ORIGINAL RESEARCH PAPER

Paediatrics

KEY WORDS: Filgrastim, ALL, Neutropenia

ROLE OF GRANULOCYTE COLONY STIMULATING FACTOR (FILGRASTIM) IN CHEMOTHERAPY INDUCED FEBRILE NEUTROPENIC PATIENTS OF PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA

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ABSTRACT

AIMS & OBJECTIVES: Primary objectives: - 1.Role of granulocyte colony stimulating factor (filgrastim) in chemotherapy induced febrile neutropenic patients of pediatric acute lymphoblastic leukemia i.e. primary outcome variables as resolution of fever and resolution of neutropenia. 2. To evaluate the secondary outcome variables such as duration of hospitalization and antibiotic usage with granulocyte colony stimulating factor (filgrastim) in chemotherapy induced febrile neutropenic patients of pediatric acute lymphoblastic leukemia

Secondary objective: - 1.To study the adverse effects of filgrastim in chemotherapy induced febrile neutropenic patients of pediatric acute lymphoblastic leukemia.

MATERIAL METHODS: This study done in government medical college and cancer hospital Aurangabad from January 2016 to August 2017. 100 chemotherapy induced febrile neutropenic patients of pediatric ALL were included. Patients were admitted, detail history taken, examination done and all necessary investigations were done. Filgrastim was administered subcutaneously in a dose of 5 mcg/kg/day, for up to 2 weeks or until the ANC count reaches 1000 cell/cumm. After the administration of filgrastim, ANC level was measured daily and temperature was documented 6 hrly. Recovery of fever and resolution of neutropenia were considered as primary efficacy parameter, while duration of hospitalization and iv antibiotic usage were recorded as secondary efficacy variables. All clinically significant adverse effects after filgrastim administration were documented. All the necessary chemotherapy drugs were administered as per the protocol to treat these patients.

RESULTS: In present study most common age group affected was between 5 to 12 years (75%) and maximum number of cases were male (63%). Commonest symptom was fever (100%) followed by organomegaly (98%) and pallor (92%). Maximum number of patients (n = 54) received filgrastim for 3 days and maximum duration of filgrastim received was 7 days. Mean time for resolution of fever was 4.6 + 0.899 days and mean time for resolution of neutropenia was 2.23 + 0.75 days. Mean duration of hospitalization was 12.72 + 3.175 days and mean duration of IV antibiotics usage was 8.844 + 2.363 days. In present study most common adverse effect noted was bony pain (52%) followed by vomiting (30%) and headache (18%) of patients.

CONCLUSION: Filgrastim (G-CSF) is found to be effective in treatment of chemotherapy induced febrile neutropenic patients of pediatric ALL and is safe in pediatric patients.

INTRODUCTION

Febrile neutropenia and resultant infections are major causes of morbidity and mortality in acute lymphoblastic leukemia patients receiving chemotherapy. In spite of the standard measures like hospitalization and antibiotics, febrile neutropenia associated with a significantly high risk of morbidity and mortality in such patients.[1] Filgrastim has potent granulopoietic effects that promote the survival proliferation, differentiation and function of progenitor and mature neutrophil cells. Filgrastim therapy started a day after chemotherapy, reduced the severity and duration of neutropenia and decreased by nearly half the incidence of febrile neutropenia and the duration of hospitalization and antibiotic usage with associated pharmaco-economic benefits to patients. The use of filgrastim to prevent episodes of febrile neutropenia in patients with acute lymphoblastic leukemia who receive chemotherapy is now approved in many countries.

A clinical trial was undertaken to assess the efficacy of filgrastim in pediatric acute lymphoblastic leukemia patients receiving chemotherapy. Efficacy of G-CSF judged primarily by the mean number of days required to restore the depressed absolute neutrophil count (ANC) and also the tolerability of regimen.

AIMS & OBJECTIVES

Primary objectives: - 1.Role of granulocyte colony stimulating factor (filgrastim) in chemotherapy induced febrile neutropenic patients of pediatric acute lymphoblastic leukemia i.e. primary outcome variables as resolution of fever and resolution of neutropenia. 2. To evaluate the secondary outcome variables such as duration of hospitalization and antibiotic usage with granulocyte colony stimulating factor (filgrastim) in chemotherapy induced febrile neutropenic patients of pediatric acute lymphoblastic leukemia

Secondary objective: - 1.To study the adverse effects of filgrastim in chemotherapy induced febrile neutropenic patients of pediatric acute lymphoblastic leukemia.

MATERIALS AND METHODS

It is prospective open phase 4 study and open non randomized clinical trial. It is done in pediatric ward in GMCH, Aurangabad after approval of institutional ethics committee, from January 2016 to August 2017. 100 chemotherapy induced febrile neutropenic patients of pediatric ALL were included in the study.

Inclusion criteria for our study was, patients with histologically confirmed ALL in less than 12 years of age, receiving chemotherapy or completed course of chemotherapy, admitted for fever (axillary temperature 38.5°Celsius in one measurement or 38°Celsius in two consecutive measurements separated by 1 hour) and severe neutropenia with ANC less than 500/cumm and willing to give informed consent. Patients with aplastic anemia, myelodysplasia, constitutional pancytopenia, neutropenia due to viral infections were excluded.

All the febrile neutropenic patients of pediatric ALL full filling inclusion criteria were admitted in pediatric ward and enrolled in this study, after taking written informed consent. All the patients were assessed with detailed history elicited by close relatives or accompanying peoples, preliminary data of the patients such as name, age, sex, weight, duration of chemotherapy and details of previous hospitalizations were recorded. Detailed history of all patients about anthropometry and immunization was recorded. The vital signs like pulse rate, respiratory rate, blood pressure and

temperature were noted. Axillary temperature were documented every 6 hrly interval and other relevant examination includes pallor, lymphadenopathy, icterus, bleeding, ENT examination, skin, skull, spine and joints examination was done in detail in all cases. A detailed examination of per abdominal system (hepatospleenomegaly), cardiovascular, respiratory and central nervous system was carried out in all cases.

Laboratory investigations advised in all cases were complete blood count (CBC), absolute neutrophil count (ANC), peripheral smear, and other investigations to detect concomitant complications and to rule out other systemic infections. Liver function test, renal function test, chest X ray PA view, urine culture, microscopic examinations and blood culture was done in cases of septicemia. Liver function test and renal function test was done to assess significant alteration after G-CSF therapy. CSF (cerebrospinal fluid) analysis done in patients presented with bleeding or purpuric spot or septicemia or disseminated intravascular coagulation (DIS).

Filgrastim was administered subcutaneously in a dose of 5 mcg/kg/day, for up to 2 weeks or until the ANC count reaches 1000 cell/cumm. After the administration of filgrastim, ANC level was measured daily and temperature was documented 6 hrly. Recovery of fever and resolution of neutropenia were considered as primary efficacy parameter, while duration of hospitalization and IV antibiotic usage were recorded as secondary efficacy variables. All clinically significant adverse effects after filgrastim administration were documented. All the necessary chemotherapy drugs were administered as per the protocol to treat these patients. Other supportive treatments like, IV fluids, blood and blood product transfusion, anticonvulsants, antifungals, antipyretics administered as per the need of patients.

Data were statistically described and analyzed using computer programme Microsoft excel 2010 (Microsoft corporation, NY, USA) and SSPS (Statistical Package for the Social Science Inc. Chicago, USA) version 19. Efficacy variable included resolution of fever, recovery of neutropenia, duration of hospitalization and antibiotics usage were analyzed using descriptive statistics. Statistical significance was done with 95% confidence limit.

RESULTS

In the present study most common age group was between 5 to 12 yrs (75%) followed by 0-5 yrs was (25%). Maximum number of cases were male (63%) with male to female ratio 1.7:1. In present study commonest symptom was fever (100%) followed by organomegaly (98%), pallor (92%), anorexia (91%) and easy fatigability (82%) as shown in table 1

TABLE 1

PARAMETER	NO. OF CASES	PERCENTAGE
AGE		
0-5 YRS	25	25%
5-12 YRS	75	75%
GENDER		
MALES	63	63%
FEMALES	37	37%
SYMPTOMS		
FEVER	100	100%
ORGANOMEGALY	98	98%
PALLOR	92	92%
ANOREXIA	91	91%
EASY FATIGABILITY	82	82%
VOMITING	58	58%
BLEEDING	26	26%
RESPIRATORY DISTRESS	24	24%
GENERALISED LYMPHADENOPATHY	78	78%
JOINT PAIN	26	26%
CONVULSIONS	6	6%
SKIN RASH	14	14%

In present study maximum number of patients (n = 54) received filgrastim for 3 days and maximum duration of filgrastim received was 7 days.

TABLE 2 - SHOWING PRIMARY EFFICACY PARAMETERS AFTER FILGRASTIM THERAPY

PARAMETERS	NO. OF PATIENTS (N=100)	DAYS (MEAN + SD)	MEDIAN	95% CI OF MEAN	RANGE
FEVER (DAYS)	100	4.6 + 0.899	5.0	4.42 – 4.78	1 - 5
RESOLUTION OF NEUTROPENIA (ANC > 500/CUMM)	100	2.23 + 0.750	2.0	2.03 – 2.38	1 - 5

In present study mean time for resolution of fever was 4.6 + 0.899 days and the median time was 5 days with 95% CI of mean was 4.42 – 4.78 days. Mean time for resolution of neutropenia was 2.23 + 0.750 days and median time was 2 days with 95% CI of mean was 2.03 – 2.38 days.

TABLE 3 – SHOWING SECONDARY EFFICACY PARAMETERS AFTER FILGRASTIM THERAPY

PARAMETER	NO. OF PATIENTS (N=100)	DAYS(MEAN + SD)	MEDIAN	95% CI OF MEAN	RANGE
DURATION OF HOSPITALISATION	100	12.72 + 3.175	14	12.085 – 13.355	6 - 30
IV ANTIBIOTIC USAGE	100	8.44 + 2.363	7.0	7.967 – 8.912	5 - 14

In present study mean duration of hospitalization was 12.72 + 3.175 days and median duration was 14 days with 95% CI of mean was 12.085 – 13.355 days. Mean duration of iv antibiotic usage was 8.44 + 2.363 days and median duration was 7 days with 95% CI of mean 7.967 – 8.912 days.

TABLE 4 – SHOWING ADVERSE EFFECTS OF FILGRASTIM

ADVERSE EFFECTS	NO. OF CASES	PERCENTAGE
BONY PAIN	12	52%
VOMITING	7	30%
HEADACHE	4	18%
TOTAL	23	100%

In present study most common adverse effect noted was bony pain in 52% patients followed by vomiting in 30% of patients and headache in 18% of patients.

DISCUSSION

All pediatric patients of acute lymphoblastic leukemia below 12 years of age on chemotherapy having febrile neutropenia admitted in pediatric ward at GMCH Aurangabad from January 2016 to August 2017 were enrolled in this study with sample size of 100.

In present study the most common age group was between 5-12 yrs (75%), followed by 0-5 yrs was (25%) and mean age group was 7.04 $\pm$ 2.71 yrs. Our results were similar to the study done by Potter MR et al[2] (2016) in the study of 86 febrile neutropenia patients found most common age group was between 6 – 15 years (66%) with the mean age of 8.1 $\pm$ 3.4 yrs. In contrast, in the study done by Ozdemir et al (2016)[3] in 96 patients between age group 1–18 yrs with the most common age group was between 1–6 yrs (62%) with mean age group was 5.9 $\pm$ 3.7 yrs. In this study maximum number of cases were males (63%) with male to female ratio of 1.7: 1. In study done by Saarinen pihkala et al (2010)[4] in 113 patients with maximum number of cases were males (64%) with male to female ratio of 1.7:1. In contrast, in the study done by Meir et al (2010)[5] in patient shows maximum number of cases were males (74%) with male to female ratio of 2.8:1. This could be due to difference in number of cases studied.

In our study commonest symptom noted was fever (100%) followed by organomegaly (98%), pallor (92%), anorexia (91%)

and easy fatigability (82%). Similar results were found by Wittmann et al (2006)[6] in study conducted in 106 patients of febrile neutropenia with commonest symptom was fever (100%) followed by pallor (80%), easy fatigability (64%) and petechial rash (24%). While in contrast, in study done by Ghalaut PS et al (2009)[7] in 38 patients found commonest symptom was pallor (96%), followed by fever (91%) and organomegaly (88%), easy fatigability (28%), this variation may be due to lesser study population and study done in adult population.

In present study maximum number of patients (54%) received filgrastim for 3 days and maximum duration of filgrastim received was 7 days. Similar results were found in the study done by Meir et al (2010)5 in 137 pediatric patients with (56%) of cases received filgrastim for less than 7 days and maximum duration of filgrastim received was 9 days. While in contrast, in the study done by Potter et al (2009)[2] in 86 patients maximum number of patients (67%) received filgrastim for 12 days and maximum duration of filgrastim received was 16 days. This difference might be due to inclusion of more relapse cases in their study and those having severe neutropenia with fungal infection.

In present study mean time for resolution of fever was 4.6 $\pm$ 0.89 days and the median time was 5 days with 95% CI of mean was 4.42 – 4.78 days. Similar results were found in the study done by Maher et al (2004)[8] showed mean time for resolution of fever was 3 + 0.9 days with CI 2.9 – 3.46 days. In the study done by Ghalaut PS et al (2009)[7] mean duration of resolution of fever was 8.2 $\pm$ 1.4 days with median of 10 days. This difference might be because of inclusion of adult patients having solid tumors and acute lymphoblastic leukemia and acute myelodysplastic leukemia patients and also included cases of bone marrow transplant in their study.In present study mean time for resolution of neutropenia was 2.23 $\pm$ 0.750 days and median time was 2 days with 95% CI of mean was 2.03 – 2.38 days. Similar results were found in Wittmann B et al (2006)[6] with mean time for resolution of neutropenia was 3.5 day with median of 5 days. While in contrast study done by Meir et al (2010)[5] shows mean time for resolution of neutropenia was 9.2 $\pm$ 2.1 days with median of 13 days. This difference might be because of study done in Middle East countries including number of prospective multicenter studies after filgrastim therapy.

In present study mean duration of hospitalization was 12.72 $\pm$ 3.175 days and median duration was 14 days with 95% CI of mean was 12.085 - 13.355 days. Similar results were found in study done by Riikonen et al (2004)[9] mean duration of hospitalization was 12 days and median duration was 15 days. In contrast study conducted by Potter MR et al (2009)[2] maximum number of patients (78%) showed duration of hospitalization 20-23 days with mean of 21 days, this might be due to analysis of multicenter studies done over duration of 10 years.In present study most common adverse effects noted were bone pain (52%) followed by vomiting (30%) and headache (18%). Similar results were found in study done by Sasse EC et al (2005)[10] in 34 patients observed most common adverse effect bony pain (38%) followed by vomiting (22%), myalgia (18%). In study done by Mitchel et al (2007)[11]in 78 patients with mean age group of 5.5 yrs observed most common adverse effect flu like symptoms (48%) followed by ear discharge (16%), this difference might be due to inclusion of more number of patients below 5 yrs of age.

CONCLUSION

Filgrastim exhibited efficacy in accelerating resolution of fever and recovery of neutropenia and also exhibited efficacy in term of duration of hospitalization and IV antibiotic usage in patients of febrile neutropenia with ALL in pediatrics. Filgrastim found to be well tolerated by pediatric patients with bony pain to be the commonest adverse effect noted.

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