The Comparison of The Efficacy and Safety of Original and Biosimilar Filgrastim in Prevention of Chemotherapy-Induced Neutropenia in Children with Cancer

Mustafa Buyukavci*, Zuhal Keskin Yildirim

ABSTRACT

Objective: In adults and children, the duration of chemotherapy-induced neutropenia and associated complications has decreased because of the prophylactic use of granulocyte colony-stimulating factors (G-CSFs). Biosimilar G-CSFs can play an important role in reducing treatment costs in daily practice. However, some concerns regarding the efficacy and safety of new biosimilar products exist among clinicians. This study compared the efficacy and safety of original and biosimilar filgrastims for the prophylaxis of chemotherapy-induced neutropenia in children.

Materials and Methods: Thirty children receiving myelosuppressive chemotherapy were enrolled in this study. Filgrastims (5 µg/kg/day) were subcutaneously administered in Group A (biosimilar, Leucostim®; Dem İlaç) and Group B (original drug, Neupogen®; Roche). Hemoglobin, white blood cell (WBC) count, platelet count, transfusion requirements, duration of hospitalization, and frequency and duration of adverse events including fever, neutropenia, and mucositis were evaluated following 25 treatment cycles in both groups.

Results: The hemoglobin value, WBC count, and platelet count on days 1, 5, and 10, and the red blood cell and platelet transfusion requirements, frequency, duration, and severity of mucositis, and durations of fever, febrile neutropenia, and hospitalization were similar in both groups. Although the mean WBC counts on days 1 and 5 were lower in Group A, the difference was statistically insignificant.

Conclusion: The biosimilar filgrastim, Leucostim, is as effective and safe as the original drug for prophylaxis of chemotherapy-induced neutropenia in children.

Keywords: Filgrastim, biosimilar, children, neutropen

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ORCID IDs of the authors:
M.B. 0000-0002-9054-3134
Z.K.Y. 0000-0001-8689-4014

Department of Pediatric Oncology, Atatürk University School of Medicine, Erzurum, Turkey

***Current address:** Department of Pediatric Hematology and Oncology, Sakarya University School of Medicine, Sakarya, Turkey

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Correspondence to: Mustafa Buyukavci
E-mail: buyukavci@hotmail.com

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Introduction

Intensified chemotherapeutic regimens cause many adverse effects, including prolonged and severe neutropenia, in addition to high rates of survival in childhood cancers. Neutropenia and subsequent infections increase hospitalization, mortality, and medical costs [1-5].

Granulocyte colony-stimulating factors (G-CSFs), which promote the proliferation, differentiation, and activation of neutrophils in the bone marrow, are widely used to prevent neutropenic complications in adults and children. The prophylactic use of G-CSFs reduces the duration of neutropenia and associated complications following chemotherapy [6, 7]. Biosimilar G-CSFs are copies of the original biological agent. They are increasingly being used in daily practice and can play a significant role in reducing costs [8, 9]. However, concerns about the efficacy and safety of the new biosimilar products, which are not chemically identical to the original drugs, exist among clinicians.

In this study, we evaluated the efficacy and safety of prophylaxis with original and biosimilar filgrastims, which are the most commonly used recombinant G-CSFs, in children receiving myelosuppressive chemotherapy.

Materials and Methods

In this study, 30 patients receiving chemotherapy for acute leukemia, Ewing sarcoma, astrocytoma, germ cell tumor, and Wilms' tumor were enrolled. We compared 2 products containing recombinant filgrastim: the biosimilar (Leucostim®; DONG-A Pharm, Daegu, South Korea) which was approved by Turkish Ministry of Health at 2009 and the original drug (Neupogen®; Roche,

Mannheim, Germany). Groups A and B consisted of 15 patients each, who received biosimilar and original drug, respectively. Both groups were retrospectively evaluated after 25 treatment cycles. Following intensive chemotherapy cycles, G-CSFs were used to reduce both the degree and duration of neutropenia following chemotherapy. Similar cycles of chemotherapeutic regimen were selected in each diagnostic group for Groups A and B. The demographic characteristics and primary diagnoses of the patients are shown in Table 1.

Filgrastims were subcutaneously administered (5 µg/kg/day) after 24 hours of completion of chemotherapy until the white blood cell (WBC) count recovered to 10,000/mm^3. The WBC count, hemoglobin level, and platelet count were obtained on days 1, 5, and 10 after the end of treatment. Transfusion requirements, duration of hospitalization, and frequency and duration of adverse events, including fever, neutropenia, and mucositis were evaluated during follow-up. Red blood cell (RBC) and platelet transfusions were administered at a dose of 10 mL/kg. RBC was substituted in patients with hemoglobin <7 g/L. Platelet transfusion was performed in case of platelet count <10,000/mm^3 or in patients with comorbid conditions such as infection, hemorrhage, and severe mucositis and platelet count <20.000/mm^3.

Febrile neutropenia (FN) was defined as an axillary temperature >38.5°C recorded once, or of >38°C recorded on 2 or more occasions over a 12-hour period in patients with absolute neutrophil count (ANC)<500/mm^3, or of 500-1000/ mm^3 but expected to decline to <500/mm^3 within the next 48 hours. The World Health Organization oral toxicity scale was used to evaluate oral mucositis [10].

Table 1. The demographic characteristics and the primary diagnosis of the patients

	Group A (Leucostim) n=15	Group B (Neupogen) n=15	p
Age (months)	84 (32-198)	78 (6-172)	0.33
Gender			0.55
Male	6 (40)	7 (46)	
Female	9 (60)	8 (54)	
Diagnosis			0.33
ALL	4 (27)	4 (27)	
AML	5 (32)	2 (13)	
Astrocytoma	1 (7)	0	
Ewing sarcoma	1 (7)	1 (7)	
NHL-B cell	2 (13)	4 (27)	
Wilms' tumor	1 (7)	2 (13)	
Germ cell tumor	1 (7)	2 (13)	

Data are reported as number (%) or median (range). ALL: acute lymphoblastic leukemia; AML: akut myeloblastic leukemia; NHL: non-Hodgkin lymphoma

Table 2. The mean WBC counts, hemoglobin values, and platelet counts on days 1, 5, and 10

	Group A (n=15) Mean±SD	Group B (n=15) Mean±SD	p
WBC count (/mm^3)			
Day 1	6.4×10^3±3.7×10^3	9.4×10^3±11.6×10^3	0.22
Day 5	2.7×10^3±1.5×10^3	4×10^3±2.4×10^3	0.31
Day 10	1.9×10^3±2.5×10^3	1.9×10^3±2.0×10^3	0.99
Hemoglobin (g/dL)			
Day 1	10.4±1.4	10.7±1.3	0.43
Day 5	8.9±1.1	9.4±1	0.14
Day 10	8.3±1.1	8.1±1.2	0.55
Platelet count (/mm^3)			
Day 1	210×10^3±128×10^3	211×10^3±63×10^3	0.96
Day 5	154×10^3±119×10^3	156×10^3±66×10^3	0.96
Day 10	58×10^3±42×10^3	69×10^3±48×10^3	0.40

WBC: White blood cell

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) software ver. 20.0 (IBM Corp.; Armonk, NY, USA). Categorical variables were compared using the chi-square test. Continuous variables with a normal distribution were compared using the *t* test, whereas variables with a non-normal distribution were compared using the nonparametric Mann-Whitney test. In all analyzes, p<0.05 was taken to indicate statistical significance.

Results

There were no statistically differences in age, gender, or primary diagnosis between Group A (six girls, nine boys) and Group B (seven girls, eight boys). No adverse events were observed related to filgrastim in either group.

The mean hemoglobin values, WBC counts, and platelet counts on days 1, 5, and 10 were similar between the groups receiving the original drug and the biosimilar (Table 2). Although the mean WBC counts on days 1 and 5 were lower in Group A, the difference was statistically insignificant. The mean RBC and platelet transfusion requirements for each course of chemotherapy were also similar between the 2 groups (Table 3).

Grade 3-4 mucositis was observed in 9 (52%) and 8 (47%) of the patients in Group A and Group B, respectively. The high rate of grade 3-4 mucositis may have been caused by the intensive chemotherapeutic regimens used in acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), and non-Hodgkin lymphoma (NHL). A diagnosis of ALL, AML, or NHL was made in 72% and 67% of the patients in Group A and Group B, respectively. The mean duration of mucositis following chemotherapy was similar between the 2 groups (Table 3).

There was no significant difference in the duration of fever between the 2 groups, and the mean durations of FN and hospitalization were also similar between the 2 groups (Table 3).

Discussion

Filgrastim, a recombinant G-CSF, has been used in clinical practice to reduce chemotherapy-induced FN and its complications. Meanwhile,

Table 3. Transfusion requirements and the duration of mucositis, fever, febrile neutropenia, and hospitalization

	Group A (n=15) Mean±SD	Group B (n=15) Mean±SD	p
RBC transfusion per course*	1.36±1.35	1.32±1.40	0.91
Platelet transfusion per course*	1.56±1.89	1.32±2.07	0.67
Duration of mucositis per course (day)	6.52±8.10	6.40±4.72	0.94
Duration of fever per course (day)	4.80±5.11	4.76±5.05	0.97
Duration of FN per course (day)	4.60±4.99	4.44±4.85	0.90
Hospitalization per course (day)	11.12±7.85	11.44±7.15	0.88

(*): 10 mL/kg per course; RBC: Red blood cell

biosimilar filgrastims can provide a significant reduction in the cost of treatment [8, 11]. In this study, we did not conduct a cost-efficiency analysis, comparing the two types of filgrastim in terms of only efficacy. The principal finding was that the biosimilar filgrastim, Leucostim, was as effective as the original drug, Neupogen, for prophylaxis of chemotherapy-induced neutropenia and its complications.

The clinical efficacy and safety of biosimilar filgrastim molecules in various clinical conditions have been reported [12]. However, most previous studies were carried out in adult patients. In these studies, different types of biosimilar filgrastims were shown to be safe, effective, and well tolerated for chemotherapy-associated neutropenia prophylaxis. The results were consistent with those reported previously in phase II and phase III trials, and for original filgrastim [13, 14]. The efficacy and safety of biosimilar filgrastim (EP2006), for the prevention of severe neutropenia in comparison to the original molecule, were also confirmed by another study [15].

One previous study evaluated biosimilar filgrastim in children, although it was not identical to our study. Cesaro et al. [16] reported that the biosimilar filgrastim, Zarzio, was as effective and safe as the original filgrastim molecule for mobilization of autologous peripheral blood stem cells in children. Leucostim, the biosimilar filgrastim used in our study, was compared with Neupogen with regard to peripheral blood stem cell mobilization in adult patients undergoing autologous hematopoietic stem cell transplantation, and no significant differences were observed between the groups [17].

The immunogenicity of biosimilar filgrastim is also important with respect to safety and efficacy. Specific anti-G-CSF antibodies may develop following filgrastim administration, and this can be assessed using different methods [18, 19]. We did not evaluate the presence of antibodies. However, in the hypothetical situation of circulating anti-G-CSF antibodies did not seem to affect hematological recovery in our study.

This study has some limitations: (1) small number of patients with different type of cancers; it would be better if the same chemotherapy regimen was used in same disease of each group; (2) lack of immunogenicity assessment; and (3) lack of long-term follow-up.

In conclusion, chemotherapy-induced hematologic toxicity, post-treatment severity and duration of mucositis, and post-treatment durations of fever, FN, and hospitalization were not different between children receiving the biosimilar filgrastim, Leucostim, and the original drug as prophylaxis. However, it needs additional studies for conclusion.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Ataturk University School of Medicine, dated 22.04.2019 and numbered 03/17.

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

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References

1. Tai E, Guy GP, Dunbar A, Richardson LC. Cost of Cancer-Related Neutropenia or Fever Hospitalizations, United States, 2012. J Oncol Pract 2017: 13: e552-e561. [CrossRef]
2. Bothra M, Seth R, Kapil A, Dwivedi SN, Bhatnagar S, Xess I. Evaluation of predictors of adverse outcome in febrile neutropenic episodes in pediatric oncology patients. Indian J Pediatr 2013; 80: 297-302. [CrossRef]
3. Luthi F, Leibundgut K, Niggli FK, et al. Serious medical complications in children with cancer and fever in chemotherapy-induced neutropenia: results of the prospective multicenter SPOG 2003 FN study. Pediatr Blood Cancer 2012; 59: 90-5. [CrossRef]
4. White L, Ybarra M. Neutropenic fever. Emerg Med Clin North Am 2014; 32: 549-61. [CrossRef]
5. Wang XJ, Lopez SE, Chan A. Economic burden of chemotherapy-induced febrile neutropenia in patients with lymphoma: a systematic review. Crit Rev Oncol Hematol 2015; 94: 201-12. [CrossRef]
6. Mhaskar R, Clark OA, Lyman G, Engel Ayer Botrel T, Morganti Paladini L, Djulbegovic B. Colony-stimulating factors for chemotherapy-induced febrile neutropenia. Cochrane Database Syst Rev 2014; (10): CD003039. [CrossRef]
7. Wittman B, Horan J, Lyman GH. Prophylactic colony-stimulating factors in children receiving myelosuppressive chemotherapy: a meta-analysis of randomized controlled trials. Cancer Treat Rev 2006; 32: 289-303. [CrossRef]
8. Aapro M, Cornes P, Abraham I. Comparative cost-efficiency across the European G5 countries of various regimens of filgrastim, biosimilar filgrastim, and pegfilgrastim to reduce the incidence of chemotherapy-induced febrile neutropenia. J Oncol Pharm Pract 2012; 18: 171-9. [CrossRef]
9. Marcianò I, Ingrasciotta Y, Giorgianni F, et al. How did the Introduction of Biosimilar Filgrastim Influence the Prescribing Pattern of Granulocyte Colony-Stimulating Factors? Results from a Multicentre, Population-Based Study,from Five Italian Centres in the Years 2009-2014. BioDrugs 2016; 30: 295-306. [CrossRef]
10. Peterson DE, Bensadoun RJ, Roila F; ESMO Guidelines Working Group. Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines. Ann Oncol 2011; 22 Suppl 6: vi78-84. [CrossRef]
11. Gardellini A, Gigli F, Babic A, et al. Filgrastim XM02 (Tevagrastim®) after autologous stem cell transplantation compared to lenograstim: favourable cost-efficacy analysis. Ecancer 2013; 7: 327.
12. Caselli D, Cesaro S, Aricò M. Biosimilars in the management of neutropenia:focus on filgrastim. Biologics 2016; 10: 17-22. [CrossRef]
13. Gascón P, Aapro M, Ludwig H, et al. Treatment patterns and outcomes in the prophylaxis of chemotherapy-induced (febrile) neutropenia with biosimilar filgrastim (the MONITOR-GCSF study). Support Care Cancer 2016; 24: 911-25. [CrossRef]
14. Tesch H, Ulshöfer T, Vehling-Kaiser U, Ottillinger B, Bulenda D, Turner M. Prevention and treatment of chemotherapy-induced neutropenia with the biosimilar filgrastim: a non-interventional observational study of clinical practice patterns. Oncol Res Treat 2015; 38: 146-52. [CrossRef]
15. Blackwell K, Semiglazov V, Krasnozhon D, et al. Comparison of EP2006, a filgrastim biosimilar, to the reference: a phase III, randomized, double-blind clinical study in the prevention of severe neutropenia in patients with breast cancer re-

ceiving myelosuppressive chemotherapy. Ann Oncol 2015; 26: 1948-53. [CrossRef]
16. Cesaro S, Tridello G, Prete A, et al. Biosimilar granulocyte-colony-stimulating factor for mobilization of autologous peripheral blood stem cells in pediatric hematology-oncology patients. Transfusion 2015; 55: 246-52. [CrossRef]
17. Sivgin S, Karakus E, Kaynar L, et al. The comparison of Filgrastim (Neupogen®), biosimilar filgrastim (Leucostim®) and Lenograstim (Granocyte®) as a first line peripheral blood stem cell mobilization strategy in autologous hematopoieitic stem cell transplantation: a single center experience from Turkey. Transfus Apher Sci 2013; 48: 315-20. [CrossRef]
18. Laricchia-Robbio L, Moscato S, Genua A, Liberati AM, Revoltella RP. Naturally occurring and therapy-induced antibodies to human granulocyte colony-stimulating factor (G-CSF) in human serum. J Cell Physiol 1997; 173: 219-26. [CrossRef]
19. Varki R, Pequignot E, Leavitt MC, Ferber A, Kraft WK. A glycosylated recombinant human granulocyte colony stimulating factor produced in a novel protein production system (AVI-014) in healthy subjects: a first-in human, single dose, controlled study. BMC Clin Pharmacol 2009; 9: 2. [CrossRef]