ORIGINAL RESEARCH

Biosimilar filgrastim vs filgrastim: a multicenter nationwide observational bioequivalence study in patients with chemotherapy-induced neutropenia

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Background: We studied the comparative effectiveness of biosimilar filgrastim vs original filgrastim in patients with chemotherapy-induced neutropenia.

Patients and methods: This multicenter, observational study was conducted at 14 centers. The study included 337 patients experiencing neutropenia under chemotherapy. Patients were given either filgrastim 30 MIU or 48 MIU (Neupogen®) or biosimilar filgrastim 30 MIU (Leucostim®). Data regarding age, chemotherapeutic agents used, number of chemotherapy courses, previous diagnosis of neutropenia, neutrophil count of patients after treatment, medications used for the treatment of neutropenia, and duration of neutropenia were collected. Time to absolute neutrophil count (ANC) recovery was the primary efficacy measure.

Results: Ambulatory and hospitalized patients comprised 11.3% and 45.1% of the enrolled patients, respectively, and a previous diagnosis of neutropenia was reported in 49.3% of the patients, as well. Neutropenia occurred in 13.7% (n=41), 45.5% (n=136), 27.4% (n=82), 11.4% (n=34), and 2.0% (n=6) of the patients during the first, second, third, fourth, and fifth cycles of chemotherapy, respectively. While the mean neutrophil count was 0.53±0.48 before treatment, a significant increase to 2.44±0.66 was observed after treatment ($p=0.0001$). While 90.3% of patients had a neutrophil count <1.49 before treatment, all patients had a neutrophil count ≥1.50 after treatment. Neutropenia resolved within ≤4 days of filgrastim therapy in 60.1%, 56.7%, and 52.6% of the patients receiving biosimilar filgrastim 30 MIU, original filgrastim 30 MIU, and original filgrastim 48 MIU, respectively. However, there was no significant difference between the three arms ($p=0.468$). Similarly, time to ANC recovery was comparable between the treatment arms ($p=0.332$).

Conclusion: The results indicate that original filgrastim and biosimilar filgrastim have comparable efficacy in treating neutropenia. Biosimilar filgrastim provides a valuable alternative; however, there is need for further studies comparing the two products in different patient subpopulations.

Keywords: chemotherapy, febrile neutropenia, neutrophil, ANC recovery, supportive care, myelosuppressive

Introduction

Despite improvements in supportive care, neutropenia and its complications remain a major issue for patients receiving myelosuppressive chemotherapy.[1–3] The most serious complication of neutropenia is febrile neutropenia (FN), which is associated with an increased risk of morbidity and mortality as well as substantial cost of hospitalization and antibiotics.[4] Dose reductions and delays are common consequences of neutropenic events and may compromise the efficacy of chemotherapy in cancer patients for whom completion of all planned cycles is essential to achieve a maximum chance of treatment success.[5]

Endogenous human G-CSF is a single polypeptide chain protein of 174 amino acids with *O*-glycosylation at one threonine residue (molecular weight 18 kDa, carbohydrate moiety 4% of total weight). It contains one free cysteinyl residue and two disulfide bonds. Cellular sources of G-CSF are monocytes, fibroblasts, and endothelial cells. The physiological role of G-CSF is to maintain neutrophil production during steady-state conditions and to increase production during acute situations such as infection.[6] The common mode of action is to mobilize hematopoietic progenitor cells into the peripheral circulation. Fully differentiated neutrophils are functionally activated by G-CSF.[7] Owing to its hematopoietic activity, G-CSF was identified as potentially useful for the prevention and treatment of neutropenia and associated complications.[8]

Neupogen® (filgrastim; F. Hoffman-La Roche Ltd. [under licence of Amgen]-Basel-Switzerland) was the first therapeutic recombinant G-CSF product approved by the US Food and Drug Administration (FDA). Filgrastim differs in structure from human G-CSF by lacking *O*-glycosylation and having an additional *N*-terminal methionine group as a result of bacterial expression, but it shows the same in vitro and in vivo activity as endogenous G-CSF. The main indication of filgrastim is to reduce the duration of neutropenia and the incidence of FN in patients receiving myelosuppressive chemotherapy.[9] Filgrastim is also approved to reduce the duration of neutropenia in patients undergoing myeloablative therapy followed by bone marrow transplantation who are considered to be at increased risk of prolonged severe neutropenia, to mobilize peripheral blood progenitor cells (PBPCs), to increase neutrophil count, and to reduce the incidence and duration of infection-related events in neutropenic patients with an absolute neutrophil count (ANC) of $<0.5\times10^9$/L.[8,9]

After the expiration of the patent of filgrastim in 2006 in Europe, several biosimilar versions of filgrastim have been approved by the European Medicines Agency (EMA) based on comparable quality, efficacy, and safety with the originator product.[9] These products offer potential benefits by reducing health care costs and expanding access to these medications.[8,10] Leucostim® (biosimilar filgrastim; Dong-A ST Co. Ltd., Daegu, South Korea) was the first biosimilar product approved by the Ministry of Health in Turkey and has been widely used across the country, since its launch in November 12, 2009. Biosimilar filgrastim has been on the market for >7 years and surpassed the use of the originator product in many hematology and oncology centers.

In the present study, as all biosimilars are unique, we aimed to investigate the bioequivalence of original filgrastim (Neupogen®) and biosimilar filgrastim (Leucostim®) by means of efficacy in treating neutropenia in cancer patients receiving chemotherapy. This study was partly presented as a poster presentation at the 9th National Medical Oncology Congress, September 12–16, 2012, Cyprus, and First Near East and Middle Asia Medical Oncology Associations (NEMA) Congress, November 29–December 2, 2012, Istanbul, Turkey.

Patients and methods
Study design and patient characteristics

This multicenter, observational study was conducted at 14 centers in Turkey after receiving approval from the clinical trials ethics committee of Gaziantep University. The study included 337 patients who were receiving chemotherapy for cancer and experienced neutropenia under chemotherapy during June 2011 and April 2012. Written informed consent has been obtained from all patients. For the treatment of neutropenia, patients were given either filgrastim 30 MIU or 48 MIU (Neupogen®) or biosimilar filgrastim 30 MIU (Leucostim®) until neutrophil recovery. Doses were calculated based on patients' weight; however, it was at the discretion of the physician to administer original filgrastim 30 MIU or 48 MIU. Since this was an observational and multicenter study, medications given by the treating physicians were selected based on their own choices, according to the 2:1 ratio rule (66% vs 33%). At the end of the study, percentage allocations of patients into biosimilar filgrastim and original filgrastim treatments were 61.9% and 38.1%, respectively. Furthermore, as this was an observational study, the study reflects routine clinical practice of the treating physician. Therefore, there were no exclusion criteria in the present study, except patients with comorbid diseases. Data regarding age, gender, weight, chemotherapeutic agents used, the number of chemotherapy courses, previous diagnosis of neutropenia, neutrophil count of the patients before and after the treatment, medications used for the treatment of neutropenia, and the duration of neutropenia were collected. Patient demographics and blood counts at baseline are given in Tables 1 and 2. Time to ANC recovery was the primary efficacy measure. ANC recovery is defined as an ANC of $\geq0.5\times10^9$/L (500 mm^3) for three consecutive laboratory values obtained on different days. Date of ANC recovery is the date of the first of three consecutive laboratory values where ANC is $\geq0.5\times10^9$/L (detailed information on ANC calculation can be obtained from the following website: https://www.cibmtr.org/manuals/fim/1/en/topic/q8-11-initial-anc-recovery).

Table 1 Patient demographics

Patient demographics	Filgrastim 48 MIU (Neupogen®)	Filgrastim 30 MIU (Neupogen®)	Biosimilar filgrastim 30 MIU (Leucostim®)
Gender, n (%)			
Females	51 (47.2)	20 (60.6)	114 (50)
Males	57 (52.8)	13 (39.4)	114 (50)
Total	108 (100)	33 (100)	228 (100)
Age (total), years, n (%)			
≤50	46 (43)	17 (51.5)	82 (36)
51–64	39 (36.4)	10 (30.3)	92 (40.4)
≥65	21 (20.6)	6 (18.2)	54 (23.6)
Age (females), years, n (%)			
≤50	19 (38)	12 (60)	49 (42.9)
51–64	23 (36.4)	6 (30)	45 (39.6)
≥65	8 (20.6)	2 (10)	20 (17.5)
Age (males), years, n (%)			
≤50	27 (47.3)	5 (38.4)	33 (28.9)
51–64	16 (28.1)	4 (30.8)	47 (41.2)
≥65	14 (24.6)	4 (30.8)	34 (29.9)
Weight, kg, n (%)			
≤70	32 (20.3)	16 (10.1)	110 (69.6)
≥71	30 (32.3)	5 (5.4)	58 (62.4)
Total	62 (24.7)	21 (8.4)	168 (66.9)

Definition of primary prophylaxis

Primary prophylaxis is defined as patients receiving myelotoxic chemotherapy with curative intent and which has a documented incidence rate of febrile neutropenia (FN) of >20% or patients receiving myelotoxic chemotherapy with curative intent and which has a documented incidence rate of FN of 10%–20%, and one or more of the following pre-disposing patients' risk factors: pre-existing neutropenia

Table 2 Blood counts at baseline

Blood counts	Average
Hematocrit (%)	
Females (n=150)	30.1
Males (n=154)	31.8
RBC (10^6/μL)	
Females (n=165)	3.5
Males (n=161)	3.66
WBC (10^3/μL)	
Females (n=181)	1.82
Males (n=182)	1.86
PLT (10^3/μL)	
Females (n=180)	174.3
Males (n=177)	152.3
Neutrophils (10^3/μL)	
Females (n=183)	1.14
Males (n=179)	0.48

Abbreviations: RBC, red blood cells; WBC, white blood cells; PLT, platelets.

due to disease infiltration of bone marrow or other etiology, age >65 years, advanced disease stage, poor performance status, previous episodes of FN whilst receiving earlier chemotherapy of a similar or lower dose intensity, extensive prior chemotherapy, previous irradiation to large volume of bone marrow, poor nutritional status, active infections or increased risk of infections, or serious co-morbidities.[27]

Statistical analyses of data

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as mean ± standard deviation or n (%), where applicable. While categorical independent variables were compared using the Pearson's chi-square test, numerical independent variables were compared using the nonparametric Mann–Whitney U test. The nonparametric Wilcoxon signed-rank test was used for the comparison of neutrophil values before and after treatment. The Kruskal–Wallis one-way analysis of variance was used to test the difference between the three treatment arms. A p-value <0.05 was considered as statistically significant.

Ethical approval

The observational study was approved by the Turkish Ministry of Health under the number 048146.

Results

A total of 337 patients from 14 centers in Turkey were included in this observational study. The mean age of the patients was 53.15±14.10 years, and 51.0% were males. There was a significant difference between the age groups in terms of gender (p=0.021). The difference was attributable to the higher number of males in the ≥65 years of age group; the majority of the patients ≥65 years of age were males (Table 1). Of the patients, 11.3% were hospitalized and 45.1% were ambulatory patients, and 49.3% had a previous diagnosis of neutropenia. Cancer types in enrolled patients are presented in Table 3. Chemotherapy courses administered to patients enrolled are presented in Table 4. Allocation of chemotherapy courses per number of patients during the entire study is given in Table 5.

Neutropenia occurred during the first cycle of chemotherapy in 13.7% (n=41) of the patients, during the second cycle of chemotherapy in 45.5% (n=136) of the patients, during the third cycle of chemotherapy in 27.4% (n=82) of the patients, during the fourth cycle of chemotherapy in 11.4% (n=34)

Table 3 Cancer types in enrolled patients

Cancer type	n	%	Cancer type	n	%
Breast	59	17.5	Bladder	2	0.6
Lung	58	17.1	Neuroendocrine	1	0.3
Colorectal	46	13.6	Brain	2	0.6
Urogenital cancers[a]	43	12.7	Primary unknown	1	0.3
Head and neck[b]	12	3.5	Malignant melanoma	2	0.6
Liver[c]	11	3.3	Medulloblastoma	1	0.3
Lymphomas[d]	36	10.5	Adenoid cystic carcinoma	1	0.3
Gastric	41	12.1	Adenocarcinomas[f]	4	1.2
Neuroectodermal	1	0.3	Renal cell carcinoma	1	0.3
Mesenchymal	2	0.6	Parotid carcinoma	1	0.3
Sarcomas[e]	18	5.3	Pancreatic	7	2.07

Notes: [a]Urogenital cancers include cervical (n=4), ovarian (n=16), testicular (n=14), seminoma (n=4), endometrial (n=2), germ cell tumor (n=2), and uterus (n=1) cancers. [b]Head and neck includes esophageal (n=3), larynx (n=2), nasopharynx (n=2), and tongue (n=1) cancers. [c]Liver includes hepatocellular carcinomas (n=4) and hepatoblastoma (n=1). [d]Lymphomas include lymphoma (n=11), NH lymphoma (n=15), and Hodgkin lymphoma (n=10). [e]Sarcomas include Ewing's sarcoma (n=2), leiomyosarcoma (n=1), Kaposi's sarcoma (n=2), fibrosarcoma (n=1), liposarcoma (n=1), mezenchymal (n=2), osteosarcoma (n=4), synovial (n=1), soft tissue sarcoma (n=1), and uterus myosarcoma (n=3). [f]Adenocarcinomas include adenocarcinoma (n=1), duodenal (n=1), prostatic (n=1), and gallbladder (n=1).
Abbreviation: NH, non-Hodgkin's.

Table 4 Chemotherapy courses administered to patients enrolled

Chemotherapeutic agents	A	B	C	D	E	Total	%[a]
Adriablastin	1	3	–	–	–	4	0.6
Bleomycin	6	9	1	–	–	16	2.2
Carboplatin	12	8	3	–	1	24	3.3
Cisplatin	57	31	8	–	–	96	13.3
Dacarbazine	1	–	–	7	–	8	1.1
Dexamethasone	4	1	6	–	–	11	1.5
Doxorubicin	13	30	12	2	3	60	8.3
Docetaxel	27	12	1	–	–	40	5.5
Epirubicin	4	6	3	–	–	13	1.8
Etoposide	2	33	7	2	–	44	6.1
Fluorouracil	52	23	30	1	–	106	14.6
Folinic acid	10	6	–	3	–	19	2.6
Gemcitabine	11	10	–	–	–	21	2.9
Ifosfamide	12	2	–	1	–	15	2.1
Irinotecan	12	2	2	1	–	17	2.3
Capecitabine	3	5	3	–	–	11	1.5
Methotrexate	1	–	–	–	–	1	0.1
Oxaliplatin	8	4	3	–	–	15	2.1
Paclitaxel	13	7	1	1	–	22	3.0
Pemetrexed	2	–	–	–	–	2	0.3
Cyclophosphamide	14	20	10	2	–	46	6.4
Cytarabin	–	3	–	–	–	3	0.4
Tamoxifen	2	–	–	–	–	2	0.3
UFT (tegafur/uracil)	1	–		–	–	1	0.1
Temozolomide	1	–		–	–	1	0.1
Topotecan	–	–	1	–	–	1	0.1
Trastuzumab	4	5	1	–	–	10	1.4
Vinblastine	–	–	7	–	–	7	1.0
Vincristine	4	3	10	12	–	29	4.0
Vinorelbine	2	6	–	–	–	8	1.1
Zoledronic acid	1	–	2	–	1	4	0.6
Total	337	337	337	337	337	724	100.0

Notes: Definition of capital letters is as follows: A, one course of therapy; B, two courses of therapy; C, three courses of therapy; D, four courses of therapy; and E, five courses of therapy. [a]Percentage of column.

Table 5 Allocation of chemotherapy courses per number of patients during the entire study

Number of courses	n	%
Patients received one course of therapy	41	13.7
Patients received two courses of therapy	136	45.5
Patients received three courses of therapy	82	27.4
Patients received four courses of therapy	34	11.4
Patients received five courses of therapy	6	2.0
Total	299	100.0

of the patients, and during the fifth cycle of chemotherapy in 2.0% (n=6) of the patients. The most commonly used chemotherapeutic agent was fluorouracil (14.6%), followed by cisplatin (13.3%) and doxorubicin (8.3%). All patients had a neutrophil count <2.19 before filgrastim treatment. While the mean neutrophil count was 0.53±0.48 before treatment, a significant increase to 2.44±0.66 was observed after treatment (*p*=0.0001). While 90.3% of the patients had a neutrophil count <1.49 before treatment, all patients had a neutrophil count ≥1.50 after treatment. Patients received either filgrastim 30 MIU, filgrastim 48 MIU, or biosimilar filgrastim 30 MIU for the treatment of their neutropenia (Table 6).

Neutropenia resolved within ≤4 days of filgrastim therapy in 60.1%, 56.7%, and 52.6% of the patients receiving biosimilar filgrastim 30 MIU, original filgrastim 30 MIU, and original filgrastim 48 MIU, respectively. However, there was no significant difference between the three arms in this respect (*p*=0.468; Table 7). Similarly, time to ANC recovery was comparable between the treatment arms (*p*=0.332; Table 8).

Although there was no significant difference between ambulatory patients receiving biosimilar filgrastim 30 MIU, original filgrastim 30 MIU and original filgrastim 48 MIU with respect to the time to ANC recovery (*p*=0.985), hospitalized patients receiving filgrastim 48 MIU had a significantly longer recovery period than those receiving biosimilar filgrastim 30 MIU and those receiving filgrastim 30 MIU (*p*=0.001; Table 9).

The mean duration of neutropenia was 5.75±4.92 days, 5.26±3.89 days, and 5.62±4.83 days in the ≤50 years of age, 51–64 years of age, and ≥65 years of age groups,

Table 6 Medications given for the treatment of neutropenia

Medication	n	%
Filgrastim 30 MIU	30	8.9
Biosimilar filgrastim 30 MIU	208	61.9
Filgrastim 48 MIU	98	29.2
Total	336	100.0

Table 7 Percentage of patients recovered from neutropenia within ≤4 days and the percentage of those recovered from neutropenia within ≥5 days

Medication	Time to ANC recovery (days)		
	≥5 days, n (%)	≤4 days, n (%)	Total
Filgrastim 30 MIU	13 (43.3)	17 (56.7)	30
Biosimilar filgrastim 30 MIU	79 (39.9)	119 (60.1)	198
Filgrastim 48 MIU	46 (47.4)	51 (52.6)	97
Total	138 (42.5)	187 (57.5)	325

Note: Compared using the chi-square test.
Abbreviation: ANC, absolute neutrophil count.

respectively (*p*=0.99). The mean duration of neutropenia was 5.08±3.70 days in male patients, while it was 6.02±5.25 days in female patients. There was no significant difference between genders in terms of the duration of neutropenia (*p*=0.57).

Among patients ≤70 kg, the percentage of those receiving biosimilar filgrastim 30 MIU was higher than the percentage of those receiving original filgrastim 30 MIU and 48 MIU. Similarly, the majority of patients ≥71 kg were receiving biosimilar filgrastim 30 MIU. However, the difference between the groups did not reach statistical significance (*p*=0.06).

The duration of neutropenia was 5.62±4.63 days, 6.00±5.75 days, and 5.67±3.75 days in patients ≤70 kg receiving biosimilar filgrastim 30 MIU, original filgrastim 30 MIU, and original filgrastim 48 MIU, respectively. The duration of neutropenia was comparable between the three treatment arms (*p*=0.39; Table 10).

Discussion

Biosimilars are biological medicinal products derived from recombinant human DNA and expressed by genetically engineered organisms to produce the target therapeutic proteins in large quantities. During the last few decades, including cytokines such as hematopoietic growth factors, interferons, and interleukins have received marketing authorization throughout the world. The term biosimilar is defined by the EMA along with the implementation of a specific regulatory framework for the marketing authorization of these products that are not identical to the innovator product because of

Table 9 Time to ANC recovery in hospitalized patients

Medication	Mean ± SD	Median (min–max)
Filgrastim 30 MIU	3.70±2.18	3 (1–12)
Biosimilar filgrastim 30 MIU	5.09±5.78	2 (2–21)
Filgrastim 48 MIU	5.70±4.20	5 (1–21)

Note: Compared using Kruskal–Wallis one-way analysis of variance.
Abbreviations: ANC, absolute neutrophil count; SD, standard deviation; min, minimum; max, maximum.

inherent variability in the biological system and their complex manufacturing process. Because of the lack of chemical identity due to minor differences in amino acid sequence or posttranscriptional glycosylation pattern, profile of different impurities, and excipients, some concerns have been raised by the medical community over the safety and efficacy of biosimilars as these may lead to increased immunogenicity, which in turn results in safety and efficacy problems.[11,12] Therefore, it must be shown by preapproval non-clinical and clinical studies that any differences in quality attributes have no impact on the efficacy and safety of the product.[11]

Clinical studies on filgrastim biosimilars have shown that these products are as safe and effective as original filgrastim in reducing the duration of severe neutropenia and the incidence of FN in different cancer settings.[13–15] In their study on breast cancer patients receiving docetaxel/doxorubicin chemotherapy, del Giglio et al[13] reported the mean duration of severe neutropenia to be 1.1 days during the first cycle of chemotherapy regimen both in Tevagrastim® (XM02) and filgrastim groups when the drugs were administered 24 hours after chemotherapy for at least 5 days and a maximum of 14 days. In the first cycle of chemotherapy, the incidence of FN was 12.1% and 12.5% in the XM02 and filgrastim groups, respectively. The authors observed no significant differences between the two treatment groups in terms of the incidence of FN, neither in the first cycle nor across all cycles of chemotherapy. Similarly, the mean time to ANC recovery in the first cycle was 8.0 and 7.8 days in the XM02 and filgrastim groups, respectively.[13] Another study under the same clinical development program on patients with non-Hodgkin's (NH) lymphoma receiving CHOP (Cyclophosphamide Doxorubicin [Hydroxydaunomycin] Vincristine Prednisolone) therapy

Table 8 Time to ANC recovery

Medication	Mean ± SD	Median (min–max)
Filgrastim 30 MIU	5.66±4.83	3.5 (2–21)
Biosimilar filgrastim 30 MIU	5.41±4.54	4 (1–21)
Filgrastim 48 MIU	5.63±4.32	4 (1–21)

Note: Compared using Kruskal–Wallis one-way analysis of variance.
Abbreviations: ANC, absolute neutrophil count; SD, standard deviation; min, minimum; max, maximum.

Table 10 Duration of neutropenia in patients ≤70 kg

Medication	Duration of neutropenia, mean ± SD, median (min–max)
Biosimilar filgrastim 30 MIU	5.62±4.63, 4 (1–21)
Filgrastim 30 MIU	6.00±5.75, 3 (2–21)
Filgrastim 48 MIU	5.67±3.75, 5 (2–21)

Note: Compared using the Kruskal–Wallis test.
Abbreviations: SD, standard deviation; min, minimum; max, maximum.

reported the mean duration of severe neutropenia to be 0.5 and 0.9 days in the first cycle in the XM02 and filgrastim groups, respectively.[16] In that particular study, the incidence of FN in the first chemotherapy cycle was 11.1% and 20.7% in the XM02 and filgrastim groups, respectively. The third study in the program conducted on cancer patients with small cell or non-small-cell lung cancer receiving platinum-based chemotherapy reported a mean duration of severe neutropenia in the first cycle of chemotherapy of 0.5 and 0.3 days in the XM02 and filgrastim groups, respectively.[14] Similar to the abovementioned studies, the two treatment groups were comparable in terms of the incidence of FN in the first cycle of chemotherapy (15.0% vs 8.8%, p=0.2347). A meta-analysis was conducted using the data of these three studies to compare XM02 and filgrastim in terms of their prophylactic effect on the development of FN during the first cycle of chemotherapy in relation to the myelotoxic potency of chemotherapy regimen.[16] Patients were allocated to one of the following chemotherapy categories: docetaxel–doxorubicin, CHOP/Pt-vinorelbine or Pt-vinblastine/Pt-etoposide, and Pt-gemcitabine/Pt-docetaxel or Pt-paclitaxel. The incidence of FN in the first cycle of chemotherapy was low (ranged between 12% and 16%), and the authors concluded that the incidence of FN was not directly correlated with the myelotoxic potency of chemotherapy regimen.[15]

A more recent study comparing filgrastim and its biosimilar Nivestim® (Hospira Zagreb, Prigorje Brdovecko, Crotia) in a breast cancer setting reported the mean duration of severe neutropenia in the first cycle of chemotherapy to be 1.6 and 1.3 days in the Nivestim® and filgrastim groups, respectively. Furthermore, the incidence of severe neutropenia in the first cycle was comparable between the two groups (77.6% and 68.2%). During the subsequent cycles of chemotherapy, the incidence of severe neutropenia remained similar between the two groups. The incidence of FN in cycles 1–3 was 2.4% in both treatment groups. The Nivestim® and filgrastim groups were also comparable with respect to the mean duration to ANC recovery. The mean time to ANC recovery in the first chemotherapy cycle was 7.8 days in both groups.[8]

In the present study, secondary prophylaxis with biosimilar filgrastim provided a similar degree of hemopoietic support with respect to the time to ANC recovery as compared with original filgrastim. The mean time to ANC recovery was 5.41±4.54 days, 5.66±4.83 days, and 5.63±4.32 days in the biosimilar filgrastim 30 MIU, original filgrastim 30 MIU, and original filgrastim 48 MIU groups, respectively.

Although all patients have a risk for developing neutropenia and its complications while receiving chemotherapy, patients at greater risk can be predicted based on several risk factors such as the use of some specific classes of chemotherapy regimen and the phase of therapy. A study on elderly patients with aggressive NH lymphoma receiving doxorubicin-based chemotherapy reported that 63% of the toxic deaths occurred after the first cycle of chemotherapy.[17] In a study on patients with intermediate-grade, NH lymphoma receiving CHOP chemotherapy, febrile neutropenic event occurred during the first cycle in one-half of 160 patients experiencing FN.[18] Moreover, in a retrospective study on 1,355 patients with intermediate-grade NH lymphoma, more than one-half of all initial hospitalizations for FN occurred in the first or second cycle of chemotherapy.[19] A more recent study reported that ~60% of febrile neutropenic events occurred during the first cycle of therapy.[20] In accordance with the literature, ~60% of neutropenic events were noted during the first two cycles of chemotherapy in the present study.

The chemotherapy regimen is one of the primary determinants of the risk of neutropenia, and some chemotherapy regimens are more myelotoxic than others.[5,21,22] High doses of cyclophosphamide or the use of etoposide in patients with NH lymphoma,[23,24] as well as high doses of anthracyclines in patients with early breast cancer,[25] have been identified as significant predictors of neutropenic complications. Recently, a multivariate model of risk developed using the data of patients with solid tumors or malignant lymphoma showed that the use of several classes of chemotherapeutic agents, including the anthracyclines, taxanes (paclitaxel and docetaxel), certain alkylating agents (cyclophosphamide and ifosfamide), type I and type II topoisomerase inhibitors, platinums (cisplatin and carboplatin), gemcitabine, and vinorelbine, were associated with an increased risk of neutropenic events.[26] However, a meta-analysis of three bioequivalence studies found no direct correlation between the development of neutropenic events and myelotoxic potency of chemotherapy regimen in patients with NH lymphoma.[16] However, in that particular study, the comparison was made between three chemotherapy regimens that were associated with a high risk of neutropenic events. In this study, the most commonly used chemotherapeutic agent was fluorouracil, followed by cisplatin and doxorubicin. The common use of these agents might have contributed to the development of neutropenia in our patients.

Conclusion

The results of this observational study indicate that original filgrastim and biosimilar filgrastim have comparable efficacy in treating neutropenia in patients receiving cancer chemotherapy. Biosimilar filgrastim provides a valuable alternative to original

filgrastim; however, there is need for further studies comparing the two products in different patient subpopulations.

Disclosure

The authors report no conflicts of interest in this work.

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