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ORIGINAL ARTICLE

Filgrastim Versus Pegfilgrastim for Neutropenia Prevention in Children with Solid Tumors: A Randomized Trial

Aziz Eghbali[1], Maryam Behtash[2], Roghayyeh Rahimi Afzal[2], Aygin Eghbali[1], Bahar Taherkhanchi[3], Bahador Bagheri[*4,5]

[1] *Aliasghar Clinical Research Development Center, Iran University of Medical Sciences, Tehran, Iran*

[2] *Department of Pediatrics, Arak University of Medical Sciences, Arak, Iran*

[3] *Department of Pediatrics, Erfan Niyayesh Hospital, Tehran, Iran*

[4] *Cancer Research Center, Semnan University of Medical Sciences, Semnan, Iran*

[5] *Department of Pharmacology, Semnan University of Medical Sciences, Semnan, Iran*

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KEYWORDS

Pegfilgrastim;
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ABSTRACT: Prophylaxis of chemotherapy-induced neutropenia by granulocyte stimulatory factors (GCSFs) has a significant effect on reducing the complications of chemotherapy. The aim of this study was to compare effects of filgrastim and pegfilgrastim (two types of GCSFs) for neutropenia prevention in children with malignancies. This crossover study was carried out in children who were admitted to oncology ward of Amir Kabir Hospital, Arak, Iran. Patients were randomly divided into 3 groups each with 30 participants. Filgrastim (group A), pegfilgrastim (group B) were injected subcutaneously 10 µg/kg/day and 100 µg/kg as a single dose, respectively and patients in group C had no medical treatment. Washout period was 30 days. Cell blood were checked at beginning and at 3, 7, 14 days of the treatment. The mean age in group A was 6.4 ±3.5 years, the group B was 6.4 ± 3.5 and the group C was 6.2 ± 1.8. The mean Absolute Neutrophil Count (ANC) was similar in all three groups prior to chemotherapy. After receiving the last dose of chemotherapy, the mean ANC was not significantly different in 3 groups (p = 0.217), and only 2 cases of mild neutropenia were seen in group B. On the 14th day, the ratio of neutropenia was different in 3 groups, and this difference was significant (p = 0.000) but there was no significant difference between the ratio of neutropenia in group A and group B. (p = 0.524). 20% of cases in group C and then 16.7% in group B were treated due to delayed neutropenia and this difference was significant (p = 0.026). Pegfligrastim was associated with better clinical response and fewer side effects as compared to filgrastim in children with solid tumors. Due to efficacy and acceptable safety profile, pegfligrastim can be a better choice. There was no significant difference between the costs of the three groups (0.064)

INTRODUCTION

Malignancies are the leading causes of death in the world. Malignant tumors are characterized by rapid, abnormal, and uncontrolled growth of cells that can quickly get into the surrounding healthy tissues or metastasize to distant tissues[1-3]. Chemotherapy might be used alone or can be

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*Corresponding author: bahadordvm@yahoo.com, Bagherib@semums.ac.ir (B. Baghri)
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combined with other treatments like radiotherapy or surgery.

Chemotherapy is usually effective against cells that are actively proliferating and dividing. However, most chemotherapeutic drugs cannot differentiate between cancer cells and normal cells [4]. Chemotherapy may weaken the immune system by suppressing the bone marrow which may lead to decrease in peripheral blood neutrophils (called neutropenia) [1, 5, 6]. Neutropenia causes complications such as fever and opportunistic infections that can result in hospitalization, decrease of chemotherapy drug dosage, delay in subsequent chemotherapy sessions, and termination of treatment[7, 8]. So far several modalities have been used for preventing neutropenia and its complications; such modalities as isolation, prophylactic broad-spectrum antibiotics[9, 10], antifungal drugs[10, 11], and granulocyte colony-stimulating factors (G-CSF)[12-14]. Filgrastim is a recombinant human G-CSF that decreases the risk of infection and neutropenia-related deaths in patients receiving chemotherapy. Filgrastim acts on hematopoietic cells to impact production and maturation of neutrophils mainly by activation of JAK/STAT receptors. Besides, it can decrease the duration of antibiotic therapy and hospitalization[14, 15]. Filgrastim has a short half-life and it is injected daily. So, there are problems like frequent referring to hospital, increased costs of treatment, and decreased compliance of patients [16, 17]. Pegfilgrastim is polyethylene glycol (peg) form of G-CSF that is injected in single-dose at every cycle. Due to longer half-life and slower elimination rate than, pegfilgrastim requires less frequent administration [17-20]. Several studies have compared the two mentioned drugs in order to choose the more appropriate one. Due to scarcity of published data in children, we decided to compare these two drugs to determine the preferred drug for decreasing chemotherapy-caused neutropenia in children.

MATERIALS AND METHODS

This randomized and cross over study was done in children of 1-15 years old affected by solid tumors and hospitalized in Amir Kabir Hospital in Arak. Prior to study, the parents became informed of the research goals and the researchers received their informed consent letters. After the end of chemotherapy, the qualified patients were assigned to one of the following three groups based on the order of referring to hospital and by systematic random method.

Group A: A day after the end of chemotherapy, patients received 10 µg/kg/day daily filgrastim (with the maximum of 300 mg) by subcutaneous injection. After the second chemotherapy period, the patients received single-dose of 100 µg/kg pegfilgrastim.

Group B: A day after the end of chemotherapy, patients received single subcutaneous injection of 100 µg/kg pegfilgrastim. After the second chemotherapy period, the patients received 10 µg/kg/day daily filgrastim (with maximum dose of 300 mg) by subcutaneous injection.

Group C: The patients did not receive any drug after the end of chemotherapy. Blood cell count was done on the first day of hospitalization and at the end of the chemotherapy protocol.

Then, on the 1st, 3rd, 7th, and 14th after receiving GCSF drugs, blood cell counts were checked.

The parents were asked to call or refer to the hospital in the case of fever or any unusual complication. Included patients were released if they did not have complications like allergy, muscle pain, and fever. They were asked to refer to the hospital for outpatient CBC test. In the case of reporting an absolute neutrophil count (ANC) of less than 1000 per μL^3, the patient was reported to be affected by neutropenia. The first and last days of the neutropenia reports were also recorded. The duration between these two days was reported as the neutropenia period. The duration of hospitalization for neutropenia and side effects of GCSFs such as fever, muscle plain, drug sensitivity, and decreased blood cell count were also recorded. In the case of any delay in starting the subsequent chemotherapy period or decrease of chemotherapy dosage as a result of neutropenia and its complication, these changes were recorded, too. The exclusion criteria were severe infections and sepsis, use of corticosteroids, and hypersensitivity to filgrastim and pegfilgrastim.

Population and samples

Based on the formula of neutropenia ratio comparison, the study performed by Emilie Milano-Bausset, and modifying the number of samples for the three groups, 30 people were assigned to each group;

$$n = \frac{\left(Z_{1-\alpha 12} + Z_{1-\beta}\right)^2 [P_1(1-P_1) + P_2(1-P_2)}{(P_1 - P_2)^2}$$

$\alpha = 0.05$
$\beta = 0.1$
P1=.21
P2=0.60
N1=N2=N3=30

Data analysis

Data are shown as mean ± SD. Data were analyzed by SPSS 19 (Chicago, US). Descriptive statistics (central tendency and dispersion) were used for analyzing the quantitative variables, and the qualitative variables were reported by frequency and percentage. Inferential statistics for quantitative variables were reported by analysis of variance, repeated measures, and post hoc test or their non-parameter equivalents; and inferential statistics for qualitative variables were reported by Chi-square or Fisher exact test. $P < 0.05$ was statistically significant.

RESULTS

Table 1 shows the clinical characteristics of study participants. No significant between-group differences in patients ’characteristics were seen at enrollment.

Table 1. Baseline characteristics of patients

Characteristics	Group A	Group B	Group C
Age, y	6.4 ± 3.5	6.4 ± 3.5	6.2 ± 1.8
Age (range)	1-12	1-12	1-12
Female	18	18	19
Male	12	12	11
Body weight (Kg)	19 ± 9.7	19 ± 9.7	23 ± 9.6
Concurrent malignancy			
Wilms' tumor	8	8	6
Neurobalstoma	5	5	4
Rhabdomyosarcoma	5	5	5
Soft tissue sarcoma	1	1	2
Osteosarcoma	4	4	7
Brain cancer	2	2	3
Ewing's sarcoma	5	5	3

**Data are shown as number or mean ± SD

Determining the initial ANC mean in the three groups

At baseline, the mean absolute neutrophil count (ANC) values in groups A, B, and C were 3070.0/mm3, 3430.0/mm3, and 3106.7/mm3, respectively; there were no significant differences among three study groups (P=0.462) (Table 2).

Table2. The mean values of ANC before starting chemotherapy for the three groups (/mm3)

	No	Mean	SD	Median	Exponent	Min	Max
Group A	30	3070.0	1665.6	2600	3800	600	8500
Group B	30	3430.0	1897.8	2600	1800	1500	8900
Group C	30	3106.7	1157.0	2800	2400	1400	6700

The mean ANC after injection of the last chemotherapy dosage

In group C, the mean ANC was 2060.0/mm3. The mean ANC values in groups A and B were respectively equal to 2461.7/mm3 and 2488.3/mm3 (Table 3). No significant difference was noted among values of ANC in three groups (P=0.217).

Table3. Mean ANC after the last chemotherapy dosage in the three groups.

	No	**Mean**	**SD**	**Median**	**Exponent**	**Min**	**Max**
Group A	60	2461.7	1159.3	2150	1200	1050	6500
Group B	60	2488.3	1349.3	2200	1600	900	7500
Group C	1	2060.0	615.7	1800	1800	1000	3500

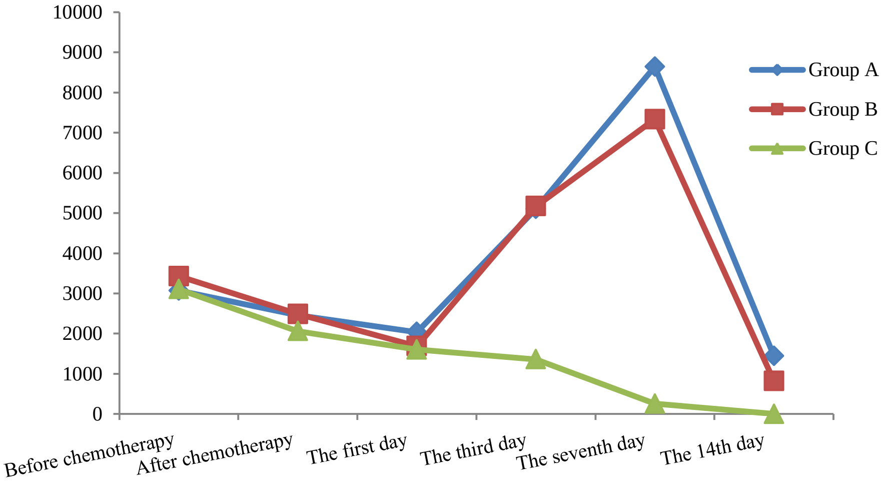

Figure 1. Comparison of neutrophil counts at different intervals in three groups.

Changes of the mean ANC at different intervals

After chemotherapy, the mean ANC was decreased in all three groups and the largest decrease (33.7%) was observed in group C (Table 4).

Table 4. Comparison of the changes in mean ANC values in the groups.

	Group A	**Group B**	**Group C**
After chemotherapy vs. before that	-19.8%	-27.5%	-33.7%
The first day vs. after chemotherapy	-17.3%	-32.2%	-22.2%
The third day vs. the first day	+150.6%	206.4%	-15.2%
The seventh day vs. the first day	+69.4%	+41.8%	-81.4%
The 14th day vs. the 7th day	-83.3%	-88.8%	-100%
The 14th day vs. before chemotherapy	-53.0%	-76.0%	-100%
The 14th day vs. before chemotherapy	-41.4%	-67.0%	-100%

Negative (-): decrease positive (+) = increase

The first day vs. after receiving the last chemotherapy dosage: the mean ANC deceased in all the three groups and the largest decrease (32.2%) was observed in group B.

The third day vs. the first day: the mean ANC increased in groups A and B and decreased in group C. The mean value of group B increased by 206.4% and the mean value of group C was decreased by 15.2%.

The seventh day vs. the third day: the mean ANC increased in groups A and B; the increase in group A was larger than group C (unlike the results of the third day), and the mean ANC decreased in group C by 81.4%.

On the 14th day vs. before chemotherapy: similar to the ratio of after chemotherapy, the mean ANC decreased in all the three groups and the values of decrease were respectively group C (100%), (53%), and (76%) in group C, group B, group A, respectively. The decrease was significant in all three groups (P=0.000).

The 14th day vs. after receiving the last chemotherapy dosage: the mean ANC decreased in all the three groups and values of decrease were C (100%), (67%), and (41.4%) in group C, group B, group A, respectively. The decrease was significant in all the three groups (P=0.000).

DISCUSSION

Comparison of the results of three study groups (treatment by filgrastim, pegfilgrastim, and no GCSF treatment) showed that the mean ANC was significantly higher in treatment groups (P=0.001). Although the decreased ANC mean at the end of the study was significant in all the three groups, only one of the subjects in group B reported neutropenia at the end of the study; and dose increase was done for this case. In group A, there was a case of moderate neutropenia with dose change due to fever. No case of dose change and reinjection until the end of the 14th day was observed in the remaining cases. However, in group C, treatment was done from the third day for reduction of neutropenia complications; therefore, at the end of the 14th day, there was only one case of severe neutropenia in group C.

Acceptable improvements were observed on the 3rd and 7th days after treatment in groups A and B; while the most unfavorable results were observed in group C. In the cohort study performed by Kourlaba et al, it was found that patients receiving pegfilgrastim are less probable of being affected by severe neutropenia and dose reduction or delay[21]. In a study by Tan, it was declared that compared with filgrastim, pegfilgrastim can more effectively decrease the risk of neutropenia and its complications. Moreover, Brito et al performed a study titled “Comparison of the effect of neostim (biologically similar to filgrastim), filgrastim, and pegfilgrastim in prevention of neutropenic fever in breast cancer patients treated by neo-adjuvant. It was found that compared with filgrastim and pegfilgrastim, the occurrence of neutropenia was observed more frequently in patients using neostim. However, there was no significant difference between the effectiveness of three groups[12]. A study performed by Ehsani et al showed no difference between effects of filgrastim and pegfilgrastim in children below 16 years affected by neuroblastoma[22].

Another study compared the effects of filgrastim and pegfilgrastim in prevention of neutropenic fever in lymphoma patients by conducting a cohort study. It was found that there was no significant difference between primary prophylaxis by filgrastim and pegfilgrastim in terms of prevention of neutropenia and its complications (dose reduction and delay) in patients with lymphoma[23]. In addition, the results of the study performed by Hiangkiat Tan et al showed that compared with filgrastim, pegfilgrastim is more effective in reduction of all causes leading to neutropenia-related hospitalization[24].

Finally, in a study performed by Weycker et al, hospitalization rate was higher in patients receiving filgrastim as compared with patients administered pegfilgrastim, [25].

CONCLUSIONS

Pegfilgrastim was associated with better clinical response and fewer side effects as compared to filgrastim in children with solid tumors. Due to its efficacy and acceptable safety profile, pegfilgrastim can be a better choice.

Study limitations

There are several limitations; it was better to have a longer period of follow-up and to monitor effects of drugs and different treatments on ANC. In addition, we could not recruit children with same malignancy.

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ETHICAL CONSIDRATION

The study was approved by local ethic committee of Arak University of Medical Sciences (IR.ARAKMU.REC.1395.312). The study was registered at Iranian Registry of Clinical Trials; IRCT2017011131878N1.

Conflict of interest

None

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