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Comparison of the effects of two different doses of Filgrastim in febrile neutropenia management in childhood malignancy: A randomized clinical trial

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Abstract

Background: Febrile neutropenia (FN) is most often caused due to chemotherapy. Solid or certain lymphoproliferative malignancies can increase the duration of hospitalization and other complications in cancer patients. Filgrastim is used in childhood FN management. This study aimed to compare the effect of two different doses of Filgrastim on hematological and paraclinical factors in hospitalized febrile neutropenic patients with cancer.

Materials and methods: In this randomized clinical trial, 60 febrile neutropenic patients with cancer complying with the inclusion criteria were assigned to both groups A and B. Thirty patients in group A received Filgrastim 5µg/kg/day whereas 30 others in group B received Filgrastim 15µg/kg/day. Hematological factors, physical examination findings, antibiotic administration period, and type of malignancy were then recorded. Complete blood count with differential (CBC diff) was also tested. Lung infiltration was examined by chest X-ray (CXR), and the spleen and abdomen were monitored by ultrasound.

Results: The mean age of patients was 6 ± 3 years old. The most prevalent malignancies included acute lymphoblastic leukemia (ALL) (35.0%), neuroblastoma (18.3%), osteosarcoma (11.7%), acute myeloid leukemia (AML) (8.3%), and Rhabdomyosarcoma (8.3%). The frequency distribution of malignancies significantly differed between the two groups (P= .01). Changes in hematological factors, including white blood cells (WBC), mature neutrophil cells, and absolute neutrophil count (ANC) in group A, appeared lower than those in the other group. However, none of the studied factors, including hematological factors, physical examination findings, and antibiotic administration period, were found to differ significantly between the two groups (P> 0.05).

Conclusion: Much as a higher dose of Filgrastim seems to bear a better effect on ANC, no significant difference was identified between the two groups. Further studies should be designed with a larger population to address the issue.

Keywords: Cancer, Filgrastim, Febrile neutropenia, Hematological factors

Introduction

Fever during neutropenia (known as febrile neutropenia (FN)) results in mortality, increased duration of hospitalization, and other complications in cancer patients. FN is a consequence of neutropenia's extended duration and severity (1). Neutropenia is defined as the low concentration of neutrophil granulocytes (lower than < 500 cells/mm3 or 500-1000/mm3 with a predicted fall of < 500 cells/mm3) (2, 3). Also, the neutrophil count < 1500/mm3 is a criterion for neutropenia in children and adults (4). FN prevalence in children is at least one FN episode for 50% of the children

receiving chemotherapy (5). FN is often induced due to chemotherapy, solid or certain lymphoproliferative malignancies.

Furthermore, radiation is another risk factor for FN that influences bone marrow proliferation in some sites. During FN, infection, and fever intervene in the cancer treatment process. Even fever delays chemotherapy administration in patients without infection (6). The use of antibiotics is an approach to decreasing mortality due to FN (1). Infection is a critical challenge in FN management as one of the causes of death in cancer patients (7). Other FN managing methods in cancer patients include modifying the dose of chemotherapy, the interval between the doses, and prophylaxis with recombinant granulocyte colony-stimulating factors (G-CSFs) (e.g., Filgrastim). These methods are used for the condition of each patient and chemotherapy regimens (6). G-CSFs induce neutropenia proliferation, reduce the duration of hospitalization and neutropenia, and accelerate the improvement process of infection. The recommended risk of FN for primary prophylaxis with G-CSFs is greater than 20% (8). The risk has been reported to be even higher (40%) before 2006 (9).

According to the existing reports, Filgrastim bears the potential to decrease the duration of antibiotic therapy and hospitalization by the significant reduction of infection-related mortality in cancer patients. Subsequently, Filgrastim can influence the febrile neutropenia rate (10). Like other G-CSFs, Filgrastim is a product of human gene expression by recombinant technology. Filgrastim is a protein containing 175 amino acids with some differences from the natural human molecule (11). This study was designed to survey an optimum dose of Filgrastim in the treatment of FN in Iranian patients with cancer by evaluating hematologic factors, the process of the antibiotic administration period, physical status, and malignancy type.

Materials and Methods

Sample collection and processing

In this randomized clinical trial (IRCT code number: IRCT20180103038196N8), sixty patients with cancer were hospitalized in the Oncology Center at Taleghani Hospital of Golestan University of Medical Sciences Gorgan (a city located in the north of Iran) were studied from March 2018 to March 2019. Informed consent forms were completed and signed by the parents of the patients. The inclusion criteria comprised absolute neutrophil count (ANC) < 1500 cells/mm3, duration of neutropenia >7-10 days, low blood pressure, profound neutropenia, sepsis, pneumonia, and fungal infections. The exclusion criteria consisted of ANC ≥ 1500 cells/mm3 in patients with active leukemia or patients without leukemia remission and patients' dissatisfaction. Patients who had met the inclusion criteria of the study (mentioned above) were categorized into groups A and B. Thirty patients in group A received Filgrastim 5µg/kg/day (AriaTinagene, Gorgan, Iran), whereas 30 others in group B received that up to 15µg/kg/day. In this hospital, Filgrastim is consumed at the dose range of 5-15 µg/kg/day. Also, According to the datasheet of filgrastim, the administrating dose of filgrastim has not been defined, and there are no limitations. So we faced no ethical restrictions to use it at the mentioned rates. According to a study by Lustberg 2012 (6), we used Intravenous injection of filgrastim. Type of malignancy, hematological factors (ANC, mature neutrophil and white blood cells (WBC)), antibiotic administration period and physical examination findings (duration of hospitalization, duration of recovery from neutropenia, and duration of fever) in both groups were evaluated initially and at the end of FN. According to the treatment protocol for FN, antibiotic therapy with Ceftriaxone and Amikacin was performed at first. Then vancomycin was added because of a lack of response to this

treatment after 48h. In case there was no response to treatment, Ceftazidime replaced ceftriaxone. According to multiple pediatric infection references, antibiotics were selected based on the infection with fever and neutropenia. The fever was set out on a fever chart. Complete blood count with differential (CBC diff) was performed every 48h, and drugs administration was stopped after ANC rose higher than 1500/mm3. Lung infiltration and other lung complications were also evaluated by chest X-ray (CXR). Spleen and abdomen were monitored by ultrasound as well.

Statistical analysis

Data were analyzed by SPSS version 18.0 and reported as mean ± standard deviation (SD). The Shapiro-Wilk test was used to determine the normality of the data. Between-group comparisons were checked by Student's T-test and the Man-Whitney U test. A P-value <0.05 was considered statistically significant.

Ethical considerations

Experimental steps and sampling were approved by the Golestan University of Medical Sciences Research and Ethics Committee (IR.GOUMS.REC.1396.289).

Results

Sixty febrile neutropenic patients with cancer (30 patients in each group) were randomly studied (Figure 1). All the patients were below 15 years old, with a mean age of 6 ± 3 years. Totally, 36 patients (60.0%) were male and 24 (40.0%) were female. In group A, the number of males and females showed to be 20 (66.7%) and 10 (33.3%), respectively. However, in group B, there were 16 (53.3%) and 14 (46.7%) males and females, respectively. The frequency distribution of the patients based on gender did not differ significantly between the groups (P= 0.18). However, the frequency distribution of patients based on malignancy type differed significantly between the groups (P= 0.01) (Table I). The mean ± SD of hematological factors was compared at the beginning and after recovery from neutropenia between the groups. Predicated on the results, with the onset of neutropenia, only WBC showed a significant difference between the groups. Although after recovery from neutropenia changes of mature neutrophil cells failed to differ significantly, the P-value was partly close to the significant level (P= 0.07). Other factors did not disclose important statistical differences (Table II). Other than recovery duration from neutropenia, the mean of paraclinical parameters appeared to be lower in group A than in B. Duration of recovery from neutropenia was almost identical in both groups. Paraclinical parameters did not differ significantly between the two groups (Table III).

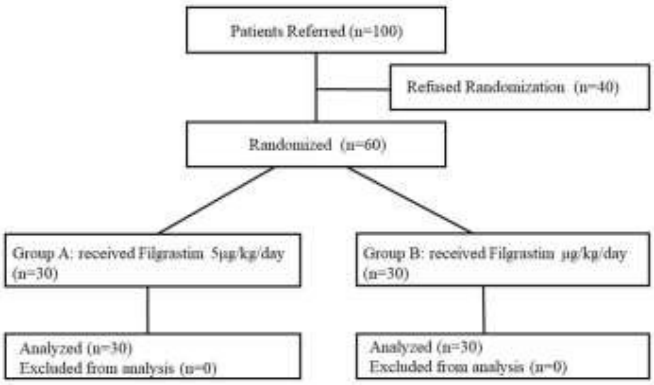

Figure 1. Study flow and distribution of procedures

Table I:. The frequency distribution of patients based on malignancy type in the two groups

Malignancy	Group A Frequency (%)	Group B Frequency (%)
Osteosarcoma	2 (6.7)	5 (16.7)
ALL	15 (50.0)	6 (20.0)
AML	3 (10.0)	2 (6.7)
Brain tumor	2 (6.7)	0 (0.0)
Wilms' tumor	1 (3.3)	1 (3.3)
Hodgkin Lymphoma	3 (10.0)	0 (0.0)
Neuroblastoma	2 (6.7)	9 (30.0)
Lymphoma	1 (3.3)	0 (0.0)
Rhabdomyosarcoma	0 (0.0)	5 (16.7)
Germ cell tumor	0 (0.0)	1 (3.3)
Ewing sarcomas	1 (3.3)	1 (3.3)

Note: ALL, Acute lymphoid leukemia; AML, Acute myeloid leukemia.

Table II. Comparison of hematological factors before and after Filgrastim treatment between the groups

Hematological factors (cells/mm^3)	Mean ± SD		*P*
	Group A	Group B	
Before Filgrastim treatment			
WBC (cells/µl)	1851.7 ± 797.6	1320.0 ± 941.5	0.02
Mature neutrophil cells (%)	41.7 ± 18.4	39.5 ± 18.9	0.67
ANC (cells/mm^3)	739.3 ± 402.3	644.3 ± 451.0	0.43
After Filgrastim treatment			
WBC (cells/µl)	7429.0 ± 1506.7	7365.5 ± 8319.6	0.98
Mature neutrophil cells (%)	17.1 ± 21.1	28.1 ± 21.0	0.07
ANC (cells/mm^3)	3852.9 ± 4862.3	4833.3 ± 6274.1	0.53

Note: WBC, white blood cells; ANC, Absolute neutrophil count; SD, standard deviation.

Table III. Comparison of physical examination findings and antibiotic administration period between the groups

Parameters	Mean ± SD		*P*
	Group A	Group B	
Duration of hospitalization (day)	8.0 ± 6.4	9.2 ± 8.4	0.51
Duration of fever (day)	2.7 ± 2.0	3.9 ± 4.2	0.26
Duration of recovery from neutropenia (day)	5.8 ± 5.2	5.7 ± 5.8	0.94
Duration of antibiotic administrating (day)	7.7 ± 6.1	9.3 ± 8.1	0.24

Discussion

Filgrastim is a stimulator of neutrophil proliferation and is used as a prophylaxis to prevent FN (12). To augment neutrophils in patients with malignancy, G-CSFs are deployed as intravenous infusion 5-6 days before chemotherapy (13). According to some previous investigations, for FN treatment in children, the optimum dose of G-CSF (Filgrastim) is 5µg/kg/day. Higher doses of Filgrastim have failed to demonstrate beneficial effects on some parameters, including infection, fever duration, hospitalization times, and survival rate of patients (14).

In the present study, the males outnumbered females, which agreed with a study by Yapici et al. (15). They reported more males (n=58) than females (n=38) in febrile neutropenic patients with solid tumors.

The frequency distribution of patients based on malignancy type differed significantly between the groups (P= 0.01). The most common malignancy in group A proved to be acute myeloid leukemia, but in group B, it was neuroblastoma. Generally, ALL was the most common malignancy in these patients.

Neutrophils are damaged in malignancies and cannot fight against infection, especially hematological malignancies. Among malignancies, chemotherapy for AML and ALL results in FN in children (16). In a study by Goruk et al. (3), ALL was one of the common malignancies among patients with FN. One of the crucial risk factors for infection in malignancies is cytotoxic chemotherapy agents. This event is triggered by damaging cells in gut mucosa (17).

Investigations have shown that a combination of Filgrastim and antibiotics can reduce the duration of neutropenia and increase neutrophils, thus lowering the duration of hospitalization, antibiotic therapy, and fever. Filgrastim can stimulate neutrophil regeneration and accelerate the maturation period of neutrophils (18).

Clinical guidelines suggest that Filgrastim administration should be continued until the WBC and ANC achieves normal levels (19). The presented results identified no significant changes in hematological parameters, including WBC, mature neutrophil cells, and ANC. However, there were some differences between the groups that can be important in clinical settings. The higher dose of Filgrastim in group B impacted changes in ANC and mature neutrophil cells. Also, the change of mature neutrophil cells at the end of neutropenia was close to the significant level (P= 0.07). The production of mature neutrophil cells diminishes in neutropenia (20). Sari et al. (11) studied 29 febrile neutropenic with solid malignancies (2-16 years old) in Turkey through which some hematological parameters were compared between the two groups receiving Filgrastim or lenograstim. Filgrastim was administered 5µg/kg/day. The results revealed changes in WBC and ANC being 750 cells/µl and 240/mm3 after five days. After seven days, the differences showed to be 1200 cells/µl and 550/mm3. Meanwhile, the changes in the parameters proved to be higher in the studied Iranian population after five days of deploying the same dose of Filgrastim. However, the response to Filgrastim was better in this population.

Based on the results, although physical examination findings and antibiotic administration period changes did not differ significantly between the two groups, these changes were more noticeable in group B than that in group A. In our study, the higher dose of Filgrastim could not lower the duration of hospitalization, fever, recovery from neutropenia and antibiotic administration. Duration of hospitalization bears a direct relationship with the number of episodes of FN. And decreasing the duration of recovery from FN induces a reduction in the duration of hospitalization that

consequently affects the quality of life of the patients (21). Ok et al. (22) compared different doses of Filgrastim (5 to 10 µg/kg/day) to treat high-risk FN in 124 children with cancer. The duration of recovery from neutropenia, duration of fever, the total length of hospital stay, duration of FN episode and G-CSF use, costs, bacteremia frequency, and other treatments did not differ significantly between them. However, the higher dose of Filgrastim imposed more costs on patients with solid tumors.

In this trial, Filgrastim was administered until the ANC escalated to more than 1500/mm3. The recovery duration from neutropenia demonstrated the period of Filgrastim therapy being a little lower in group B (~ 6 days in total). Further, in a study on 324 patients with breast cancer, Clemons et al. (23) demonstrated that Filgrastim received primary FN prophylaxis for five days proves to be non-inferior up to 7/10 days. So, a more extended period of Filgrastim therapy showed no critical impact on clinical outcomes. However, in FN, shortening the duration of neutropenia is essential (24). Despite the probable effects of Filgrastim on ANC in group B, the higher dose of Filgrastim is not suggested for the treatment of FN due to lake of a statistical difference between the groups in this study. Cytotoxicity, side effects such as bone pain, headache, fever, and costs will increase in higher doses (22).

Conclusion

Although the effect of Filgrastim on ANC was higher in group B in terms of quantity, no significant differences between the groups were observed. These results can be clinical of crucial importance for similar Iranian populations. These findings can pave the way for FN management and confirm previous findings that have demonstrated no significant beneficial effects for higher doses of Filgrastim. Further studies need to be carried out with a larger population and higher doses of Filgrastim to settle the controversies.

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Conflict of interest

The authors declare no conflict of interest.

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