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Original Article

Effectiveness of Filgrastim and Polyethylene Glycol-Filgrastim in the Treatment of Postchemotherapy Neutropenia in Children: Phase I Clinical Trial

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Abstract

Background: One of the most common side effects of chemotherapy in cancer patients is neutropenia that can result in hospitalization. The purpose of this study was to evaluate the efficacy and tolerability of polyethylene glycol (PEG)-filgrastim compared with filgrastim in the recovery of neutropenia. **Methods:** This study was a Phase I clinical trial conducted among patients with acute lymphoblastic leukemia aged <16 years who were referred to the Ali Asghar Hospital, Tehran, Iran, from April 2012 until October 2013. Eleven patients were selected, and filgrastim and PEG-filgrastim were injected subcutaneously at a dose of 5–10 μg/kg/day for 7 days and 100 μg/kg as a single dose, respectively. Absolute neutrophil count (ANC) was checked 7 days after the last injection in the two groups. **Results:** The mean age of the patients was 8.82 ± 4.36 years (3–15 years). Six boys (54.5%) and five girls (45.5%) participated in the study. ANC increase among patients treated with PEG-filgrastim or filgrastim was analyzed separately, and the results showed statistically significant differences between the study groups ($P = 0.038$). **Conclusions:** According to the findings, it can be concluded that the PEG-filgrastim is better than filgrastim alone to improve neutropenia induced by chemotherapy in patients with acute lymphoblastic leukemia.

Keywords: *Chemotherapy, children, filgrastim, neutropenia, polyethylene glycol-filgrastim*

Introduction

Neutropenia is one of the most common side effects after chemotherapy in patients with malignancy. This is caused by chemotherapeutic drugs and cytotoxic agents due to the lack of the detection of tumor cells from myeloid normal cells.[1,2] Severe or prolonged neutropenia may lead to treatment discontinuation in addition to patients' admission to the hospital for the treatment of neutropenia and fever with it. Neutropenia following chemotherapy may occur in patients receiving a standard dose that is prescribed for the treatment of various malignancies.[3-5] Severe decrease in neutrophil cell counts (<500 cells/ml) results in decreased immunity and increased risk of infection. Hence, the patient will be susceptible to bacterial and fungal infections.[3,4]

Recombinant human granulocyte colonystimulating factor (G-CSF) and recombinant human granulocyte-macrophage CSF are two drugs that are commonly used to reduce the risk of infection in patients with neutropenia. These drugs could decrease the severity and duration of neutropenia in patients with malignancy after chemotherapy.[1,2]

G-CSF can be used as a secondary prophylaxis of neutropenia at the end of, chemotherapy which reduces the cases of hospitalization to receive antibiotics, infection, and fever associated with neutropenia.[5-7] However, fewer studies have been performed in children compared to adults.[8,9]

Polyethylene glycol (PEG)-filgrastim is a pegylated G-CSF and new drug. The half-life of PEG-filgrastim is 46–62 h and is used as a single dose instead of the daily dose of G-CSF. One molecule of PEG binds to N-terminal of filgrastim and gets converted to PEG-filgrastim that provides low antigenicity, minimal toxicity, and appropriate excretion.[10,11] The recommended dose of PEG-filgrastim is 6 mg in adults and 100 μg/kg in children (maximum 6 mg) that is given to patients 24 h after chemotherapy.[12,13]

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PEG-filgrastim in adults has better efficiency and can be easily administered compared to G-CSF,[14,15] but research on the effectiveness these drugs in children is limited.[16,17]

This study is the 1st clinical trial in Iran that was done for evaluating the side effects and the efficacy of PEG-filgrastim.

Materials and Methods

This clinical study (Phase I clinical trial) was conducted among patients that referred to the Oncology Department at Ali Asghar Hospital, Tehran, Iran, in 2013–2014. Inclusion criteria were as follows: age <16 years, leukemia, neutropenia followed by chemotherapy, and no leukemia induction phase. Exclusion criteria were as follows: intolerable side effects of drugs in patients, potentially dangerous complications after initiation of drug use, lack of patient cooperation in conducting follow-up visits, need for other concomitant medicines to improve the patient's neutropenia, and existence of other causes for neutropenia such as infection and patient death before completing the study.

Convenience sampling was performed, and the patients who met the inclusion criteria were selected for the study. This study was done as self-control study, and the same patients were considered as a control group in the specified time interval.

All the patients were treated with filgrastim in the 1st period. The same patients were been placed in the opposite group if the patient was readmitted after the 1st treatment period at least one course later. All the patients had similar chemotherapy regimens in both groups. In the 1st period, the patients were treated by filgrastim (PDgrastim® 300 μ, Pooyesh Darou Pharma, Tehran, Iran). Filgrastim was administered at a dose of 5–10 μg/kg/day subcutaneously for 7 consecutive days (standard dose). The patients received PEG-filgrastim after the 2nd course. Each prefilled syringe contains 6 mg of PEG-filgrastim (Pega Gen®, 6 mg/syringe, Cinna Gen, Co, Iran) in 0.6 ml (0.6 mg/ml). The patients received a single subcutaneous injection of 100 μg/kg of PEG-filgrastim. Absolute neutrophil count (ANC) was checked 7 days after the last injection in the two groups. Chemotherapy regimens were similar in the two groups.

Paired *t*-test and Chi-square test were utilized to determine the difference between categorical variables of the two groups. This study was approved by the Ethics Committee of Tehran University of Medical Sciences and also was recorded in the Iranian Registry of Clinical Trials with IRCT201205279875N1.

Results

A total of 11 patients, 6 boys (54.5%) and 5 girls (45.5%), participated in the study. None of the patients were excluded from the study. The mean age of the patients was 8.82 ± 4.36 years (3–15 years). The patient characteristics are described in Table 1.

Demographic variables were similar in both groups, and there was no statistical difference between them.

Table 1: Characteristics of the patients

Groups	Year	Sex	Malignancy	Pretreatment ANC	Posttreatment ANC
Filgrastim	7	Male	Leukemia	250	2000
Filgrastim	12	Female	Leukemia	350	400
Filgrastim	7	Female	Leukemia	250	450
Filgrastim	15	Male	Leukemia	400	500
Filgrastim	5	Female	Leukemia	500	1500
Filgrastim	15	Male	Leukemia	100	150
Filgrastim	4	Female	Leukemia	450	7000
Filgrastim	12	Female	Leukemia	150	4000
Filgrastim	12	Male	Leukemia	250	6000
Filgrastim	3	Male	Leukemia	500	2000
Filgrastim	5	Male	Leukemia	400	8000
PEG-filgrastim	7	Male	Leukemia	300	5000
PEG-filgrastim	12	Female	Leukemia	450	2500
PEG-filgrastim	7	Female	Leukemia	400	3000
PEG-filgrastim	15	Male	Leukemia	400	4000
PEG-filgrastim	5	Female	Leukemia	300	4000
PEG-filgrastim	15	Male	Leukemia	300	1500
PEG-filgrastim	4	Female	Leukemia	500	15,000
PEG-filgrastim	12	Female	Leukemia	400	12,000
PEG-filgrastim	12	Male	Leukemia	500	12,000
PEG-filgrastim	3	Male	Leukemia	500	8000
PEG-filgrastim	5	Male	Leukemia	450	30,000

ANC – Absolute neutrophil count; PEG – Polyethylene glycol

There was no significant difference between the two groups in ANC before treatment (P = 0.102). ANC after treatment revealed a significant difference compared to pretreatment in both groups.

In the filgrastim group, the average number of pretreatment ANC was 327.27 cells/mm^3 that elevated to 2909.09 cells/mm^3 (P = 0.013). In the PEG-filgrastim group, the average number of pretreatment ANC was 409.09 cells/mm^3 that elevated to 8818.18 cells/mm^3 (P = 0.007) [Figure 1]. Comparison of the ANC after treatment indicated significant differences between the two groups (P = 0.037) [Table 2].

Discussion

The use of filgrastim as recombinant G-CSF may reduce the duration of neutropenia after chemotherapy. This drug is being used as a supportive therapy in patients undergoing chemotherapy. However, it should be administered daily due to short half-life. A new and long-acting form of this medication is known as PEG-filgrastim that is already built and used. The half-life of this drug is more than that of filgrastim due to the different molecular composition to the extent that it can be administered as a single dose.[11,12]

The results of this study showed that a statistically significant difference was in the patients' ANC before and after treatment in both groups. te Poele *et al*.[15] also reported that the use of PEG-filgrastim therapy, regardless of the type of cancer, could be effective in improving neutropenia induced by chemotherapy, which is consistent with our findings. The major advantage of PEG-filgrastim is that a single dose may be used that is particularly important in child and adolescent patients.[16-18] In the present study, the comparison of the effectiveness between the two regimens showed PEG-filgrastim efficacy to be better than filgrastim, which was consistent with most previous studies.[15-17]

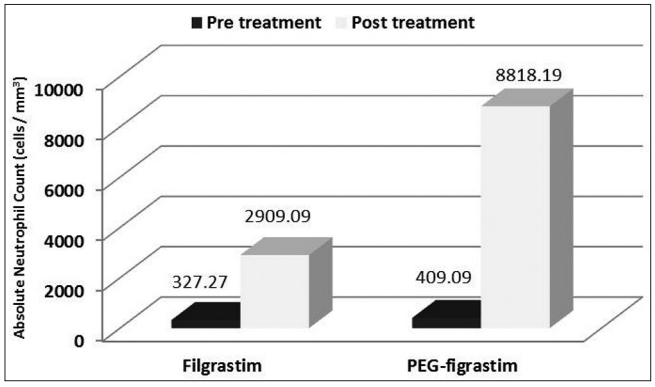

Figure 1: Differences between pre- and post-treatment absolute neutrophil count

Table 2: The mean absolute neutrophil count in two groups

ANC	Treatment groups		$P^{¥}$
	Filgrastim	PEG-filgrastim	
Pretreatment (cells/mm^3)	327.27	409.09	0.102
Posttreatment (cells/mm^3)	2909.29	8818.18	0.038
P*	0.013	0.007	-

*Data were analyzed by paired t-test, P<0.05 was considered significant. ¥Data were analyzed by Student's t-test, P<0.05 was considered significant. ANC – Absolute neutrophil count; PEG – Polyethylene glycol

Wendelin *et al*.[14] reviewed the effectiveness of these drugs to improve severe neutropenia in children with Ewing's sarcoma. They found that the effectiveness of PEG-filgrastim to be better and easier to use than filgrastim. A retrospective study was performed by Milano-Bausset *et al*.,[16] and the findings showed the lower incidence of severe neutropenia, a shorter duration of severe neutropenia and antibiotic treatment in PEG-filgrastim group less than filgrastim group.

Fox *et al*.[18] compared the effectiveness and tolerability of PEG-filgrastim with filgrastim. They showed that a single dose of PEG-filgrastim is better than filgrastim. This conclusion was observed based on the frequency and duration of severe neutropenia and febrile neutropenia.

In the present study, no side effects were reported in patients. However, bone pain and headache were reported in some studies such as those by Andre and Shi.[19,20]

This study showed the high cost of PEG-filgrastim is compensated by reducing the number of visits and less injections. Frequent injections of filgrastim can increase the risk of drug reactions, several traveling for patients and their families, pain and fear for children in each injection, and many other problems. However, a more accurate conclusion requires separate studies in this field.

Limitation

Preparing of PEG-filgrastim by patients was not possible because of no public access and the high cost of drug. Furthermore, one malignancy was studied due to the limitation of access to drugs in Iran. We will try to continue our study in other malignancy in Iranian Children.

Since Iran has restricted access to foreign drugs and because drugs are not covered by public insurance, their preparation is difficult for patients and their families and even impossible in some cases. Performing such studies can show the effectiveness of PEG-filgrastim treatment of neutropenia in malignant children to health managers and insurance policymakers.

Conclusions

According to the findings, it can be concluded that from is better than filgrastim to improve neutropenia induced by chemotherapy in patients with acute lymphoblastic leukemia.

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Conflicts of interest

There are no conflicts of interest.

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