (1.0)                     |
| Back pain                                  | 2 (0.8)                     | 2 (1.6)                        | 1 (1.0)                     |
| Blood alkaline phosphatase increased       | 1 (0.4)                     | 1 (0.8)                        | 1 (1.0)                     |
| Constipation                               | 1 (0.4)                     |                                |                             |
| Hepatitis acute                            | 1 (0.4)                     |                                |                             |
| Hypotension                                | 1 (0.4)                     | 1 (0.8)                        |                             |
| Injection site pain                        | 1 (0.4)                     |                                |                             |
| Musculoskeletal pain                       | 1 (0.4)                     | 1 (0.8)                        |                             |
| Musculoskeletal stiffness                  | 1 (0.4)                     |                                |                             |
| Myalgia                                     | 1 (0.4)                     |                                |                             |
| Pyrexia                                     | 1 (0.4)                     | 1 (0.8)                        |                             |

with DLBCL; a similar level to the overall population in the HEXAFIL study (1.8%), an observational study assessing use of biosimilar filgrastim in routine clinical practice in Germany. Of the 1432 patients included in HEXAFIL, 156 (10.9%) had NHL; however, data have not been published for the NHL group alone. There are limitations to comparing results between different populations, given the different types of cancer, chemotherapy regimens and clinical settings. However, this again highlights a need for real-world evidence regarding use of G-CSF in patients with NHL to best inform clinical practice.
Amgen: honoraria, speakers bureau, expert testimony; Helsinn Healthcare: advisory role, speakers bureau, research funding; Hospira: advisory role, speakers bureau, research funding; Teva: advisory role, speakers bureau; Merck KGaA: advisory role; Merck: advisory role; Sandoz: advisory role, speakers bureau, research funding; Vifor Pharma: advisory role, speakers bureau; Tesaro: advisory role, speakers bureau; Novartis: speakers bureau, research funding; Roche: speakers bureau; Johnson & Johnson: speakers bureau.

AUTHOR CONTRIBUTIONS
PG contributed to the study design, data analysis and interpretation, manuscript preparation (including preparation of first draft), manuscript editing and manuscript review. AK contributed to the study design, data analysis and interpretation, manuscript preparation (including preparation of first draft), manuscript editing and manuscript review. NH contributed to the study design, data analysis and interpretation, statistical analysis, manuscript preparation (including preparation of first draft), manuscript editing and manuscript review. MA contributed to the study design, data analysis and interpretation, manuscript preparation (including preparation of first draft), manuscript editing and manuscript review.

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