Role of Granulocyte Colony Stimulating Factor (G-CSF) in Chemotherapy Induced Neutropenia

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Abstract

Background: In the past decade, there have been many clinical trials investigating the potential benefits of adjunctive therapy with colony stimulating factors (CSFs) both to ameliorate or prevent profound neutropenia and its potentially life threatening consequences. Neutropenia is the most common dose limiting side effects of cytotoxic chemotherapy. We decided to study the effect of same in our patients coming to haematology clinic.

Aims and Objectives: To see the effect of G-CSF on severity of neutropenia following chemotherapy in patients of haematological malignancies and to see the effect of G-CSF on duration of hospitalization, documented infections and duration of fever as compared to control group in patients with neutropenia following chemotherapy in haematological malignancies.

Material and Methods: Thirty patients of acute leukemia were prospectively studied. Patients were given G-CSF 24 hours following chemotherapy induced neutropenia and following parameters were observed. (a) median time to ANC recovery (b) incidence and duration of fever (c) duration of hospitalization following chemotherapy (d) incidence of documented infections. The patients were given G-CSF until the neutrophil count was >1000/ml for 3 days or maximum of 7 days.

Results: Mean age was 29.33±14 years in G-CSF group and 27.53±13.75 in control group. Mean duration of neutropenia was 11.4 days (p<0.05) in G-CSF group and 15.8 days in control group. Mean duration of fever was 8.2 days in G-CSF group and 13.53 days in control group (p<0.05). Mean duration of hospital stay was 21.33 days in G-CSF group and 25 days in control group (p>0.05).

Conclusions: The study demonstrates that G-CSF administration is efficacious in chemotherapy induced neutropenia by decreasing the duration of neutropenia and duration of fever.

INTRODUCTION

Haematological malignancies are associated with a high rate of infectious morbidity and mortality due to neutropenia, either as a direct result of disease itself or as a result of the intensive chemotherapy regimens now employed to combat these diseases. In fact, neutropenia and infection are the major dose limiting side effects of chemotherapy. The incidence of neutropenia depends upon number of factors, including the dose intensity and chemotherapy, the prior history of the patient and the presence or absence of any comorbid conditions.]

Endogenous granulocyte colony stimulating factor (G-CSF) is a lineage specific colony stimulating factor which is produced by monocytes, fibroblasts and endothelial cells. G-CSF has been shown to have minimal direct in vivo or in vitro effects on the production of hematopoietic cell types other than neutrophil lineage approved pharmaceutical forms of G-CSF for human use include a recombinant non glycosylated form expressed in Escherichia coli (Filgrastim) and a glycosylated form expressed in Chinese hamster ovary cell (Lenograstim). Both forms have similar biological activities and bioavailability following subcutaneous or intravenous administration.

Also, the risk of developing fever with severe neutropenia (defined as ANC <500/ml) following chemotherapy increase by approximately 10%/day. Since the 1960s the incidence of gram negative sepsis, in neutropenic patients has declined with the use of potent antibiotics but mortality rate is still between 10-30% over the same period. Gram positive sepsis has become more common with high mortality rates. About one third to half of patients with febrile neutropenia (defined as fever >38.2°C for more than 1 hour associated with ANC and <1000/ml) have documented bacterial infections. G-CSF reduced the duration and severity of neutropenia, the incidence of febrile neutropenia and
documented infections, the duration of hospitalisation and possibly the need for chemotherapy reduction and delay.4-7

MATERIAL AND METHODS

A total of 30 diagnosed cases (on the basis of complete blood count, bone marrow examination and bone biopsy) were taken for the study. Patients over 14 years of age who received standard chemotherapy for hematological malignancy (acute leukemia) were included. G-CSF was given to patients of neutropenia (ANC less than 1000/ml). 5 mg/kg subcutaneous OD, until the neutrophil count was >1000/ml for 3 consecutive days or maximum of 7 days. Patients with known hypersensitivity to E. coli protein, G-CSF or others were excluded from the study. Other conditions included pregnant / lactating women, patients with severe heart lung disease, myelodysplastic syndrome, blast crisis of chronic myeloid leukemia (CML) or severe neurologic disease. Once the study was discontinued. It was not started again during that particular course, even if the neutrophil count fell below 1000/ml. Patients were observed for the following during the study.

1. Median time to ANC recovery
2. Incidence and duration of fever
3. Duration of hospitalisation
4. Incidence of documented infections

The observations were recorded in special performa designed for this study. The results were analysed by using Student’s t-test (paired t-test, unpaired t-test) and Chi-square test. Parameters analysed included age, sex, duration of neutropenia, duration of fever and duration of hospital stay.

RESULTS

Baseline patient characteristics are shown in Table 1. Out of 30 patients of chemotherapy, induced neutropenia at our centre from August 2006 to January 2008. 15 were given G-CSF and 15 were kept as control.

Hematological recovery: The median time to ANC recovery is shown in Table 2. It was 12 days in G-CSF group (range 3-23 days) and 17 days in control group (range 6-26) when two groups were compared this difference was found to be statistically significant (p<0.05).

Incidence and duration of fever: All the patients were febrile except one in G-CSF group whereas the median duration of fever was 9 days (range 0-19) in G-CSF group and 12 days in control group (range 1-31) when two groups were compared, this difference was found to be statistically significant (p<0.05).

Incidence of documented infections: Incidence of microbiologically and clinically defined infections was found to be more in control group (52.8%) than in G-CSF group (33%). Most common site of infection was blood followed by oral cavity.

Total duration of hospital stay: It was 21 days in G-CSF group (range 15-30) and 25 days in control group (range 17-44, p>0.05).

Limitations of the study

Since the study was conducted in small number of patients, larger study is needed in large number of patients to unravel the exact response of this drug in patients of chemotherapy induced neutropenia.

DISCUSSION

In our study patients were randomised (1:1) to be treated with either G-CSF or without this drug. One group was given G-CSF at dose of 5mg/kg/day one day after neutropenia in AML/ALL patients up to maximum of 7 days. Other group was kept as control. This study is similar to studies of Heil et al and Larson et al.

The total duration of neutropenia decreased in a series of de novo AML by Heil et al from 25 days (range 0-38) to 20 days (range 0-43). While in study of Larson et al median duration of neutropenia was 16 days in G-CSF group (interquartile range 15-18 days) and 22 days (interquartile range 19-29 days) in placebo group. While in our study it was 12 days (range 3-23) in G-CSF group and 17 days (range 6-26) in control group. The result was in accordance with the observations of Heil et al and Larson et al.

In study by Heil et al, the median duration of fever was 7 days in G-CSF group (range 0-38 days) and 8.5 days in control group (range 0-38). While Larson et al showed that median number of days with fever > 38.5°C was 3 days in G-CSF group (interquartile range 1-5) and 3 days in control group (interquartile range 2-7). In our study it was 9 days (range 0-19) for G-CSF group and 12 days (range 1-31) in control group which was more than of Heil et al and Larson et al. The difference in the duration of fever was probably attributed to the study center and difference in local factors such as environmental factors, different type of organisms.
causing infection etc.

The total duration of hospital stay in study by Heil et al\textsuperscript{8} was 23 days (range 2-104) in G-CSF group and 29 days in placebo group (range 7-93). Larson et al\textsuperscript{9} showed that median range of hospitalization in G-CSF patients was 22 days (interquartile range 18-29 days) and 28 days (interquartile range 22-33 days) in placebo group. In study of Carbonero et al\textsuperscript{10} median duration of hospital stay was 5 days in G-CSF group (95% confidence interval 5 to 5) and 7 days in control group (95% confidence interval 6 to 8). In series by Hartmann et al\textsuperscript{11} among patients who required hospitalization, the median number of days in hospital was 6 (range 2-21) in G-CSF group and 5 (range 4-23) in placebo group. While total duration of hospital stay was 21 days (range 15-30) and 25 days (range 17-44) in our study for G-CSF and control groups. The hospital stay in these patients were comparable with studies of Heil et al\textsuperscript{8} and Larson et al.\textsuperscript{9}

The nature and incidence of reported side effects were similar in both treatment groups for all phases of study. The most frequent side effect was rash. No other side effect was reported in G-CSF group.

**Summary And Conclusions**

A randomized comparative study was conducted to evaluate the efficacy of G-CSF in chemotherapy induced neutropenia in 30 patients of acute leukemia admitted in PGIMS, Rohtak. Mean duration of neutropenia was 11.4 days in G-CSF and 15.8 days in control group (p<0.05) mean duration of fever was 8.2 days in G-CSF group and 13.53 days in control group. Fever was observed in 93% of patients of G-CSF group and 100% in control group. Incidence of documented infection was 33% in G-CSF group and 52.8% in control group with majority being gram negative bacilli. Mean duration of hospital stay was 21.33 days in G-CSF group and 25 days in control group. The study demonstrates that G-CSF administration is efficacious in chemotherapy induced neutropenia by decreasing the duration of neutropenia and duration of fever. Since the study was carried out in small number of patients, larger study is needed in large number of patients to unravel the exact response of this drug in patients of chemotherapy induced neutropenia.

**References**