

## RESEARCH COMMUNICATION

# Outcome of Febrile Neutropenic Patients on Granulocyte Colony Stimulating Factor in a Tertiary Care Hospital

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### Abstract

**Introduction:** Febrile neutropenia is a relatively frequent event in cancer patients treated with chemotherapy and improvement in absolute neutrophil count (ANC) has been linked directly to improved outcome. Evaluation of granulocyte colony stimulating factors (GCSFs) for treatment has shown reduced incidences of episodes of prolonged neutropenia and protracted hospitalization. To determine absolute neutrophil counts with GCSF in febrile neutropenic cancer patients admitted to a tertiary care centre and to co-relate the improvement in ANC with mortality and hospital discharge. **Methods:** A prospective cross sectional study was carried at an oncology ward at Aga Khan University hospital from January 2010 to June 2011. All adult patients who were admitted and treated with GCSF for chemotherapy induced febrile neutropenia were included. Multivariable regression was conducted to identify the factors related with poor outcomes. **Results:** A total of 131 patients with febrile neutropenia were identified with mean age of 43.2 (18-85) years, 79 (60%) being  $\leq 50$ . Seventy-five (57%) had solid tumors and 56 (43%) hematological malignancies, including lymphoma. Fifty seven (43.5%) had an ANC less 100 cells/mm<sup>3</sup>, 34 (26%) one between 100-300 cells/mm<sup>3</sup> and 40 (31%) an ANC greater than 300 cells/mm<sup>3</sup>. Thirty (23%) patients showed ANC recovery in 1-3 days, and 74 (56%) within 4-7 days. Thirteen (10%) patients showed no recovery. The overall mortality was 18 (13.7%) patients. The mean time for ANC recovery seen in hematological malignancies was 6.34 days whereas for solid tumors it was 4.88 days. Patients with ANC <100 cells/mm<sup>3</sup> were more likely to die than patients with ANC >300 cells/mm<sup>3</sup> by a factor of 4.3. Similarly patients >50 years of age were 2.7 times more likely to die than younger patients. **Conclusion:** Our study demonstrated that use of GCSF, in addition to intravenous antibiotics, in treatment of patients with chemotherapy induced febrile neutropenia accelerates neutrophil recovery, and shortens antibiotic therapy and hospitalization. We propose to risk classify the patients at the time of admission to evaluate the cost effectiveness of this approach in a resource constrained setup.

**Keywords:** Febrile neutropenia - GCSF - absolute neutrophil count (ANC) - recovery time

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### Introduction

Febrile neutropenia is a relatively frequent event in cancer patients treated with chemotherapy. In the United States, an estimated 60,000 patients a year are hospitalized for febrile neutropenia and neutropenia related infections (Caggiano et al., 2005). Our single institution data in previous two studies have shown the frequency to be ranging from 10 to 12 per month (Lal et al., 2008; Shaikh et al., 2011).

Defined as "A single oral temperature  $\geq 38.0^{\circ}\text{C}$  for  $\geq 1$  hour with a neutrophil count of  $\leq 0.5 \times 10^9/\text{L}$  or a neutrophil count of  $\leq 1 \times 10^9/\text{L}$  which was predicted to fall below  $\leq 0.5 \times 10^9/\text{L}$  (Pettengell et al., 2011), febrile neutropenia is a potentially life threatening situation and requires prompt medical intervention. The availability of antibiotics have dramatically improved the outcome at the expense of increased cost (Kuderer et al., 2007) and hence

a substantial economic burden on patients and families (Carbonero et al., 2001).

Hemopoietic colony stimulating factors, such as G-CSF and GM-CSF have been shown to promote proliferation, differentiation and functions of progenitor and mature cells of myeloid lineage (Souza et al., 1986). These cytokines circulate bactericidal functions of mature neutrophil (Metcalf et al., 1990). When administered as a preventive adjunct to chemotherapy, CSF's have shown in clinical trials to shorten neutropenic period and reduce 50% incidences of Febrile Neutropenia in high risk patients (Crawford et al., 1991). Also the effect of G-CSF and GM-CSF in increasing the number of neutrophil has provided the background for clinical studies designed to assess their role as an adjunct therapy to antibiotics in febrile neutropenia (Clarke et al., 2005). The improvement in absolute neutrophil count has been linked directly to the improved outcome of patients with febrile neutropenia.

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Some studies have evaluated the role of CSF's in the treatment Febrile neutropenia (Maher et al., 1994; Riikonen et al., 1994; Mayordomo et al., 1995) and showed reduced incidences of episodes of prolonged Neutropenia and protracted hospitalization among cytokine treated patients but cost effectiveness of this approach for resource restricted settings is debatable. Therefore, we conducted this study to evaluate the role of G CSF in the treatment of patients with Febrile Neutropenia and to justify its use in resource constrained setting on the basis of evidence.

To determine the improvement of absolute neutrophil count with GCSF in Febrile Neutropenic cancer patients admitted to a tertiary care centre. To co-relate the improvement in ANC with the mortality and hospital discharge among patients who were administered Granulocyte colony stimulating factor and determine their outcomes based on recovery or mortality

## Materials and Methods

This is a prospective cross sectional study conducted from January 2010 to June 2011. All patients 18 years and above admitted with the diagnosis of chemotherapy induced neutropenic fever (Pettengell et al., 2011) under hematology and oncology services at The Aga Khan University Hospital (AKUH) were included. The AKUH is a renowned 560 bedded tertiary care center in Karachi, Pakistan The data set included the information on age, sex and types of cancers, WBC counts with differential counts at presentation, number of Chemotherapy cycles and days since last cycle. All patients were initially evaluated in the emergency room or clinic. A comprehensive history, physical examination, necessary laboratory and radiological investigations were done on all the patients. All febrile neutropenic patients were treated initially empirically with broad spectrum intravenous antibiotics and Granulocyte colony stimulating factors (G CSF) at dose of 5 micrograms/kg subcutaneously. Empiric antibiotics were modified later based on culture results However, for decision of vancomycin and amphotericin B was based on established guidelines for the management of febrile neutropenia (Carbonero et al., 2001). All patients were managed in the oncology unit while neutropenic septic shock patients were managed in intensive care unit. Treatment with GCSF was discontinued as soon as ANC rose above 1500 cells/mm<sup>3</sup>. Blood products were transfused as per requirement of individual patient.

### Study Variable

Study outcome, death / discharged.

### Independent variables

Age was collected as continuous later categorized as <50 and >50 years. Similarly ANC at presentation was also collected as continuous, later arbitrary cutoff was created based on the presentation of data as less than 100cells/mm<sup>3</sup>, between 100-300 cells/mm<sup>3</sup> and more than 300cells/mm<sup>3</sup>

### Statistical analysis

Data are summarized as relative frequencies for

categorical variables and mean (SD) for normally distributed continuous variables. Comparisons between groups were performed using Student t test and Pearson Chi-square according to the variables type and distribution. To explore the relationship between use of GCSF and outcome (death and discharged), logistic regression model was employed with adjustment for potential confounders. Significance level was established as a two tailed p-Value  $\leq 0.05$ . Calculations were made with SPSS 17.0, Chicago, U.S.A.

## Results

### Patients

Total of 131 patients with febrile neutropenia identified during the study period. The mean age was 43.2 (18-85) years. There were slightly more patients 79 (60%) who were <50 years of age. There was almost equal gender distribution with 66 males and 65 females. Only 36 patients had other co-morbidities related to health like diabetes mellitus, chronic obstructive pulmonary disease, or congestive cardiac failure.

There were 75 (57%) patients with solid tumors and 56 (43%) with hematological malignancies including lymphoma. More patients 86 (66%) were receiving the curative treatment in adjuvant setting while remaining received the palliative treatment. The demographics of the study patients is shown in the Table 1.

### ANC recovery

The patients who had recovered and were discharged had mean ANC of 282 cells/mm<sup>3</sup> at presentation, whereas patients who died had mean ANC of 127 cells/mm<sup>3</sup> (P value 0.001). There were 57 (43.5%) patients with ANC less 100 cells/mm<sup>3</sup>, 34 (26%) between 100-300 cells/mm<sup>3</sup>

**Table 1. Baseline Demographic and Clinical Characteristics of Patients Receiving GCSF**

Characteristics	No. of Patients
Median age, years (Range)	43.3 years (18-85)
Sex, Male/Female	66/65
Types of cancer (%) merge as discussed:	
<b>HEMATOLOGICAL MALIGNANCIES</b>	
a. Lymphoma	36 (27.5%)
b. Leukemia	20 (15.3%)
<b>SOLID TUMOUR</b>	
a. Sarcoma	21 (16%)
b. Head & Neck	09 (6.9%)
c. Lung	07 (5.3%)
d. Breast	15 (11.5%)
e. Genitourinary	15 (11.5%)
f. Gastrointestinal	08 (6.1%)
Chemotherapy given with	
Curative/Palliative intent	86/45
Median WBC at presentation	700/mm <sup>3</sup> (100-3100)
Median ANC at presentation	119/mm <sup>3</sup> (0-1000)
ANC <100/mm <sup>3</sup> , No.(%)	58 (44.2%)
ANC b/w 100-500/mm <sup>3</sup> , No.(%)	55 (41.9%)
ANC b/w 500-1000/mm <sup>3</sup> , No.(%)	18 (13.7%)
Median Monocyte at Presentation	70 (0-1100)
Median No. of Days since last cycle, No.(Range)	10 (1-51)
Median No. of previous cycle, No.(Range)	2 (1-15)

and 40 (30.5%) greater than 300 cells/mm<sup>3</sup>. Thirty(23%) patients showed ANC recovery in 1-3 days, while 74 (56%) patients had ANC recovery in 4-7 days. Fourteen (10.6%) had ANC recovery in more than 7 days. Thirteen (10%) patients showed no recovery in ANC counts. The overall mortality resulted in 18 (13.7%) patients. The mean time for ANC recovery seen in hematological malignancies was 6.34 day. Whereas, mean time for ANC recovery seen in solid tumors was 4.88 days.

Mean monocyte at presentation was 190 cells/mm<sup>3</sup> in patients who were discharged and 39 cell/mm<sup>3</sup> in patients who died during hospital stay (P value = 0.00) Table 2.

One hundred & thirteen (86%) patients had recovered from febrile neutropenia and were discharged from hospital out of which 101 (78%) patients had hospital course of less than 7 days.

There were 57 patients with ANC less 100 cells/mm<sup>3</sup> of

**Table 2. Crude Unadjusted Odds Ratios for Predictor of Poor Outcome in Patients Admitted with Febrile Neutropenia.**

Variable	Discharged	Death	P-value	Un-adjusted Odds Ratios	95% CI
Age (years)					
>50	48 (42.5)	4 (22.2)	1		
≤ 50	65 (57.5)	14 (77.8)	0.1	0.38	0.12-1.2
Gender					
Male	55 (48.7)	11 (61.1)	1		
Female	58 (51.3)	7 (38.9)	0.32	0.6	0.2-1.6
Types Of Cancer					
Solid	66 (58.4)	9 (50)	1		
Hematological	47 (41.6)	9 (50)	0.5	0.7	0.2-1.9
ANC At Presentation	283 (29.4)	127 (30.4)	0.001	1.1	1.0-1.1
ANC At Presentation					
>300	38 (33.6)	2 (11)	1		
<100	47 (41.6)	10 (55.6)	0.07	4.1	1.1-19.5
100 - 300	28 (24.8)	6 (33.3)	4		1.3-21.6
Co Morbidities					
No	82 (72.6)	13 (72.2)	1		
Yes	31 (27.4)	5 (27.8)	0.97	0.98	0.3-2.9
Intent Of Treatment					
Curative	77 (68)	9 (50)	1		
Palliative	36 (31.9)	9 (50)	0.13	0.46	0.1-1.2
Monocyte At Presentation	190 (26.1)	39 (12.1)	0	1.1	1.1-1.2
Days To ANC Recovery					
No Recovery	1 (0.9)	12 (66.7)	--		
1-3 Days	30 (26.5)	0	0	--	
4-7	70 (61.9)	4 (22.2)	--		
Beyond 7 Days	12 (10.6)	2 (11.1)	--		

**Table 3. Multivariable Analysis Along with Adjusted Odds Ratios and 95% CI for Predictor of Poor Outcome in Patients Admitted with Febrile Neutropenia**

Variables	Odds Ratios (Adjusted)	95% CI	P-value
Monocyte At Presentation			
>300	1		
<100	4.3	1.2-21	0.05
100 - 300	4	1.1-22	
Age (years)			
>50	1		
≤ 50	2.7	2.8-9.1	0.04

which 47 patients were discharged and 39 had hospital stay less than 7 days. Thirty four patients had ANC between 100-300 cells/mm<sup>3</sup> of which 28 were discharged. Forty patients had ANC greater than 300 cells/mm<sup>3</sup> of which 38 were discharged.

### Multivariable regression

Our multivariable analysis Table 3 shows that, odds of ANC at presentation <100 cells/mm<sup>3</sup> are 4.3 times more likely to die compare to those with ANC >300 cells/mm<sup>3</sup>. Similarly patients with ANC 100-300 cells/mm<sup>3</sup> are 4 times more likely to die, adjusting for all other variables. Similarly, after adjusting for other covariates the effects of age suggests that those with greater than 50 years are 2.7 times more likely to die as compare to those with age less than 50 years (Table 3).

### Discussion

Our study demonstrated that the age was a predictor of poor outcome in patients admitted with febrile neutropenia. Patients younger than 50 years of age gained more benefit in primary endpoints from routine use of GCSF as compared to older patients by factor of 2.7.

Patients older than 50 years of age had more co morbidities which also were associated with higher mortality or worse outcomes as previously studied (Kuderer et al., 2006). Also, the ANC of less than 100 was associated with the worst outcome. Our study population was heterogeneous as far as diagnoses and treatments were considered. Most of our patients were younger than 50 years (60%) and this population of patients had a better outcome. The gender distribution was equal in the study group, but mortality had a slight male predominance. The overall mortality was 13.7% which is comparable from international studies (Berghmans et al., 2002)

Use of GCSF did improve the outcome in older patients and assumed to decrease the mean duration of hospital stay. However, it remained debatable whether this was a cost effective strategy or not especially when 34% of our study patients received chemotherapy for metastatic disease. Monocytopenia at presentation has been shown to be associated with worse outcomes in the literature (Rankoff et al., 1996). Monocytopenia is linked with bacteremia in children with febrile neutropenia (Rankoff et al., 1996) and monocytopenia after chemotherapy is correlated neutropenia while monocytosis indicates neutrophil recovery (Oguz et al., 2006). This was seen in our study as well, as in present study there was a trend towards significantly better outcomes in patients with high monocyte count at presentation. Hence, for a resource constrained setup, this simple parameter can be followed at presentation in addition to other variables to predict the course of the patient and GCSF can be avoided in patients with good monocyte count. Majority of patients had ANC recovery in 3 to 7 days. Mean ANC recovery in Solid tumours was slightly better than hematological malignancies probably because bone marrow takes longer time to recover in treatment of acute leukemias and even in lymphomas. Similar recovery patterns were observed in (Maher et al., 1997; Carbonero et al., 2001) studies.

However when compared with (Ghault et al., 2008), the ANC recovery in hematological malignancies seen in our patients were significantly better.

Delayed ANC recovery was associated with longer periods of hospitalization which not only increases the cost but also adversely affect the outcome. In our study 14 (10.6%) patients took longer than 7 days for ANC to recover and hence had longer hospital stay. These results suggested that age, ANC and monocytes at presentation and types of malignancy were independent indicators of patients outcome. We observed that younger patients who received GCSF recovered and were discharged home, similarly older patients with better ANC and higher monocytes at presentations also recovered quickly. A study previously done at our institution showed that hematological malignancies, age above 50 years, severity of dehydration, pneumonia and positive blood cultures were significantly associated with increase in length of hospital stay and mortality, but the study did not mention whether the study subjects received G-CSF or not (Lal et al., 2008). In another study, independent indicators like ECOG  $\geq 2$ , chronic obstructive airway disease, chronic heart failure, stomatitis grade  $\geq 2$ , monocytes  $<200\text{mm}^3$  and hyperglycemia have been studied for prognostic evaluation in apparently stable patients with febrile neutropenia. These simple assessments can classify cancer patients with febrile neutropenia according to risk of complication (Carmonera-Bayonas et al., 2011).

GCSF treatment offers substantial potential for saving lives of hospitalized patients with established neutropenia over a wide range of model assumption and our study showed the similar results (Cosler et al., 2007). Our study results though very pertinent but cannot be generalized as this was a single centre cross sectional study. It revealed that delayed ANC recovery prolonged the hospitalization and adversely affects the outcome. We have seen the benefit of GCSF in our patients despite the minimal benefit of GCSF in established febrile neutropenic patients in the reported literature. (Maher et al., 1997; Carbonero et al., 2001). Therefore, we suggest using GCSF in febrile neutropenia for every patient admitted to hospital. The (Carbonero et al., 2001) model can be incorporated in the initial assessment of patients along with the monocyte count at presentation for considering the decision for GCSF for high risk patients where cost is the major limiting factor.

In conclusion, our study demonstrates that use of G-CSF, in addition to intravenous antibiotics, in treatment of patients with chemotherapy induced Febrile Neutropenia accelerates neutrophil recovery, shortens antibiotic therapy and hospitalization. We propose to risk classify the patients at the time of admission to evaluate the cost effectiveness of this approach in resource constrained setup.

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