

Comparative study on the effects of filgrastim and pegfilgrastim in the treatment of fever and neutropenia in patients with leukemia in the west of Iran

Mohammad Reza Golpayegani¹, Pooya Faranoush^{2,3,*}, Mohammad Hossein Rasouli⁴, Mohammadreza Foroughi-Gilvaei^{2,3}, Negin Sadighnia^{2,3}, Ashkan Zandi³, Seyed Mohammad Sadegh Mosavi-Kiasary³, Mohammad Faranoush^{2,5}

1. Department of Pediatrics, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran.

2. Pediatric Growth and Development Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, P.O. Box: 1996713883, Tehran, Iran.

3. Nano Bio Electronic Devices Lab, Cancer Electronics Research Group, School of Electrical and Computer Engineering, College of Engineering, University of Tehran, P.O. Box: 14395/515, Tehran, Iran.

4. School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran

5. Cardio-Oncology Research Center, Rajaie Cardiovascular Medical & Research Center, Iran University of Medical Sciences, P.O. Box: 1996911151, Tehran, Iran.

*Corresponding author: Dr Pooya Faranoush, Hospital of Dr. Mohammad Kermanshahi, Kermanshah, Iran. Email: faranoush.m@iums.ir, Faranoush47@gmail.com. ORCID ID: 0000-0001-9329-6426

Received: 06 July 2021

Accepted: 17 November

Abstract

Background: The current research seeks to present a comparative study of the effect of filgrastim and pegfilgrastim in the treatment of fever and neutropenia in leukemia patients.

Materials and Methods: The present study is a blind randomized clinical trial. The study population is comprised of 120 children with acute lymphoblastic leukemia (ALL) who were admitted to the hospital due to mild febrile neutropenia during 2019. Included patients were divided into two groups. Filgrastim (10 micrograms/ kilogram, daily subcutaneously) and pegfilgrastim (100 micrograms per kilogram of a subcutaneous dose) were used for groups, respectively. Fever monitored every 6 hours, and neutrophil count was performed every 48 hours. The questionnaire designed in the study included age, type of drug side effects, number of days of neutropenia, and fever cessation time. Then, the data were analyzed by SPSS software.

Result: Leukemic children with fever and neutropenia (N=120) were included in the study, which was 59 (49.1%) male and 61 (50.9%) female by the mean age of 79 ± 44 months. The mean days of neutropenia correction in the filgrastim and pegfilgrastim groups were 5 and 4 days, respectively, which was not significantly different ($p = 0.08$). There was no correlation between patients' complications and types of treatments ($p > 0.05$). Muscular pain was the most common complication observed among 4 cases and 1 case following filgrastim and pegfilgrastim administration, respectively. Furthermore, hyperleukocytosis following pegfilgrastim consumption was observed in two cases.

Conclusion: There was no significant correlation between the duration until the cessation of fever and the number of neutropenia days in the two groups receiving pegfilgrastim and filgrastim. Therefore, the fever and neutropenia improve with pegfilgrastim earlier than filgrastim; besides, fewer injections, patient comfort, and less musculoskeletal pain can be observed.

Keywords: Children, Febrile neutropenia, Filgrastim, Leukemia, Pegfilgrastim

Introduction

Neutropenia, fever, and consequent infections are the most common intricacies of dose-limiting toxicities associated with cytotoxic cancer chemotherapy (1). Filgrastim (human granulocyte colony-stimulating factor (G-CSF) produced by recombinant DNA technology is a hematopoietic growth factor that primarily

stimulates the proliferation and differentiation of committed progenitor cells of the granulocyte-neutrophil lineage into functionally mature neutrophils.

Endogenous G-CSF is a glycoprotein produced by monocytes, endothelial cells, and fibroblasts (2). Filgrastim will be administered to patients with acute lymphoblastic leukemia (ALL) during the

first few days of neutropenia post-remission course of chemotherapy. Administering G-CSF may shorten the duration of neutropenia (3). In these patients, the risk of febrile neutropenia (FN) increases, which is one of the causes of hospitalization and administration of intravenous antibiotics (4-11). In severe neutropenia, the risk of life-threatening infections is grave. Filgrastim is administered following chemotherapy or neutropenia, and reduces the prevalence of infection (5,6). Numerous retrospective studies have shown that the use of filgrastim minimizes the duration of severe neutropenia compared to placebo. Various researches have shown that taking filgrastim after bone marrow transplant reduces the number of days of intravenous antibiotics consumption and the length of hospital stay (12, 13). G-CSF should be administered at an initial dose of 5 µg/kg/day subcutaneously or by short intravenous infusion (15 to 30 minutes) or continuous intravenous infusion. Complete blood count (CBC) and platelet count should be obtained before instituting G-CSF therapy and monitored twice weekly during treatment. If the absolute neutrophil count (ANC) increases beyond 10000/mm³ using G-CSF should be stopped. Neutrophil count was improving 1 to 2 days after initiation of filgrastim therapy. The duration of filgrastim therapy effect may be dependent on the myelosuppressive potential of the chemotherapy regimen employed. Pegfilgrastim is a pegylated form of filgrastim that has a longer half-life and is easier to use than filgrastim, and a dose of it is sufficient for each cycle of chemotherapy (14, 15). Due to the lack of previous research on the administration of pegfilgrastim in fever and neutropenia, the current article presented a comparative study of the effect of filgrastim and pegfilgrastim in the treatment of mild to moderate neutropenia and fever in patients with leukemia in Mohammad Kermanshahi Hospital.

Materials and Methods

Study description

This randomized clinical trial study was conducted on 120 leukemia children with mild and moderate febrile neutropenia (mild neutropenia if the ANC ranges from 1000-1500/µL, moderate neutropenia with an ANC of 500-1000/µL, and severe neutropenia if the ANC is below 500/µL). The study population was leukemia patients admitted to Mohammad Kermanshahi Hospital, Kermanshah, Iran, in 2019.

Study design

The study was a blinded fashion randomized interventional clinical trial with parallel assignment design to assess the effect of filgrastim and pegfilgrastim in 120 participants with leukemia who were hospitalized at Dr. Mohammad Kermanshahi Hospital. The patients were randomly divided into two groups. The first group was treated with filgrastim (10 micrograms per kilogram daily), and the second group was treated with a single dose of 100 micrograms per kilogram of pegfilgrastim subcutaneously. The fever was monitored every 6 hours, and neutrophil count was measured every 48 hours. The questionnaire in this study contains age, type of drug side effects, number of days of neutropenia, and fever cessation time. Then, the data was entered into SPSS software and finally analyzed.

Eligibility criteria

Inclusion criteria included patients with ALL and mild to moderate febrile neutropenia (absolute neutrophil count 500 to 1500), and stable hemodynamics. Exclusion criteria included patients with severe febrile neutropenia (absolute neutrophil count less than 500), toxic patients, and patients with unstable hemodynamics. Due to the significance of the issue and the lack of the previous study, patients with severe neutropenia were excluded from the study.

After taking consent from parents of children, 120 leukemia patients with mild to moderate febrile neutropenia were randomly assigned to two groups (with the help of a table of random numbers), according to the inclusion and exclusion criteria. The two groups were evaluated in parallel. To treat neutropenia, filgrastim (10 micrograms per kilogram daily subcutaneously, until ANC increase to upper than 1500/ μ l) manufactured from Pooyesh Daroo company was used for one group of patients. For another group, pegfilgrastim (100 micrograms per kilogram of subcutaneously in a single dose) manufactured from Iranian brand Kidipeg manufactured from Cinnagen company was used. The drugs were prepared in similar packages and were distinguished by codes one and two. The patient-caregiver, as well as the patient evaluator were blinded.

Administration of antibiotics and other supportive measures were performed according to the protocol relevant to the patients with fever and neutropenia. Fever control was performed every 6 hours, and neutrophil count was done every 48 hours. The number of days to increase neutrophils to more than 1500 and the time to stop fever for each patient was recorded. For this study, a questionnaire was prepared that included age, gender, efficacy, side effects of the drug, number of neutropenia days, and duration of fever cessation.

Human rights were respected in accordance with the Helsinki Declaration 1975, as revised in 1983.

Ethical Consideration

This study was approved by both the Ethics Committee of Iran University of Medical Sciences (Ethical code; IR.KUMS.REC.1395.764) and its IRCT code is IRCT20130812014333N8011800000. The informed consent was taken from parents and first relatives.

Randomization

Patients were stratified by institution and randomly assigned via computer-generated random numbers in a blinded fashion at the time of registration on the study for treating with filgrastim or pegfilgrastim.

Statistical analysis

Data were given as frequency and percentage for classified variables. The mean, and standard deviation (with maximum and minimum values) were used for continuous quantitative variables. The comparison of categorical variables was conducted using chi-square testing or fisher exact test. Statistical analysis was performed using SPSS 20 statistical software. $P < 0.05$ was considered significant.

Results

The mean age of the subjects was 79 ± 44 months. Out of 120 patients included in the study, 59 (49.1%) were male and 61 (50.9%) were female, the highest frequency of patients in the age group was 3.5 to 6.5 years, which included 48 (39.9%) cases. Figure 2, a) shows population gender ratio pie chart. Figure 2, b) shows distribution of the age in the participated patients.

The maximum time required to correct neutropenia was 4-6 days with 43 cases (35.9%). ($P = 0.08$). The mean number of days required to correct neutropenia in the filgrastim group was 5 days, and in the pegfilgrastim group was 4 days, and the difference between the mean number of days required to correct neutropenia in the two groups was not statistically significant ($p=0.08$). Figure 3, a) shows comparison table of mean and number of days required to correct neutropenia. Figure 3, b) shows comparative bar chart of neutropenia duration.

Out of 120 patients with leukemia under treatment, adverse drug reactions were reported in seven patients. The most common complication was muscular pain, which was observed among 4 cases after receiving filgrastim, and 1 case after

receiving pegfilgrastim. Two cases of hyperleukocytosis occurred following pegfilgrastim consumption, which were improved within 10-14 days. There was no significant relationship between the type of treatment and the type of complications ($p = 0.001$) (Table I).

There was no significant correlation between the type of treatment and the duration of fever cessation (Figure 4). The highest frequency of fever cessation in both groups occurred on days 3-4 of treatment (24 cases, 40%) in the pegfilgrastim group and 21 cases (35%) in the filgrastim group ($P > 0.05$).

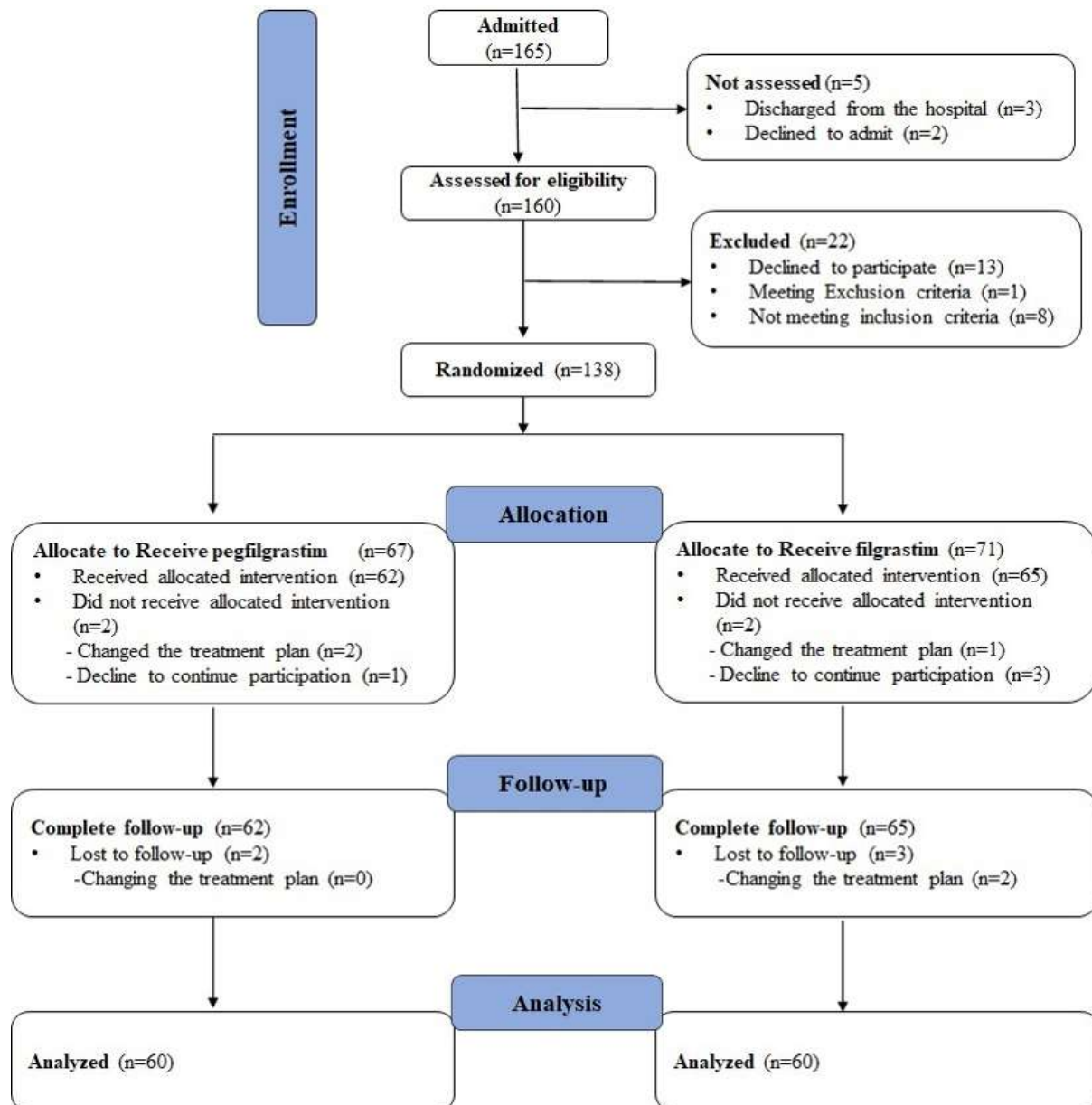


Figure 1, Consort flow diagram.

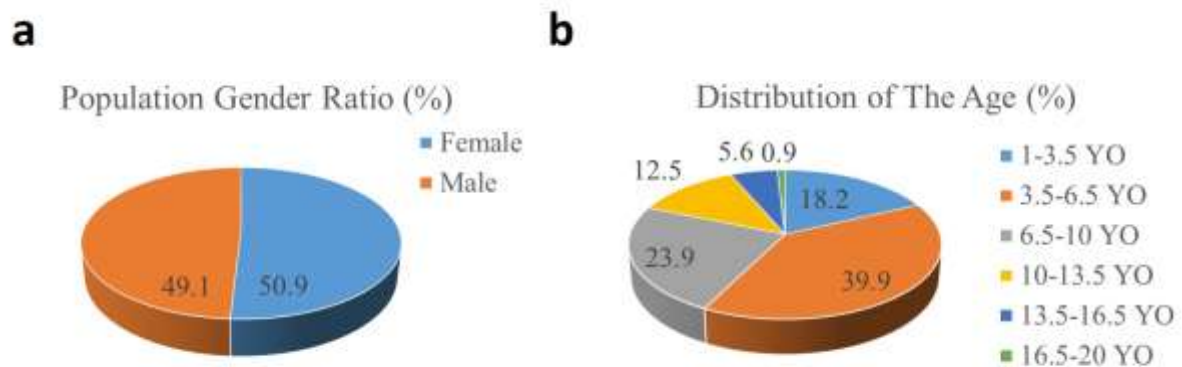


Figure 2, a) Population gender ratio pie chart. As it is obvious, both gender populations are almost equal. b) Distribution of the age in the participated patients (YO: years old).

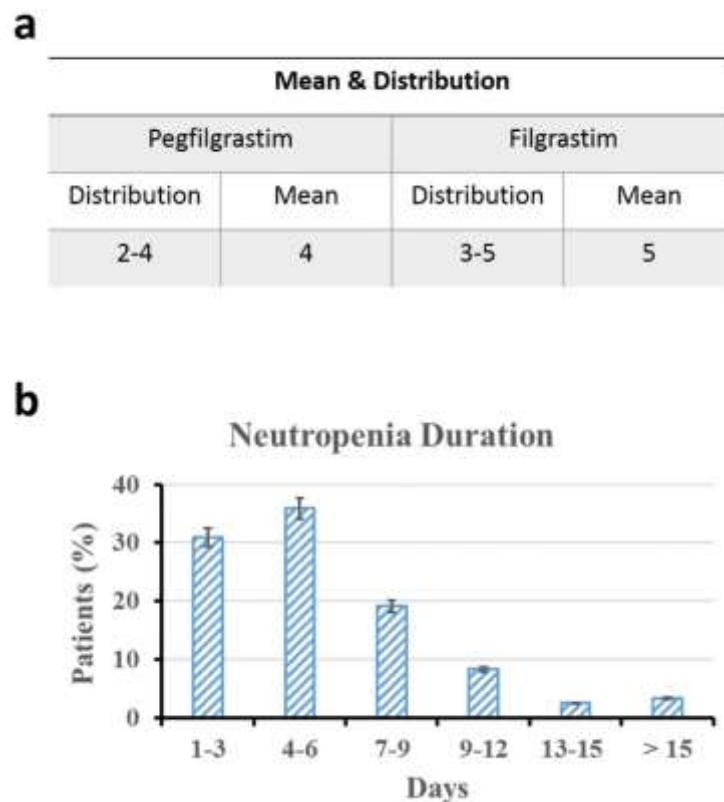


Figure 3, a) Comparison table of mean and number of days required to correct neutropenia. b) Comparative bar chart of neutropenia duration.

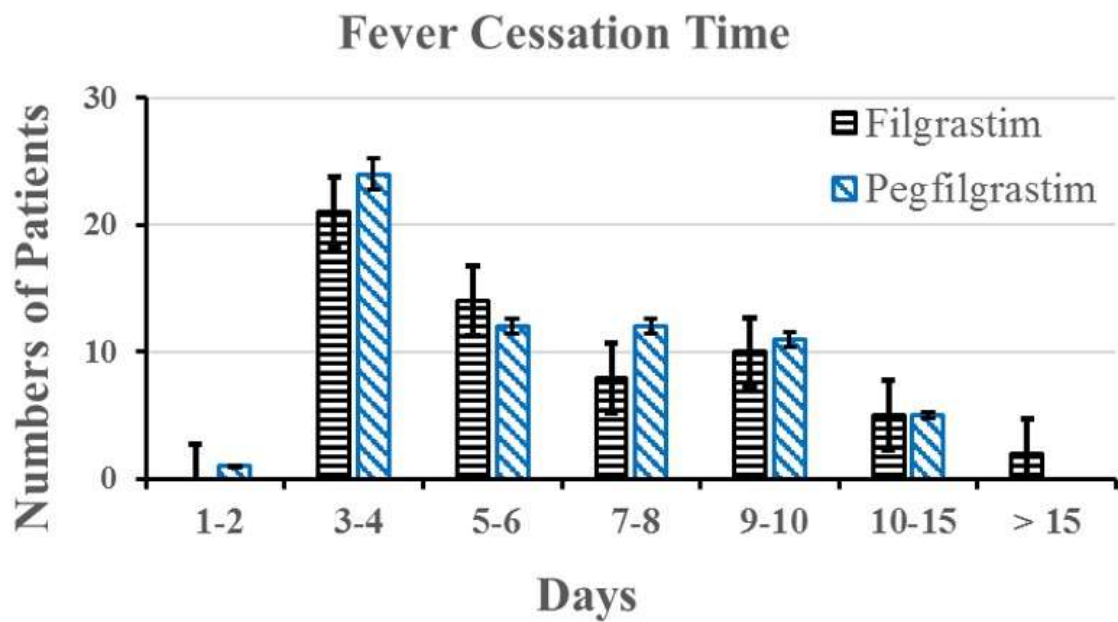


Figure 4, Frequency distribution of fever cessation time by type of treatment.

Table I: Frequency distribution of complications in terms of the type of treatment in the subjects (ARDS: Acute respiratory distress syndrome).

Type of Complication						
	Headache	Muscular Pain	Peripheral Edema	Anaphylactic Shock	Hyperleukocytosis	ARDS
Filgrastim	0(0%)	4(6.66%)	0(0%)	0(0%)	0(0%)	0(0%)
Pegfilgrastim	0(0%)	1(1.6%)	0(0%)	0(0%)	2(3.2%)	0(0%)

Discussion

Granulocyte colony stimulating factor (G-CSF) for the prevention of fever and neutropenia was considered as an acceptable standard of care on leukemia during chemotherapy. The advantage of a single-dose pegfilgrastim injection in comparison with repeated and daily injections of filgrastim can be highlighted. The research conducted by Aapro et al. evaluated the effect of filgrastim, and

concluded that the drug can reduce the duration of neutropenia and antibiotic use while the duration of hospitalization and onset of fever and neutropenia remains unchanged(16, 17). In a study conducted by Abolghasmi et al, administration of filgrastim in prevention and treatment of neutropenia did not show promising results. Borinstein et al., in a research, corroborated the effect of filgrastim, yet revealed that the drug had little impact on

fever cessation and infection control. In the study performed by Ehsani, it was found that G-CSF administration has no significant effect on the prevention of neutropenia (18). In Jorge Sierra's study, no significant difference was observed between the therapeutic effects of pegfilgrastim and filgrastim (19). Both recent types of research were consistent with this study. Weycker's analysis indicated that a single dose of pegfilgrastim was more effective in curing neutropenia than filgrastim (20). In Lyman's study, pegfilgrastim was more effective than filgrastim in improving neutropenia (21). In a meta-analysis study, single-dose administration of pegfilgrastim compared to filgrastim for 14 to 10 days contributed to further reduction in the incidence of fever/neutropenia and neutropenia alone, and further decrease in muscular pains and arthralgia was observed among the users of pegfilgrastim (22). In this research, muscular pains were more common after taking filgrastim. The research results attained by Lyman indicated that administration of pegfilgrastim was more effective than filgrastim in reducing the duration of neutropenia (23). Moafi's study showed a clear difference in ANC, febrile neutropenia, hospitalization, and white blood cell level, and pegfilgrastim was superior to filgrastim (24). The findings of the research by Weycker revealed that the administration of pegfilgrastim was more effective than filgrastim (25). Wang depicts that early administration of filgrastim within 5 days after confirmation of hypoplastic early assessment of bone marrow biopsy was correlated with shorter length of hospitalization, faster absolute neutrophil count recovery, fewer IV antibiotic using days, and cost-effective (26). As the administration of PEG-filgrastim was a costly medication, Yousofian demonstrated that it can compensate by decreasing visit and injection time. According to retrospective studies, increasing the number of

filgrastim injections may enhance the drug reactions complications, multiple visiting times, and many other issues (27). Different levels of response to G-CSF were detected from Zhang's study. They found that patients with vigorous G-CSF neutrophil response compared to those with weak levels of G-CSF had a higher risk for respiratory decompensation. They also indicated a considerable increase in the neutrophil to lymphocyte ratio after G-CSF administration; therefore, it can be considered as an independent risk factor in hospitalized patients with COVID-19. Interestingly, neutropenia separately was not correlated with the hospitalization of the patients (28).

The efficiency and safety of mobilization of hematopoietic stem cells for allogeneic hematopoietic stem cell transplantation with Tenvagra were assessed by Danylesko.

The healthy donors received Tenvagra or filgrastim in a dose of 10 mg/kg body weight (BW) subcutaneously for 4 days. A comparable outcome of CD34⁺ stem cell mobilization in the Tenvagra study and the filgrastim historical control groups was observed. Tenvagra administration was safe with minimal side effects and toxicity. The lack of fundamental differences for all parameters of stem cell collection, engraftment, and safety with the biosimilar XMO2 Tenvagra demonstrate the "similarity" of the biosimilar and recombinant human G-CSF in this indication (29).

Sivgin in the peripheral blood stem cells collection procedure demonstrated that biosimilar filgrastim (Leucostim®) has equivalent potency compared to original filgrastim (Neupogen®). The investigation confirmed the only data in Turkey regarding the potency and safety of biosimilar filgrastim (Leucostim®) in hematopoietic stem cell transplantation recipients (30). The conclusion of the investigation of WinKuan was considered novel because there was no previous study regarding the compare of pegfilgrastim

administered at different time points against daily filgrastim. In this study, the internal validity has been preserved through data collection, strict adherence to randomization, sequence allocation, , and data cleaning procedures. Financial and logistic restrictions were the main limitation of the investigation (31).

The meta-analysis of randomized clinical trials of patients with breast cancer receiving myelosuppressive chemotherapy conducted by Botteri elucidates no differences between G-CSF reference biologics and biosimilar medicines in efficacy and safety. Duration of severe neutropenia was the primary end-point in the investigations. Secondary efficacy end-points were absolute neutrophil count, and febrile neutropenia also indicated minimal and not significant differences between G-CSF reference and biosimilar medicines (32). Mitchell's research concluded that the side effects associated with fever and neutropenia in pegfilgrastim were lower than those in filgrastim (33). Some herbal medicine such as aloe vera increased efficacy of colony stimulating factor and decrease the duration of fever and hospitalization(34). Although the last few studies were inconsistent with the results of this study, they are in agreement with the investigation in confirming the use of pegfilgrastim.

Conclusion

The current study indicated that there was no significant correlation between the duration of fever cessation and number of days of neutropenia in the two groups consuming pegfilgrastim and filgrastim. Therefore, pegfilgrastim can be effective in mild neutropenia and fever as much as filgrastim. In addition, some other advantages of pegfilgrastim included fewer injections, patient comfort, and less musculoskeletal pain.

Conflict of interest

The authors declare no conflict of interest.

References

1. Majem M, Galán M, Pérez FJ, Muñoz M, Chicote S, Soler G, et al. The oncology acute toxicity unit (OATU): an outpatient facility for improving the management of chemotherapy toxicity. *Clin Transl Oncol* 2007;9(12):784-788.
2. Filgrastim. Drugs and Lactation Database (LactMed). Bethesda 2006;1-9
3. Hoshina H, Takei H. Granulocyte-colony stimulating factor-associated aortitis in a woman with advanced breast cancer: a case report and review of the literature. *BMC Cancer* 2019;19(1):1217-1220.
4. Caggiano V, Weiss RV, Rickert TS, Linde-Zwirble WT. Incidence, cost, and mortality of neutropenia hospitalization associated with chemotherapy. *Cancer* 2005;103(9):1916-1924.
5. Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity, and cost associated with febrile neutropenia in adult cancer patients. *Cancer* 2006;106(10):2258-2266.
6. Lyman GH, Lyman CH, Agboola O. Risk models for predicting chemotherapy-induced neutropenia. *Oncologist* 2005; 10(6):427-437.
7. Weycker D, Malin J, Edelsberg J, Glass A, Gokhale M, Oster G. Cost of neutropenic complications of chemotherapy. *Ann Oncol* 2008;19(3):454-460.
8. Weycker D, Malin J, Glass A, Oster G. Economic burden of chemotherapy-related febrile neutropenia. *J Support Oncol* 2007; 5(2):44-45.
9. Schilling MB, Parks C, Deeter RG. Costs and outcomes associated with hospitalized cancer patients with neutropenic complications: A retrospective study. *Exp Ther Med* 2011;2(5):859-866.
10. Kozma CM, Dickson M, Chia V, Legg J, Barron R. Trends in neutropenia-related inpatient events. *J Oncol Pract* 2012; 8(3):149-155.
11. Borjianyazdi L, Froomandi M, Noori Shadkam M, Hashemi A, Fallah R.

The effect of granulocyte colony stimulating factor administration on preterm infant with neutropenia and clinical sepsis: A randomized clinical trial. *IJPHO* 2013; 3(2):64-68.

12. Trivedi M, Martinez S, Corringham S, Medley K, Ball ED. Optimal use of G-CSF administration after hematopoietic SCT. *Bone Marrow Transplant* 2009; 43(12):895-908.

13. Samaras P, Blickenstorfer M, Siciliano R, Haile S, Buset E, Petrausch U, et al. Pegfilgrastim reduces the length of hospitalization and the time to engraftment in multiple myeloma patients treated with Melphalan 200 and auto-SCT compared with filgrastim. *Ann Hematol* 2011;90:89-94.

14. Bond TC, Szabo E, Gabriel S, Klastersky J, Tomey O, Mueller U, et al. Meta-analysis and indirect treatment comparison of lipegfilgrastim with pegfilgrastim and filgrastim for the reduction of chemotherapy-induced neutropenia-related events. *J Oncol Pharm Pract* 2018; 24(6):412-423.

15. Renwick W, Pettengell R, Green M. Use of filgrastim and pegfilgrastim to support delivery of chemotherapy: twenty years of clinical experience. *BioDrugs* 2009; 23(3):175-186.

16. Aapro MS, Bohlius J, Cameron DA, Dal Lago L, Donnelly JP, Kearney N, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. *Eur J Cancer* 2011; 47(1):18-32.

17. Borinstein SC, Pollard J, Winter L, Hawkins DS. Pegfilgrastim for prevention of chemotherapy-associated neutropenia in pediatric patients with solid tumors. *Pediatr Blood Cancer* 2009; 53(3):375-378.

18. Ehsani MA, Ordoue M, Salamati P, Shahgholi E, Sotoudeh K, Hatami S, et al. Evaluation of efficacy and side effects of filgrastim versus pd-grastim in

prevention of neutropenia in patients with neuroblastoma under treatment with opec chemotherapy protocol@ a comparative study. *Iran J Pediatr* 2006; 16 (3): 319-324.

19. Sierra J, Szer J, Kassis J, Herrmann R, Lazzarino M, Thomas X, et al. A single dose of pegfilgrastim compared with daily filgrastim for supporting neutrophil recovery in patients treated for low-to-intermediate risk acute myeloid leukemia: results from a randomized, double-blind, phase 2 trial. *BMC Cancer* 2008; 8(1):195-199.

20. Weycker D, Malin J, Kim J, Barron R, Edelsberg J, Kartashov A, et al. Risk of hospitalization for neutropenic complications of chemotherapy in patients with primary solid tumors receiving pegfilgrastim or filgrastim prophylaxis: A retrospective cohort study. *Clin Therapeutics* 2009; 31(5):1069-1081.

21. Lyman GH, Lalla A, Barron RL, Dubois RW. Cost-effectiveness of pegfilgrastim versus filgrastim primary prophylaxis in women with early-stage breast cancer receiving chemotherapy in the United States. *Clin Ther* 2009;31(5): 1092-1104.

22. Pinto L, Liu Z, Doan Q, Bernal M, Dubois R, Lyman G. Comparison of pegfilgrastim with filgrastim on febrile neutropenia, grade IV neutropenia and bone pain: a meta-analysis of randomized controlled trials. *Curr Med Res Opin* 2007; 23(9):2283-2295.

23. Lyman GH, Reiner M, Morrow PK, Crawford J. The effect of filgrastim or pegfilgrastim on survival outcomes of patients with cancer receiving myelosuppressive chemotherapy. *Ann Oncol* 2015; 26(7):1452-1458.

24. Moafi A, Soheilipoor F, Amini A, Beheshti M. Comparing efficacy and side effects of Pd-Grastim and Neupogen for prevention of neutropenia after chemotherapy in children. *Iranian J Pediatr* 2006;1-8.

25. Weycker D, Malin J, Barron R, Edelsberg J, Kartashov A, Oster G. Comparative effectiveness of filgrastim,

pegfilgrastim, and sargramostim as prophylaxis against hospitalization for neutropenic complications in patients with cancer receiving chemotherapy. *Am J Clin Oncol* 2012; 35(3):267-274.

26. Wang J, de Lima M, Cooper BW, Boughan K, Metheny L, Otegbeye F, et al. Efficacy and cost-benefit of filgrastim administered after early assessment bone marrow biopsy during induction therapy for acute myeloid leukemia. *Leukemia & Lymphoma* 2021; 62(6):1450-1457.

27. Yousofian S, Miri-Aliabad G, Kiumarsi A, Ramim T. Effectiveness of filgrastim and polyethylene glycol-filgrastim in the treatment of postchemotherapy neutropenia in children: Phase I clinical trial. *IJMPO* 2019;40(01):101-104.

28. Zhang AW, Morjaria S, Kaltsas A, Hohl TM, Parameswaran R, Patel D, et al. The Effect of neutropenia and filgrastim (G-CSF) in cancer patients with COVID-19 infection. *Clin Infect Dis* 2021;1-9.

29. Danylesko I, Sareli R, Bloom-Varda N, Yerushalmi R, Shem-Tov N, Shimoni A, et al. Biosimilar filgrastim (Tevagrastim, XMO2) for allogeneic hematopoietic stem cell mobilization and transplantation in patients with acute myelogenous leukemia/myelodysplastic Syndromes. *BBMT* 2016; 22(2): 277-283.

30. Sivgin S, Karakus E, Keklik M, Zararsiz G, Solmaz M, Kaynar L, et al. Evaluation of the efficacy and safety of original filgrastim (Neupogen®), biosimilar filgrastim (Leucostim®) and Lenograstim (Granocyte®) in CD34+ peripheral hematopoietic stem cell mobilization procedures for allogeneic hematopoietic stem cell transplant donors. *Transfus ApherSci* 2016; 54(3):410-415.

31. Kuan J-W, Su A-T, Wong S-P, Sim XY-H, Toh S-G, Ong T-C, et al. A randomized double blind control trial comparing filgrastim and pegfilgrastim in cyclophosphamide peripheral blood hematopoietic stem cell mobilization. *Transfusion and Apheresis Science* 2015; 53(2):196-204.

32. Botteri E, Krendyukov A, Curigliano G. Comparing granulocyte colony-stimulating factor filgrastim and pegfilgrastim to its biosimilars in terms of efficacy and safety: A meta-analysis of randomised clinical trials in breast cancer patients. *EJC* 2018; 89:49-55.

33. Kourlaba G, Dimopoulos MA, Pectasides D, Skarlos DV, Gogas H, Pentheroudakis G, et al. Comparison of filgrastim and pegfilgrastim to prevent neutropenia and maintain dose intensity of adjuvant chemotherapy in patients with breast cancer. *MASCC* 2015;23(7):2045-2051.

34. Hashemi A, Kokab M, Kamalian M, Zarezadeh M, Sheikhpour E, Azod L, et al. The effect of Aloe vera syrup on prevention of fever and neutropenia in children with acute lymphoid leukemia. *IJPHO* 2020;10(3):144-149.