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GRANULOCYTE COLONY-STIMULATING FACTOR IN CHILDREN WITH CHEMOTHERAPY-INDUCED FEBRILE NEUTROPENIA

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ABSTRACT… Objective: To determine if granulocyte colony-stimulating factor (G-CSF) with empirical antibiotics therapy accelerates febrile neutropenia resolution compared with antibiotics without it. **Study design:** Experimental study. **Place and Duration of Study:** Study was conducted for a period of one year from march 2012 to february 2013 in oncology/haematology department Children Hospital Lahore (PAKISTAN). **Subject and Methods:** A total of 56 children with febrile neutropenia due to chemotherapy were included in the study. Two groups were made A and B. Twenty eight patients were included in each group. Patients included in the group A were given granulocyte colony stimulating factor with the dose of 5 microg/kg/day for five days and the patients included in group B were not given granulocyte colony stimulating factor. Subcutaneous administration was recommended. Patients remained on study until absolute neutrophil count (ANC) >500/microl and > or =48 hr without fever. Every child in both groups was given antibiotic treatment in the hospital whenever there is need, antibiotics changed according to the blood culture sensitivity. Admitted patients were followed daily for fever and signs of sepsis. Number of days of admission in hospital and number of days of treatment was calculated in both groups and compared with each other. Duration of febrile neutropenia and mortality was also analysed for both groups. **Results:** Out of 56 patients 46 had acute lymphoblastic leukemia (ALL), 06 patients were of wilm tumour and 04 patient were having rhabdomyosarcoma. Twenty eight patients were given only antibiotics(GROUP B) and 28 patients were given G-CSF plus antibiotics(GROUP A). Addition of G-CSF significantly reduced neutropenia and febrile neutropenia recovery times. Median days to febrile neutropenia resolution was 4.3 days earlier with G-CSF (5.3 vs. 9.6 days) ($P < 0.0001$). Resolution of fever was one day earlier in patients who were given G-CSF (GROUP A). Hospitalization was 2.1 days shorter with G-CSF (6.1 vs. 8.2 days) ($P = 0.02$). (Table II). There was difference of 2.2 days in the duration of IV and oral antibiotic treatment. Addition of antifungal therapy was done in 4 patients in group B and only in one patient in group A. All the patients recovered and no death occurred in the study. **Conclusions:** It is concluded that addition of G-CSF to empiric antibiotic therapy accelerates chemothserapy-induced febrile neutropenia resolution by 4.3 days in pediatric patients with malignancy. It is a significant difference in duration of hospitalization. By bearing expenses of G-CSF we can decrease the expenses of hospitalization and antibiotics.

Key words: Granulocyte colony-stimulating factor (G-CSF), Absolute neutrophil count (ANC)

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INTRODUCTION

Neutropenia is a major dose-limiting toxicity of myelosuppressive chemotherapy that predisposes patients to serious infections. Febrile neutropenia (FN), generally defined as fever (single oral temperature ≥38.3°C or ≥38.0°C for >1 h) with grade 3/4 neutropenia (absolute neutrophil count [ANC] <1.0 or $<0.5 \times 10^9$/l), is associated with substantial morbidity, escalation of costs and mortality risk. Severe neutropenia and febrile neutropenia episodes are also major drivers of chemotherapy dose delays and reductions ,which have been shown to compromise survival outcomes in various curative

settings[1,2,3,4,5,6,7,8].
Adding G-CSF to empiric antibiotic coverage accelerates chemotherapy-induced febrile neutropenia resolution by 9 days in pediatric patients, mainly with ALL, which results in a small but significant difference in the median length of hospitalization[12].

Updated international guidelines published in 2006 have broadened the scope for the use of granulocyte colony-stimulating factor (G-CSF) in supporting delivery of myelosuppressive chemotherapy. G-CSF prophylaxis is now recommended when the overall risk of febrile neutropenia (FN) due to regimen and individual patient factors is =20%, for supporting dose-dense and dose-intense chemotherapy and to help maintain dose density where dose reductions have been shown to compromise outcomes. Indeed, there is now a large body of evidence for the efficacy of G-CSFs in supporting dose-dense chemotherapy[13].

Prophylaxis with recombinant granulocyte colony-stimulating factors (G-CSFs) reduces the severity and duration of chemotherapy-induced neutropenia and the consequent risk of FN and is playing an increasingly broad role in supporting the delivery of myelosuppressive chemotherapy[9,10,11].

There is now a growing body of evidence that improved chemotherapy delivery and reduction in FN with G-CSF may translate into better survival outcomes. Three meta-analyses of randomised studies comparing prophylactic G-CSF or granulocyte-macrophage colony-stimulating factor (GM-CSF) with placebo or no treatment have been conducted recently[14,15].

MATERIALS AND METHODS

Study was conducted for a period of one year from march 2012 to february 2013 in oncology/haematology department Children Hospital Lahore (PAKISTAN).

Total 56 children (28 in group A & 28 in group B) were taken and sampling technique was Convenience sampling. children with febrile neutropenia due to chemotherapy which was defined as absolute neutrophil count (ANC) <500/microl and fever >102F were included in the study. Patients included in the group A were given granulocyte colony stimulating factor with the dose of 5 microg/kg/day for five days and the patients included in group B were not given granulocyte colony stimulating factor. Subcutaneous administration was recommended. Patients remained on study until absolute neutrophil count (ANC) >500/microl and > or=48 hr without fever.

Every child in both groups was given antibiotic treatment in the hospital whenever there is need, antibiotics were changed according to the blood culture sensitivity.

Admitted patients were followed daily for fever and signs of sepsis.

Number of days of admission in hospital and number of days of treatment was calculated in both groups and compared with each other.

Duration of febrile neutropenia and mortality was also analysed for both groups.

Every child was followed for total duration of illness. Patients remained on study until absolute neutrophil count (ANC) >500/microl and > or =48 hr without fever.

Effect of G-CSF was noted on clinical improvement of the patient like reduction in fever and improvement of absolute neutrophil count (ANC).

Children reporting to Children Hospital Lahore at oncology and haematology department and diagnosed clinically and on decreased absolute neutrophil count were registered. Children meeting the inclusion criteria were included in the sample. All the children with absolute neutrophil count (ANC) >500/microl or without fever and the children who were not on chemotherapy were excluded from the sample. Informed consent from

the parents or attendants was taken. The study was without any harm to participants. The basic demographic information including name, age sex and address was recorded. History of present illness was inquired with regard to symptoms, their severity and duration.

Children included in the study were randomly and equally divided into two groups A and B. After a child had been included in group A , next consecutive child was enrolled in group B. G-CSF was given to group A and the group B was not given G-CSF. Both groups were given similar conventional treatment for febrile neutropenia.

Descriptive statistic like mean or proportion was calculated for age, sex, nutritional status and days of febrile neutropenia.

During data analysis two groups A and B were compared with each other with respect to age, sex, days of illness before hospitalization, nutritional status and severity of illness to ensure that these confounding variables were equally distributed in both groups.

An intention to treat analysis for comparison of duration of neutropenia, duration of fever, duration of hospitalization, duration of antibiotic therapy and mortality in both groups was performed to test the study hypothesis.

Means and standard deviation of duration of neutropenia, duration of fever, duration of hospitalization, duration of antibiotic therapy was calculated of both groups and student t-test was applied.

Level of significance was ($p<0.05$).

All the patients in both groups recovered and no death observed during the study.

RESULTS

Present study tested the effect of granulocyte colony stimulating factor (G-CSF) in children suffering from chemotherapy induced febrile neutropenia. A total of 56 patients were studied.

Twenty eight patients were given granulocyte colony stimulating factor (G-CSF) and 28 patients were not given granulocyte colony stimulating factor (G-CSF), A and B groups were made respectively.

All the patients of group A and B were matched with each other with respect to age, nutritional status and degree of severity of symptoms.

Patients who were having fever >102f and ANC < 500microl were included in the study.

Mean duration of neutropenia in group A (G-CSF given) was 5.3±0.25 days. While mean duration of neutropenia in group B (G-CSF not given) was 9.6±0.29 days (Table I).

	Group A (n=28)	Group B (n=28)	Significance
Duration of neutropenia	5.3±0.25 days	9.6±0.29 days	0.001
Duration of treatment	8.20±0.154 days	10.4±0.1 3 days	0.002
Duration of hospitalization	6.1±0.125 days	8.2±0.26 9 days	0.02
Duration of fever	7.6±0.214 days	8.6±0.23 1 days	0.001
Need to change antibiotics	2 (7%)	6 (21%)	-
Antifungal therapy	1 (3%)	4 (14%)	-
Deaths	-	-	-

Table-I. Summary of effect of G-CSF in children with febrile neutropenia (n=56)

Group A: G-CSF given Group B: G-CSF not given

Mean duration of hospitalization in group A (G-CSF given) was 6.1±0.125 days. While mean duration of illness in group B (G-CSF not given) was 8.2±0.269 days (Table I).

All the patients recovered and no death observed in both groups (Table I).

All the children in both groups were given

antibiotic therapy. Mean duration of antibiotic treatment in group A(G-CSF given) was 8.20±0.154 days. While mean duration of antibiotic treatment in group B(G-CSF not given) was 10.4±0.13 days (Table I).

Twenty eight patients were given only antibiotics(GROUP B) and 28 patients were given G-CSF plus antibiotics(GROUP A) (Table II).

	Group A (n=28)	Group B (n=28)
Sex Male Female Mean age	 16 (57%) 12 (42%) 3.4 years	 15 (53%) 13 (58%) 3.7 years
Clinical features during episode of febrile neutropenia		
Fever	100%	100%
Cough	10 (35%)	12 (42%)
Respiratory distress	3 (11%)	3 (11%)
Burning micturation	2 (7%)	2 (7%)
Nutritional status Malnourished Antibiotics used G-CSF used	 18 (64%) 100% 100%	 16 (57%) 100% -

Table-II. Comparison of group A&B (n=56)

Resolution of fever was one day earlier in patients who were given G-CSF (GROUP A). Mean duration of fever in group A(G-CSF given) was 7.6±0.214 days. While mean duration of fever in group B(G-CSF not given) was 8.6±0.231 days (Table I).

Hospitalization was 2.1 days shorter with G-CSF (6.1 vs. 8.2 days) (P = 0.02). (Table I).

There was difference of 2.2 days in the duration of IV and oral antibiotic treatment. Tanzo and Amikacin was given to all the patients included in the study. Antibiotics had to be changed in eight patients. Two were from group A(G-CSF given) and six patients were in group B (G-CSF not given) (Table I).

Addition of antifungal therapy was done in 4 patients in group B and only in one patient in group A. (Table I).

Out of 56 patients, 31 were males and 25 were females (Table II).

Fever(100%), cough(38%), respiratory distress(12%) and burning micturition(8%) were the chief complaints of the patients. Absolute neutrophil count <500 microl was seen in 100% patients (Table II).

All the patients recovered and no death occurred in the study. (Table I).

DISCUSSION

This study shows that G-CSF has a significant beneficial effect in children suffering from febrile neutropenia .It decreases the total duration of neutropenia and decreases the total duration of treatment and duration of hospitalization. It also decreases the expenses of hospital stay and antibiotics. There is a mean reduction of 4.3 days in duration of neutropenia in group A (G-CSF given) (Table I).

Severity of the disease, age of the patients, month of presentation of the patients and nutritional status of the patients was tried to be kept similar in both groups (Table II).

Ozkaynak and Krailo in 2005 stated that adding G-CSF to empiric antibiotic coverage accelerates chemotherapy-induced febrile neutropenia resolution by 9 days in pediatric patients, mainly with ALL[12].

In 2006 Matti Aapro and Jeffrey Crawford stated that G-CSF prophylaxis can save the patient from neutropenia when it is necessary to give high dose chemotherapy[13].

Crawfold in 2002 and Aapro in 2006 stated that prophylaxis with recombinant granulocyte colony-stimulating factors (G-CSFs) reduces the severity and duration of chemotherapy-induced neutropenia and the consequent risk of FN[9,10].

CONCLUSIONS

It is concluded that addition of G-CSF to empiric antibiotic therapy accelerates chemotherapy-induced febrile neutropenia resolution by 4 days in pediatric patients with malignancy. It is a significant difference in duration of hospitalization. By bearing expenses of G-CSF we can decrease the expenses of hospitalization and antibiotics.

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