A non-interventional study of biosimilar granulocyte colony-stimulating factor as prophylaxis for chemotherapy-induced neutropenia in a community oncology centre

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Abstract:

Objectives: Prophylaxis with granulocyte colony-stimulating factor (G-CSF) reduces the severity of chemotherapy-induced neutropenia. Biosimilar G-CSF is now approved for use, based on comparable efficacy, safety and quality with the originator product.

Methods: We conducted a retrospective review of patients' charts following the switch from originator G-CSF (Neupogen®) to biosimilar G-CSF (Zarzio®/Filgrastim Hexal®) in a large community oncology practice. A total of 77 consecutive patients with cancer who received biosimilar G-CSF were reviewed, as were 25 patients who received originator G-CSF at the same centre.

Results: The median age of patients in the biosimilar G-CSF cohort was 67 years (range 20–83). In this cohort 48% had chemotherapy with a febrile neutropenia risk of >20%. Biosimilar G-CSF was given as primary prophylaxis in 52% and as secondary prophylaxis in 48% of patients. Age and febrile neutropenia in medical history or in previous chemotherapy were factors that triggered the use of G-CSF in patients with a febrile neutropenia risk of <20%. One patient developed febrile neutropenia. Neutropenia led to chemotherapy dose reductions in five patients (6.5%) and discontinuation in two patients (2.5%). No unexpected safety findings were observed. Patient characteristics were generally similar in the originator G-CSF cohort. Only 24% of patients had a febrile neutropenia risk >20% and 36% received primary prophylactic G-CSF. One patient developed febrile neutropenia. Neutropenia led to chemotherapy dose reductions in two patients (8%) and discontinuation in two patients (8%).

Conclusions: Biosimilar G-CSF was effective and prevented dose reductions/discontinuation in the majority of patients. Biosimilar G-CSF was considered clinically comparable to its reference product.

Keywords: biosimilars, chemotherapy, granulocyte colony-stimulating factor, neutropenia

Introduction

Chemotherapy-induced neutropenia is a frequent problem in patients with cancer and is associated with substantial morbidity, increased mortality and higher healthcare costs. Dose reductions and/or delays in chemotherapy as a result of neutropenia have been shown to have a negative effect on survival outcomes in various curative settings [Aapro *et al.* 2010]. Prophylaxis with recombinant granulocyte colony-stimulating factor (G-CSF) reduces the severity of chemotherapy-induced neutropenia and plays an important role

in supporting the delivery of myelosuppressive chemotherapy.

Recent European Organization for Research and Treatment of Cancer (EORTC) clinical guidelines have broadened the scope for the use of G-CSF with prophylaxis recommended when the overall risk of febrile neutropenia due to the planned chemotherapy regimen is $\geq 20\%$ [Aapro *et al.* 2011a]. For regimens that are associated with an intermediate risk of febrile neutropenia of 10–20%, individual patient factors must be

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considered when determining the need for G-CSF, for example, age (>65 years), advanced-stage disease, history of prior febrile neutropenia and lack of antibiotic prophylaxis. However, data from real-world practice settings suggest that the use of G-CSF is not always consistent with clinical guidelines, with patients either not receiving G-CSF at all or given shorter courses than recommended [Almenar *et al.* 2009; Falandry *et al.* 2010]. Such suboptimal use of G-CSF is associated with poorer outcomes, with patients facing a reduced level of protection against febrile neutropenia [Weycker *et al.* 2006].

Cost considerations may be one reason for the restricted use of G-CSF, especially in an era of increasing healthcare cost restraints. Biosimilar versions of G-CSF are now approved for use in Europe, based on comparable efficacy, safety and quality with the originator product. The use of biosimilar G-CSF to prevent febrile neutropenia is recommended together with that of originator filgrastim (as well as lenograstim and pegfilgrastim) in the EORTC clinical guidelines, with the choice of formulation a matter of individual clinical judgement [Aapro *et al.* 2011a]. The increased affordability of biosimilar G-CSF may encourage physicians to adhere more closely to clinical guideline recommendations, including wider use of G-CSF as primary prophylaxis. This may be particularly pertinent in patients at intermediate risk, since these are the patients for whom G-CSF use is most likely to be restricted.

Clinical experience with biosimilar G-CSF is of significance, given the questions initially raised over the use of biosimilars as well as their possible impact on patterns of use. This retrospective single-centre clinical audit assessed the efficacy and safety of biosimilar G-CSF following the switch from originator G-CSF in a large community oncology practice.

Methods

We conducted a retrospective review of patients' charts available over a 2.5-year period during the time that the centre gradually switched from originator G-CSF (Neupogen®, Amgen, Thousand Oaks, CA, USA) to biosimilar G-CSF (Zarzio®/Filgrastim Hexal®, Sandoz/Hexal, Holzkirchen, Germany) in a large single-centre community oncology practice in Hamburg, Germany. The aims of the study were to describe

patient and treatment characteristics of the cohort receiving G-CSF in clinical practice and to assess whether there were any observable differences between biosimilar and originator products. Patients in the clinical database were considered eligible if aged ≥ 18 years old with a confirmed diagnosis of a solid tumour or haematological malignancy and had received G-CSF during at least one chemotherapy cycle. G-CSF was administered to patients in accordance with EORTC clinical guidelines [Aapro *et al.* 2011a], with the decision to treat based on expected risk of febrile neutropenia of $\geq 20\%$ based on their chemotherapy regimen. Patient-specific factors, such as age, gender, previous febrile neutropenia and compromised immune system, were taken into consideration for lower-risk patients ($< 20\%$ based on chemotherapy). G-CSF was administered as daily subcutaneous injections (300 μg) for 5 days, with treatment continued if neutropenia was present after 5 days. Previous G-CSF use was not consistently recorded, in part because many patients were referred from other clinical centres. Patients with a febrile neutropenia risk of $\geq 20\%$ also received prophylactic oral antibiotics (sulfamethoxazole/trimethoprim and acyclovir) for neutropenia.

A total of 77 consecutive patients who received biosimilar G-CSF for the prevention of chemotherapy-induced neutropenia between March 2009 and February 2011 were identified. For comparison, we also retrospectively assessed a cohort of 25 consecutive patients who received originator G-CSF at the same centre between May 2008 and December 2010. A direct formal comparison between treatment groups was not considered appropriate given the retrospective observational nature of the study.

Results

Biosimilar G-CSF cohort

Patient characteristics are shown in Table 1. Patients in the biosimilar G-CSF cohort consisted mainly of elderly patients, with a median age of 67 years (range 20–83, 50% ≥ 65 years); 64% of patients were female. Patients were diagnosed with a range of tumour types with breast cancer (29%), lymphoma (18%) and colon cancer (13%) being the most frequent. Three-quarters (75%) were receiving combination chemotherapy. Of the patients receiving biosimilar G-CSF, 48%

Table 1. Patient characteristics.

		Zarzio® (n = 77)	Neupogen® (n = 25)
Gender, n (%)	Male	36 (33.8%)	9 (36%)
	Female	64 (66.2%)	16 (64%)
Age, median (range)		67 (20-83)	64 (31-81)
Cancer classification, n (%)	Haematological malignancy	17 (19%)	7 (28%)
	Solid tumour	60 (81%)	18 (72%)
Tumour type	Aggressive NHL	9.2%	4.0%
	Indolent NHL	9.1%	20.0%
	Leukaemia	3.9%	4.0%
	Breast	28.6%	40.0%
	Colon	13.0%	12.0%
	Lung	5.2%	4.0%
	Stomach	2.6%	4.0%
	Pancreatic	2.6%	0
	Prostate	1.3%	4.0%
	Cervical	5.2%	0
	Endometrial	1.3%	0
	Ovarian	3.9%	0
	Other	14.3%	2.0%
Therapy, n (%)	Adjuvant	11 (16.9%)	13 (52%)
	Neo-adjuvant	0	1 (4%)
Tumour therapy before index line, n (%)		38 (49.4%)	6 (24%)
Alive at last contact, n (%)		59 (76.6%)	19 (76%)
Cancer-related mortality, n (%)		18 (23.4%)	6 (24%)

had chemotherapy with a febrile neutropenia risk of >20% (42% of patients with breast cancer). Three patients had a febrile neutropenia risk of <10% based on chemotherapy.

Biosimilar G-CSF was given as primary prophylaxis during the first chemotherapy cycle in 52% of patients (57% of patients with breast cancer) and as secondary prophylaxis in 48% of patients. Age and febrile neutropenia in medical history or febrile neutropaenia in previous chemotherapy were additional factors that triggered the decision to use G-CSF in patients with a chemotherapy-related febrile neutropenia risk of <20%.

Only one patient in the biosimilar G-CSF cohort developed febrile neutropenia, which resolved without further complications after treatment with antibiotics. Neutropenia led to chemotherapy dose reductions in five patients (6.5%) and dose discontinuation in two patients (2.5%). No unexpected safety findings were observed.

Originator G-CSF cohort

In the originator G-CSF cohort, only 24% of patients had a chemotherapy-related febrile neutropenia risk of >20% (eight patients [32%] had a febrile neutropaenia risk <10%) and 36% received G-CSF as primary prophylaxis. Thirteen patients (52%) received originator G-CSF to support adjuvant chemotherapy while one patient was undergoing neoadjuvant chemotherapy. Otherwise, patient characteristics were generally similar to the biosimilar G-CSF cohort with respect to age (median 64 years), gender (64% female), tumour type (breast cancer 40%, lymphoma 24%, colon cancer 12%) and combination chemotherapy (80%).

One patient in the originator G-CSF cohort developed febrile neutropenia. Neutropenia led to chemotherapy dose reductions in two patients (8%) and dose discontinuation in two patients (8%).

Conclusion

Treatment with biosimilar G-CSF in the community oncology setting was effective in the prophylaxis of chemotherapy-induced febrile neutropenia and prevented neutropenia-related dose reductions/discontinuation in the majority of patients. Biosimilar G-CSF (Zarzio®/Filgrastim Hexal®) was considered clinically comparable to its reference product (Neupogen®).

Biosimilar G-CSF products are now widely used in clinical practice across Europe, surpassing the use of the originator product in some regions. Biosimilars may offer potential benefits by reducing healthcare costs and improving access to biological treatments. In an analysis of G-CSF use for the prevention of chemotherapy-induced neutropenia, biosimilar use was associated with cost savings of around 25% compared with the originator product [Aapro *et al.* 2011b].

Biosimilars are approved on the basis of having shown comparable efficacy, safety and quality to a biological reference product. For Zarzio®/Filgrastim Hexal®, this was demonstrated by extensive physicochemical and biological protein characterization as well as comparative pharmacodynamic response *versus* originator G-CSF in healthy subjects [Sörgel *et al.* 2010; Gascon *et al.* 2010]. This approach is in accordance with regulatory guidelines for the demonstration of clinical efficacy of biosimilar G-CSF, which state that pharmacodynamic studies may be sufficient to demonstrate comparability, with absolute neutrophil count and CD34+ cell count used as surrogate markers of efficacy [Gascon *et al.* 2010]. Zarzio®/Filgrastim Hexal® was also effective and well tolerated in a supportive noncontrolled phase III study in patients with breast cancer receiving cytotoxic chemotherapy [Gascon *et al.* 2010].

The switch to biosimilar G-CSF in this study was accompanied by a trend towards increased use of G-CSF as primary prophylaxis (52% *versus* 36% of patients). Given that this was a retrospective study with a nonmatched historical group of consecutive patients for comparison and limited patient numbers, this may have simply been attributable to differences in patient and/or treatment characteristics between groups, for example, the increased use of dose-intense chemotherapy in the biosimilar group. However, it is possible that the observation may also reflect an increased willingness to use G-CSF earlier, given the lower cost of the biosimilar. The possible impact of biosimilar

G-CSF on real-world clinical usage patterns warrants further investigation in larger studies.

No unexpected safety findings were observed with the use of biosimilar G-CSF. This finding appears to be consistent with the previously reported phase III trial [Gascon *et al.* 2010], as well as other postapproval studies of biosimilar G-CSF use in the prevention of chemotherapy-induced neutropenia [Tesch *et al.* 2011; Salesi *et al.* 2012]. However, it should be noted that, since this was not a prospective clinical trial, adverse events were not formally recorded. Moreover, the outpatient setting may mean that not all adverse effects were observed, although it is likely that any severe or serious events were recorded. Ongoing pharmacovigilance, mandatory for all biologics including biosimilars, is required to provide the ultimate evidence of safety and confirm the comparable safety of the biosimilar and originator products.

In approximately 50% of patients, specific factors in addition to the chemotherapy regimen triggered the decision to use prophylactic G-CSF. Other than a medical history of neutropenia, age was the most frequently cited patient-specific risk factor that triggered G-CSF use. This is consistent with guidelines that indicate age over 65 years is the most important patient-related risk factor for neutropenia.

To conclude, this study shows that biosimilar G-CSF appears to be comparable with the originator product when used for the prevention of neutropenia in patients with cancer in routine clinical practice. Greater use of biosimilars may allow important cost savings in the supportive care of patients with cancer.

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Conflict of interest statement

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had full control of data and agree to allow the journal to review these data if requested.

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