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

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ABSTRACT

Objective: The duration of chemotherapy-induced neutropenia and associated complications has decreased in adults and children due to 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, there are some concerns among clinicians regarding the efficacy and safety of new biosimilar products. In this study, we 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 administered subcutaneously in Group

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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 cycles of treatment 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.**

Conclusions: 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, neutropenia

Öz

Amaç: Profilaktik granülosit-koloni stimulan faktör (G-CSF) kullanımını sonucunda erişkin ve çocuklardaki kemoterapiye bağlı nötropeni süresi ve buna bağlı komplikasyonlar azalmıştır. Biobenzer G-CSFler günlük pratikte tedavi maliyetini düşürmekte önemli bir rol oynayabilirler. Ancak klinisyenler, yeni çıkan biobenzer ürünlerin etkinlik ve güvenilirliği ile ilgili bazı kaygılar taşımaktadırlar. Biz bu çalışmada, çocuklardaki kemoterapiye bağlı nötropeni profilaksisinde orijinal ve biobenzer filgrastim preparatlarının etkinlik ve güvenilirliğini karşılaştırdık.

Gereç ve Yöntem: Çalışmaya myelosupressif tedavi alan 30 çocuk dahil edildi. Filgrastim (5 µg/kg/gün), Grup A (biobenzer, Leucostim®-Dem İlaç) ve Grup B (orijinal ilaç, Neupogen®-Roche) için subkutan olarak uygulandı. Her iki gruba uygulanan 25 kür tedavi sonrasında hemoglobin, beyaz küre ve trombosit sayıları; transfüzyon ihtiyacı, hastanede yatış süresi; ateş, nötropeni ve mukozit gibi yan etkilerin sıklığı ve süresi değerlendirildi.

Bulgular: Birinci, 5. ve 10. günlerdeki hemoglobin değerleri, beyaz küre ve trombosit sayıları; transfüzyon gerekliliği; mukozit sıklığı, süresi ve şiddeti ile ateş, febril nötropeni ve hastanede yatış süreleri her iki grupta da benzerdi. **Birinci ve 5. günlerdeki ortalama beyaz küre sayıları Grup A'da daha düşük olmasına rağmen aradaki fark istatistik olarak önemsizdi.**

Sonuç: Biobenzer filgrastim (Leucostim), çocuklardaki kemoterapiye bağlı nötropenin önlenmesinde orijinal ilaç kadar etkin ve güvenlidir.

Anahtar Kelimeler: Filgrastim, biobenzer, çocuk, nötropeni

Introduction

Intensified chemotherapeutic regimens lead to 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 has been shown to reduce the duration of neutropenia and associated complications following chemotherapy [6,7]. Biosimilar G-CSFs, which are copies of the original biological agent, are increasingly being used in daily practice and can play a significant role in reducing costs [8,9]. However, there are concerns among clinicians about the efficacy and safety of the new biosimilar products, which are not chemically identical to the original drugs.

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

Thirty patients receiving chemotherapy for acute leukemia, Ewing sarcoma, astrocytoma, germ cell tumor or Wilms' tumor were enrolled in this study. We compared two 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 both consisted of 15 patients, receiving biosimilar and original drug, respectively. **Both groups were evaluated retrospectively after 25 cycles of treatment in total. Granulocyte colony-stimulating factors were used following intensive chemotherapy cycles for reducing both the degree and duration of neutropenia following chemotherapy. Similar cycles of chemotherapeutic regimen were selected in each diagnostic group for Group A and B.** The demographic characteristics and primary diagnoses of the patients are shown in Table 1.

Filgrastims were administered subcutaneously (5 µg/kg/day) beginning 24 hours after completion of chemotherapy until the white blood cell (WBC) count recovered to

10,000/mm³. 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 less than 7 g/L. Platelet transfusion was performed in case of platelet count < 10,000/ mm³ or in patients with comorbid conditions such as infection, hemorrhage and severe mucositis and platelet count < 20,000/ mm³.

Febrile neutropenia (FN) was defined as an axillary temperature > 38.5°C recorded once, or of > 38°C recorded on two or more occasions over a 12-hour period in patients with absolute neutrophil count (ANC) < 500/mm³, or of 500–1,000/ mm³ but expected to decline to < 500/ mm³ within the next 48 hours. The World Health Organization (WHO) oral toxicity scale was used to evaluate oral mucositis [10].

Data were analyzed using SPSS software (ver. 20.0; SPSS, Inc., Chicago, IL). 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 analyses, *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 two groups (Table 3).

Grade 3–4 mucositis was observed in nine (52%) and eight (47%) of the patients in Group A and Group B, respectively. The high rate of grade 3–4 mucositis may have been due to 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 two groups (Table 3).

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

Discussion

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

There has been only one previous study evaluating 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 the present 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 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 the present 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 final conclusion.

Conflict of interest

The authors declare no conflicts of interest.

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

	Group A (Leucostim) n=15	Group B (Neupogen) n=15	p value
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 1st, 5th and 10th days.

	Group A (n=15)	Group B (n=15)	p value
	Mean±SD	Mean±SD	
WBC count (/mm³)			
1. day	6.4x10 ³ ±3.7x10 ³	9.4x10 ³ ±11.6x10 ³	0.22
5. day	2.7x10 ³ ±1.5x10 ³	4x10 ³ ±2.4x10 ³	0.31
10. day	1.9x10 ³ ±2.5x10 ³	1.9x10 ³ ±2.0x10 ³	0.99
Hemoglobin (gr/dL)			
1. day	10.4±1.4	10.7±1.3	0.43
5. day	8.9±1.1	9.4±1	0.14
10. day	8.3±1.1	8.1±1.2	0.55
Platelet count (/mm³)			
1. day	210x10 ³ ±128x10 ³	211x10 ³ ±63x10 ³	0.96
5. day	154x10 ³ ±119x10 ³	156x10 ³ ±66x10 ³	0.96
10. day	58x10 ³ ±42x10 ³	69x10 ³ ±48x10 ³	0.40

WBC: White blood cell

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

	Group A (n=15)	Group B (n=15)	p value
	Mean±SD	Mean±SD	
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