

Original Article

The Comparison of the Biosimilar Filgrastim (Tevagrastim) and the Original Filgrastim (Neupogen) in the Autologous Hematopoietic Stem Cell Mobilization: A Single Center Experience

Otolog Hematopoetik Kök Hücre Mobilizasyonunda Biobenzer Filgrastim (Tevagrastim) ile Orjinal Filgrastimin (Neupogen) Karşılaştırılması (Tek Merkez Deneyimi)

Merve Pamukçuoğlu¹, Ahmet Kürşad Güneş¹, Mehmet Ali Uçar², Funda Ceran¹, Mesude Falay³, Gülsüm Özet¹, Simten Dağdaş¹

¹City Hospital Of Ankara, Department Of Hematology And Bone Marrow Transplantation

²Cukurova University Faculty Of Medicine, Department Of Hematology

³Duzen Laboratory Group, Biochemistry Department

ABSTRACT

Objective : Autologous hematopoietic stem cell transplantation is a significant treatment modality for several hematological malignancies and some solid tumors. A sufficient dose of CD34+ stem cell mobilization is a prerequisite for successful autologous hematopoietic stem cell transplantation. Granulocyte colony stimulating factor (G-CSF) is usually used alone or in combination with chemotherapy for mobilization. Two types of G-CSF are used in peripheral blood stem cell mobilization; filgrastim (original or biosimilar) and lenograstim. It was aimed to compare the original filgrastim (Neupogen) with the biosimilar filgrastim (Tevagrastim) in terms of effectiveness in peripheral blood stem cell mobilization.

Materials and Methods: Ninety-five patients who underwent stem cell mobilization between January 2015 and November 2018 in the Bone Marrow Transplant Service of Ankara Numune Training and Research Hospital were analyzed retrospectively. We used Cyclophosphamide (low dose: 2g/m² or high dose: 3-4 g/m²), as a mobilization regimen, on the first day and G-CSF (Neupogen or Tevagrastim) at a dose of 5 g/kg was started one day after chemotherapy, as a mobilization regimen in all patients.

Results: Thirty-nine patients were female and 56 were male. The mean age was 51.24±12.38 years. Sixty-four (67.4%) patients had Multiple Myeloma (MM), 20 (21.1%) patients had non-Hodgkin lymphoma (NHL), and 11 (11.6%) patients had Hodgkin lymphoma (HL). Stem cell mobilization was performed with Neupogen in 50 of ninety-five patients and with Tevagrastim in 45 of them. While there was no statistically significant difference between the demographic characteristics of the patients in terms of age, diagnosis, and whether they received radiotherapy or not (p> 0.05); There was a significant difference in terms of the dose of cyclophosphamide (higher dose cyclophosphamide was used more in the arm receiving Neupogen) and gender (gender distribution in the Neupogen arm was equal, there were more male patients in the Tevagrastim arm) (p<0.05). No statistically significant difference was found between the use of original and biosimilar products in terms of achieving the target of 2x10⁶/kg, which is the minimum CD34+ cell dose required for adequate engraftment, and 4x10⁶/kg for double transplantation (p>0.05). However, if the target level of CD34+ stem cell was above 6x10⁶/kg, a statistically significant difference was observed in favor of Neupogen compared to the Tevagrastim arm (p=0.021). When the neutrophil engraftment days after autologous stem cell transplantation were compared, it was observed that the neutrophil engraftment was shorter in the Neupogen arm compared to the Tevagrastim arm (approximately 1 day) (p=0.015), while the platelet engraftment was similar in the Neupogen and Tevagrastim arms (p=0.186).

Conclusion: While the original and biosimilar filgrastim CD34+ cell dose show similar efficacy in reaching the target of 2x10⁶/kg for transplantation and 4x10⁶/kg for double transplantation. The difference was observed in favor of the Neupogen arm, when stem cell collection was aimed at above 6x10⁶/kg. The reason for this difference was thought to be related to the higher dose of cyclophosphamide used in the original molecule (Neupogen) arm. We need further studies that were included more cases which are used high-dose cyclophosphamide for comparing the biosimilar molecule (Tevagrastim) with the original molecule (Neupogen).

Keywords: autologous stem cell transplantation, biosimilar G-CSF, stem cell mobilization

ÖZET

Giriş ve amaç: Başarılı otolog hematopoetik kök hücre nakli için yeterli dozda CD34⁺ kök hücre mobilizasyonu ön koşuldur. Yapmış olduğumuz çalışmada orjinal filgrastim (Neupogen) ile biyobenzer filgrastimin (Tevagrastimin) çevre kanı kök hücre mobilizasyonunda etkinlik açısından karşılaştırılması amaçlanmıştır.

Yöntem ve gereçler: Ankara Numune Eğitim ve Araştırma Hastanesi Kemik İliği Nakil servisinde Ocak 2015 ile Kasım 2018 tarihleri arasında kök hücre mobilizasyonu yapılan 95 hasta retrospektif olarak analiz edildi. Tüm hastalara mobilizasyon rejimi olarak birinci gün siklofosamid (düşük dozda: 2g/m² veya yüksek dozda: 3-4 g/m²) ve kemoterapiden 1 gün sonra 5 g/kg dozunda G-CSF başlanmıştır.

Bulgular: Doksan beş hastanın 50'sine neupogen ile, 45'ine tevagrastim ile kök hücre mobilizasyonu yapıldı. Hastaların demografik özellikleri arasında yaş, tanı, radyoterapi alıp almaması açısından istatistiksel anlamlı farklılık yok iken (p> 0.05); alınan siklofosamid dozu (neupogen alan kolda daha çok yüksek doz siklofosamid kullanılmıştır.) ve cinsiyet (neupogen kolunda cinsiyet dağılımı eşit iken, tevagrastim kolunda daha çok erkek hastalar vardı.) açısından farklılık tespit edildi (p<0.05). Yeterli engraftman için gereken minimum CD34⁺ hücre dozu olan 2x10⁶/kg ve çift nakil için 4x10⁶/kg lik hedefe ulaşmak açısından orjinal ve biyobenzer ürün kullanımı arasında istatistiksel olarak anlamlı bir fark saptanmadı (p>0,05). Ancak 6x10⁶/kg'ın üzerinde kök hücre hedefine bakıldığında neupogen lehine tevagrastim koluna göre istatistiksel olarak anlamlı bir fark izlenmiştir (p=0,021). Otolog kök hücre nakli sonrası nötrofil engraftman günleri karşılaştırıldığında, nötrofil engraftman zamanının neupogen grubunda tevagrastim grubuna göre daha kısa olduğu gözlenirken (yaklaşık 1 gün) (p=0.015), trombosit engraftman zamanı neupogen ve tevagrastim gruplarında benzerdi (p=0.186).

Tartışma ve sonuç: Çalışmamızda 6x10⁶/kg'ın üzerinde kök hücre toplanması hedeflendiğinde neupogen lehine farklılık gözlenmiştir. Bu farklılığın nedeni kullanılan olan siklofosamid dozunun orjinal molekül (Neupogen) kolunda daha yüksek olması ile ilişkili düşünülmüştür. Daha çok vaka serileri içeren, yüksek doz siklofosamidin kullanıldığı, biyobenzer molekül (tevagrastim) ile orjinal molekülün (neupogen) kıyaslandığı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: otolog kök hücre nakli, biyobenzer G-CSF, kök hücre mobilizasyonu

Introduction:

In recent years, peripheral blood stem cells have been preferred to use in stem cell transplantation. Granulocyte colony-stimulating factors (G-CSF) are often used either as a single agent or in combination with the chemotherapy at peripheral stem cell mobilization. Physicians have been using two types of G-CSF: filgrastim (original or biosimilar) and lenograstim. Lately, the biosimilar filgrastim products have been using in neutropenia after chemotherapy and in stem cell mobilization for getting benefit for the cost. A Biosimilar product is produced from the biotechnical product of the original molecule and it is also similar to the original molecule. However, we could not say that the biosimilar product is identical to the original. For this reason, it is very important for comparing the biosimilar molecule with the original molecule.

In recent years, various biosimilar filgrastim products have been used in neutropenia and stem cell mobilization after chemotherapy. Biosimilar G-CSFs (Zarzio®, Sandoz International GmbH, Holzkirchen, Germany; Nivestim®, Hospira Worldwide, Lake Forest, Illinois, USA; Tevagrastim®, Teva

Pharmaceutical Industries, Petah Tiqwa, Israel; Ratiograstim®, in all indications of original filgrastim Ratiopharm, Ulm, Germany) has been approved by the European Medicines Agency (EMA). This approval is based on prospective randomized studies in which biosimilar filgrastim have similar efficacy and side effect profile compared to the original filgrastim in chemotherapy-induced neutropenia [1,2]. However, there are no prospective studies about its use in peripheral stem cell mobilization.

Biosimilar G-CSFs has been approved by the European Medicines Agency (EMA) in all indications of the original filgrastim. In Turkey, Tevagrastim (filgrastim XM02) was licensed and approved in 2015 and has been used in our hospital since 2016. There are few data in the literature which was comparing the Tevagrastim and Neupogen at peripheral stem cell mobilization, also there is not any report from Turkey in the literature about the issue [3]. This study's aim is to compare the effectiveness and the side effects of biosimilar Filgrastim (Tevagrastim) and original product (Neupogen) in peripheral stem cell mobilization.

Materials And Methods :

We retrospectively evaluated 95 patients who had a stem cell mobilization in Ankara Numune Training and Research Hospital Bone Marrow Transplant Service between January 2015 and November 2018. The patients of the study were divided into two arms as patients using the Original Filgrastim (Neupogen) and Biosimilar Filgrastim (Tevagrastim). None of the patients had a stem cell mobilization before.

All patients received cyclophosphamide (2-4 g/m²) on day 1 and G-CSF (Neupogen or Tevagrastim) at a dose of 5 µg / kg one day after the chemotherapy. Stem cells were collected using an apheresis device (Fresenius, Com. Tec cell separator) via a peripheral or central venous catheter. When the total number of peripheral blood leukocytes increased up to 1500/mm³ in the patients and the peripheral CD34 positive cell count was at least 15x10⁶/lt, the leukapheresis was started." The FacsCanto, Becton Dickinson" flow cytometry device was used for counting the CD 34⁺ cells. Apheresis products were frozen at - 196°C, using 10% dimethylsulfoxide and 40% patient plasma.

The minimum CD34⁺ cell dose for adequate engraftment was reported as 2x10⁶/kg for a single transplant and 4 x 10⁶ / kg for a double transplant. Optimal CD34⁺ cell dose was >4x10⁶/kg for single transplants and 8-10x10⁶/kg for double transplants (4). Therefore, patients in the Neupogen and Tevagrastim arms were compared based on these values.

The patients were re-hospitalized to our clinic for autologous peripheral stem cell transplantation 3-4 weeks after the mobilization procedure. The transplantation was performed using a melphalan regimen (200 mg/m²/day) in multiple myeloma and performed using a high-dose BEAM (Carmustine 300mg/m², (-7 day); Etoposide 200 mg/m², (-6/-3 days); Cytarabine 200 mg/m², (-6/-3 days); Melphalan 140 mg/m², (-2 day)) regimen in non-Hodgkin and Hodgkin lymphoma patients.

This retrospective study was approved by the Ankara Numune Training and Research Hospital Local Ethics Committee (11/04/2018-R=E-18-1882).

Statistical Analysis

Descriptive statistics were presented as mean ± standard deviation and median (minimum-maximum) for numerical variables, and as number (percentage) for categorical variables. The compliance of numerical variables to normal distribution was determined by the Shapiro-Wilk test. The Mann-Whitney-U Test was used to compare the mean of the two groups in terms of numerical variables, and the Kruskal Wallis Test was used to compare the means of more than two groups. Pearson Chi-Square Test or Fisher's Exact Test was used to comparing two categorical variables. The change between two measurements of a numerical variable and the interaction of this change with a categorical variable was evaluated by analysis of variance (repeated measures ANOVA) in repeated measures. All statistical evaluations were made using the Statistical Package for Social Sciences (SPSS) for Windows 14.01 (IBM SPSS Inc., Chicago, IL) program. Statistical significance was accepted as p <0.05 in all analyzes.

Results

The research group consisted of 95 patients, including 39 women and 56 men. Patient characteristics and demographics were summarized in table 1. The mean age of the patients was 51.24 ± 12.38 years. Neupogen in 50 patients and Tevagrastim in 45 patients were used during the peripheral stem cell mobilization. 64 (67.4%) of the patients had MM, 20 (21.1%) of NHL, and 11 (11.6%) of HL. The age range of the patients having received the Neupogen and Tevagrastim did not differ. The rates of the patients diagnosed with MM, NHL, and HL and those receiving and not receiving radiotherapy were similar in the Neupogen and Tevagrastim arms (p > 0.05). The proportion of male patients was higher in the Tevagrastim arm compared to

Table.1: Patient characteristics and demographics

	All population n=95	Neupogen n=50	Tevagrastim n=45	<i>p</i>
Age	51.24±12.38 55(18-70)	50.26±12.02 54(21-70)	52.33±12.83 57(18-69)	0.203
Gender				
Female	39(41.1)	29(58.0)	10(22.2)	<0.001
Male	56(58.9)	21(42.0)	35(77.8)	
Diagnosis				
MM	64(67.4)	37(74.0)	27(60.0)	0.202
NHL	20(21.1)	7(14.0)	13(28.9)	
HL	11(11.6)	6(12.0)	5(11.1)	
Radiotherapy				
Yes	26(27.4)	15(30.0)	11(24.4)	0.544
No	69(72.6)	35(70.0)	34(75.6)	
Cyclophosphamide dose				
2 g/m ²	33	7	26	<0,001
3 g/m ²	23	11	12	
4 g/m ²	39	32	7	

Table- 2. Comparing the original and biosimilar filgrastim according to the CD34⁺ cells

CD34 ⁺ cells	Allpopulation n=95	Neupogen n=50	Tevagrastim n=45	<i>p</i>
<2x10 ⁶ /kg	3(3.2%)	0(0.0%)	3(6.7%)	0.103
≥2x10 ⁶ /kg	92(96.8%)	50(100.0%)	42(93.3%)	
<4x10 ⁶ /kg	14(14.7%)	4(8.0%)	10(22.2%)	0.051
≥4x10 ⁶ /kg	81(85.3%)	46(92.0%)	35(77.8%)	
<6x10 ⁶ /kg	37(38.9%)	14(28.0%)	23(51.1%)	0.021
≥6x10 ⁶ /kg	58(61.1%)	36(72.0%)	22(48.9%)	

Categorical variables are shown as number (%)

Table.3: Generic-original difference in terms of PLT before and after mobilization

Variables	All population n=95	Neupogen n=50	Tevagrastim n=45	<i>P</i>		
				PLT	G-CSF	PLT*G-CSF
PLT level before mobilization	232(107-630)	235(109-630)	229(107-443)			
PLT level after mobilization	64(24-223)	67(24-223)	61(24-178)	<0.001*	0.357**	0.658***

Numeric variables are shown as median (minimum-maksimum)

*PLT levels before and after collection showed a statistically significant difference.

**While pre-collection platelet values were normal in both Neupogen and Tevagrastim arms, post-collection platelet values decreased

***There was no statistically significant difference between the Neupogen and Tevagrastim groups in terms of the change in PLT levels before and after collection

Table-4: Biosimilar and original difference in terms of neutrophil and platelet engraftment day

Variables	All population n=95	Neupogen n=50	Tevagrastim n=45	<i>p</i>
Neutrophil engraftment day	11(7-19)	10(7-13)	11(9-19)	0.015
PLT engraftment day	11(7-37)	11(7-27)	11(7-37)	0.186

Numeric variables are shown as median (minimum-maksimum)

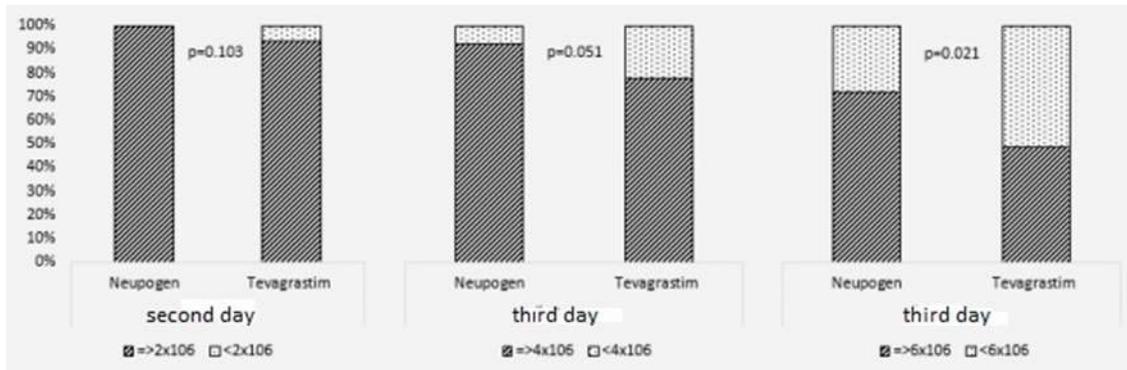


Figure-1. Comparing the original and biosimilar filgrastim according to the CD34⁺ cells

the Neupogen arm ($p < 0.001$). The cyclophosphamide dose was significantly higher in the Neupogen arm compared to the Tevagrastim arm ($p < 0.001$).

No statistically significant difference was found between the use of the original and biosimilar products in terms of achieving the target of $2 \times 10^6/\text{kg}$, which is the minimum CD34⁺ cell dose required for adequate engraftment, and $4 \times 10^6/\text{kg}$ for double transplantation. With both drugs, the minimum and optimum amount of CD34⁺ stem cells required for a single transplant could be collected at similar rates. However, if target level of CD34⁺ stem cell target above $6 \times 10^6/\text{kg}$, a statistically significant difference was observed in favor of Neupogen compared to the Tevagrastim arm. ($p = 0.021$) (Table 2, Figure 1).

PLT levels before and after collection showed a statistically significant difference. While pre-collection platelet values were normal in both Neupogen and Tevagrastim arms, post-collection platelet values decreased ($p < 0.001$). However, there was no statistically significant difference between the Neupogen and Tevagrastim groups in terms of the change in PLT levels before and after

collection ($p = 0.658$). (Table 3) (Figure 2). Both products caused a similar decrease in platelet values.

When the neutrophil engraftment days after autologous stem cell transplantation were compared, it was observed that the neutrophil engraftment time was shorter in the Neupogen arm compared to the Tevagrastim arm (approximately 1 day) ($p = 0.015$), while the platelet engraftment time was similar in both arms ($p = 0.186$). (Table 4).

Discussion

Granulocyte colony stimulant factor or G-CSF and chemotherapy have been using in peripheral stem cell mobilization. In cases which stem cell mobilization could not be performed, the mobilization process is completed with plerixafor. G-CSF followed by cyclophosphamide was preferred to use in stem cell mobilization in this study. There are very few data in the literature that comparing the biosimilar and original molecule after using cyclophosphamide. The main goal during autologous stem cell transplantation is to provide patients with adequate number and quality of CD34⁺ stem cells for neutrophil and platelet engraftment as early as possible. For

this reason, it is important to collect sufficient number and quality CD34⁺ cells in stem cell mobilization. While all of these are targeted, the low cost are getting importance [5]. In recent years, low cost biosimilar molecules are preferred rather than original molecule. For this reason, the studies which are comparing the cost and efficacy in biosimilar and original molecule, are getting importance. We concluded that: If CD34⁺ stem cells collected below the 6x10⁶/kg (2x10⁶/kg, p = 0.103 and 4x10⁶/kg, p = 0.051), there was no difference between the two products (biosimilar versus original). The other result we obtained that no significant differences were found on the platelet engraftment day (p=0.186, however, the neutrophil engraftment day was 1 day shorter in favor of the original molecule (10.34±1.02 days in the Neupogen arm, 11.00±1.65 days in the Tevagrastim arm; p=0.015) after autologous stem cell transplantation. This difference in neutrophil engraftment days between original and biosimilar products is important in terms of shortening the hospitalization period of the patients and reducing the infection rates. On the other hand, considering that other factors have an effect on the duration of hospitalization and infection rates. We think that 1-day differences in neutrophil engraftment was an acceptable for original product and the biosimilar product. Ergene et al. examined the factors that might have an effect on the neutrophil engraftment after autologous stem cell transplantation. These factors are age, gender, amount of CD34⁺ cells, conditioning regimen, type of disease, and time to initiate G-CSF after autologous stem cell transplantation. They concluded that only the amount of CD34⁺ cells had a significant effect on the neutrophil engraftment [6]. Other studies in the literature also support this finding: The most important factor affecting hematopoietic reconstruction after autologous stem cell transplantation is the quantity and quality of CD34⁺ cells [7,8,9].

There are some studies in the literature that showing that biosimilars are as effective as the

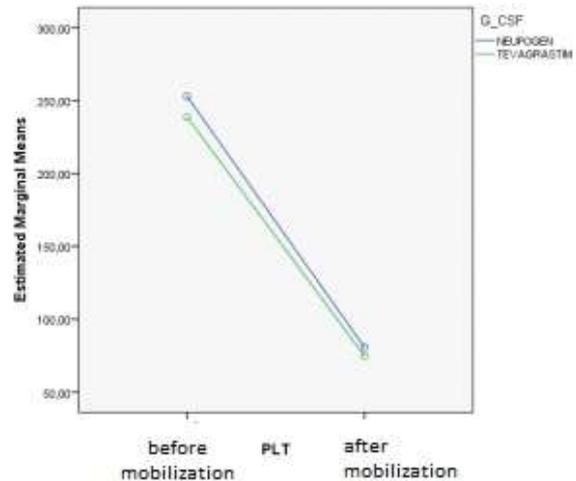


Figure-2. Generic-original difference in terms of PLT before and after mobilization

original molecule in neutropenia caused by chemotherapy as a result of the comparison of the original molecule and biosimilars [10,11,12]. Waller [10] and et al. compared the Amgen filgrastim with the biosimilar Hospira filgrastim in the phase-III study, in patients of breast cancer, and it was observed that the biosimilar Hospira filgrastim was as effective as the original molecule on neutropenia. Engert [11] et al. examined the effects of Tevagrastim (XMO2) and original filgrastim in patients with NHL. They found that both molecules could be similarly effective in neutropenia and febrile neutropenia. Sevic et al. were compared the original filgrastim (Neupogen) and biosimilar filgrastim (Tevagrastim) in oncologic patients [12]. This was a multicenter study that was included 337 patient from 14 centers. This studies' result indicate that original and biosimilar filgrastim have comparable efficacy in treating neutropenia [12]. Bassi et al. also compared two biosimilar products (Tevagrastim (®) and Zarzio (®)). Fifty-six MM and lymphoma patients who underwent autologous stem cell transplantation, were included in this study. They compared Tevagrastim® and Zarzio® according to the cost effect and engraftment days. While there is no difference between the two biosimilar products in terms of neutrophil engraftment

days, however, Tevagrastim has been shown to reduce costs by 56% and Zarzio by 86% [13]. In the literature, comparative studies of the original molecule and biosimilar product regarding peripheral stem cell mobilization are still insufficient [14,15]. Lefrere et al. examined 40 patients who had peripheral stem cell mobilization. They found no differences between the biosimilar molecule (Zarzio) and the original molecule (Neupogen) in terms of the median CD34⁺ cell ratio obtained by [14]. Other study done by Schmitt et al. The original molecule and its biosimilars XM02 (Ratiograstim, Tevagrastim and Biograstim) were compared in 22 healthy donors, and no significant difference was found in terms of the amount of CD34⁺ cells collected by peripheral stem cell mobilization [15]. Şıvgın and et al. reported another study from Turkey, which was comparing the original filgrastim (Neupogen) with biosimilar filgrastim (Leucostim) and lenograstim (Granulosyte). A total of 96 patients who were planned to undergo peripheral autologous stem cell transplantation, were included in this study. The highest level of CD34⁺ cell were observed in the biosimilar filgrastim (leucostim) arm as a result of peripheral stem cell mobilization. This study has been emphasized that; the biosimilar filgrastim (leucostim) may be more advantageous than the original molecule and lenograstim [16].

Healthy donors of acute myeloid leukemia and myelodysplastic syndrome patients' were examined by Danylesko et al. There were two arms in this study. CD34⁺ cells were collected with the original molecule in one arm, and biosimilar filgrastim in the other arm. No significant difference were found between the median CD34⁺ cells and the quality of the graft. The quality of graft was decided according to the similarity of neutrophil and thrombocyte engraftment days

in allogeneic hematopoietic stem cell transplant patients [17]. Short time and rapidly engraftment means that high quality and quantity of CD34⁺ cells according to Danylesko and et al [17]. Consequently; Danylesko et al, were concluded that the biosimilar filgrastim can be used in CD34⁺ cell mobilization from healthy donors as like as the original molecule[17].

We found no difference between the two products in terms of single transplantation or two transplantation in the quantity of CD34⁺ cells (<6x10⁶ CD34⁺ cells). The thrombocyte engraftment days are the same in two product, while the neutrophil engraftment day is only 1 day shorter in favor of the original molecule. This was showing that the graft quality is similar for the two products. The difference between the two products had been arised, when the target level of CD34⁺ cell is higher than the 6x10⁶. We thought that, this difference may depend on cyclophosphamide doses. The mean dose of cyclophosphamide in the original molecule arm was statistically significant higher than the dose of cyclophosphamide in the biosimilar arm (p <0.001). Hamadini et al. concluded the same result in the literature. They compared the patients who had low/ median/ high level of cyclophosphamide in peripheral stem cell mobilization. They observed that quantity of CD34⁺ cells (> 5x10⁶ CD34⁺) was higher in the patients who had high level of cyclophosphamide [18]. Similarly to the data, the original and biosimilar filgrastim showed similar efficacy in stem cell collection in our study; however; different cyclophosphamide doses in the two arms cause a limitation for this study. Therefore, we need more studies involving case series with using high-dose cyclophosphamide which will compare the biosimilar molecule and the original molecule.

References:

1- Engert A, Giglio AD, Bias P, Lubenau H, Gatzemeier U, Heigener D. Incidence of febrile neutropenia and myelotoxicity of chemotherapy: a meta-analysis of biosimilar G-CSF studies in

breast cancer, lung cancer, and non-Hodgkin's lymphoma. 2009;32(10):599-604.

2- Marchesi F, Mengarelli A. Biosimilar filgrastim in autologous peripheral blood hematopoietic stem cell mobilization and post-transplant

- hematologic recovery. *Curr Med Chem.* 2016; 23(21): 2217-29.
- 3- Sever M, Domanovic D, Vrtovec B et al. Mobilization of heart failure patients using biosimilar granulocyte colony stimulating factor (TevaGrastim) for autologous CD34+ cells preparation and application into the heart. *Bone Marrow Transplant.* 2012; 47: S243.
- 4- Duong HK, Savani BN, Copelan E et al. Peripheral Blood Progenitor Cell Mobilization for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation *Biol Blood Marrow Transplant* 2014; 20(9): 1262-73.
- 5- Duong HK, Savani BN, Copelan E et al. Peripheral blood progenitor cell mobilization for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant.* 2014; 20(9): 1262-73.
- 6- Ergene U, Cağırhan S, Pehlivan M, Yılmaz M, Tombuloğlu M. Factors influencing engraftment in autologous peripheral hematopoietic stem cell transplantation (PBSCT). *Transfus Apher Sci.* 2007; 36(1):23-9.
- 7- Lowenthal RM, Fabères C, Marit G, et al. Factors influencing haemopoietic recovery following chemotherapy-mobilised autologous peripheral blood progenitor cell transplantation for haematological malignancies: a retrospective analysis of a 10-year single institution experience. *Bone Marrow Transplant.* 1998; 22(8): 763-70.
- 8- Mounier N, Larghero J, Manson J et al. Long term hematologic recovery after autologous stem cell transplantation in lymphoma patients: impact of the number of prefreeze and post-thaw CD34+ cells. *Bull Cancer.* 2005; 92(3): E31-8.
- 9- Jillella AP, Ustun C. What is the optimum number of CD34+ peripheral blood stem cells for an autologous transplant? *Stem Cells Dev.* 2004; 13(6): 598-606.
- 10- Waller CF, Semiglazov VF, Tjulandin S, Bentsion D, Chan S, Challand R. A phase III randomize de-quivalence study of biosimilar filgrastim versus Amgen filgrastim inpatients receiving myelosuppressive chemotherapy for breast cancer. *Onkologie.* 2010; 33: 504-511.
- 11- Engert A, Griskevicius L, Zyuzgin Y, Lubenau H, Giglio AD. XM02, the first granulocyte colony-stimulating factor biosimilar, is safe and effective in reducing the duration of severe neutropenia and incidence of febrile neutropenia in patients with non-Hodgkin lymphoma receiving chemotherapy. *Leuk Lymph.* 2009; 50: 374-379.
- 12- Sevinç A, Özkan M, Özet A et al. Biosimilar filgrastim vs filgrastim: a multicenter nationwide observational bioequivalence study in patients with chemotherapy-induced neutropenia. *Onco Targets Ther.* 2018; 18 (11): 419-426.
- 13- Bassi S, Stroppa EM, Moroni CF et al. Safety and efficacy of granulocyte colony-stimulating factor biosimilars in engraftment after autologous stem cell transplantation for haematological malignancies: a 4-year, single institute experience with different conditioning regimens. *Blood Transfus.* 2015; 13(3): 478-83.
- 14- Lefrere F, Brignier AC, Elie C, et al. First experience of autologous peripheral blood stem cell mobilization with biosimilar granulocyte colony-stimulating factor. *Adv Ther.* 2011; 28: 301-310.
- 15- Schmitt M, Xu X, Schneider C, et al. Mobilization of PBSC for allogeneic transplantation by the use of the G-CSF biosimilar XM02 in healthy donors. *Bone Marrow Transplant.* 2013; 48: 922-925.
- 16- 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 hematopoietic stem cell transplantation: A single center experience from Turkey. *Transf Apher Sci.* 2013; 48: 315-320.
- 17- Danylesko I, Sareli R, Bloom-Varda N et al. Biosimilar Filgrastim (Tevagrastim, XM02) for Allogeneic Hematopoietic Stem Cell Mobilization and Transplantation in Patients with Acute Myelogenous Leukemia/Myelodysplastic Syndromes. *Biol Blood Marrow Transplant.* 2016; 22: 277-283.
- 18- Hamadani M, Kochuparambil ST, Osman S et al. Intermediate-dose versus low-dose

cyclophosphamide and granulocyte colony-stimulating factor for peripheral blood stem cell mobilization in patients with multiple myeloma

treated with novel induction therapies. Biol Blood Marrow Transplant. 2012; 18(7): 1128-35.

Corresponding author e-mail: drmpamuk@yahoo.com

Orcid ID:

Merve Pamukçuoğlu 0000-0002-4591-2025

Ahmet Kürşad Güneş 0000-0001-5522-8342

Mehmet Ali Uçar 0000-0002-6041-7364

Funda Ceran 0000-0003-3173-7614

Mesude Falay 0000-0001-7846-3476

Gülsüm Özet 0000-0003-3173-7614

Simten Dağdaş 0000-0003-0901-2043

Doi: