ROLE OF GRANULOCYTE- COLONY STIMULATING FACTOR (G-CSF) IN FEBRILE NEUTROPENIA AMONG PEDIATRIC CANCER PATIENTS IN RESOURCE-LIMITED SETTINGS

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ARTICLE INFO

ORIGINAL ARTICLE

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Vol: 3 | Issue: 4
ISSN Print: 2960-2580
ISSN Online: 2960-2599

Publisher:
Medical Research and Statistical Consultancy Training Centre (SMC-PRIVATE) Limited
CONTRIBUTION
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Keywords:
Chemotherapy-induced febrile neutropenia; Granulocyte-colony stimulating factor; Pediatric oncology; Resource-limited settings; Hospital stay; Solid malignancies

ABSTRACT

Background: Chemotherapy induced Febrile neutropenia (FN) is a potentially catastrophic complication in childhood cancer, requiring urgent management and hospitalization, with a heightened risk of mortality. Granulocyte- colony stimulating factors (G-CSFs) are used both prophylactically to decrease FN episodes and therapeutically during febrile neutropenia. However, evidence supporting their role in resource-limited settings remains scarce. **Objectives:** To evaluate the effect of granulocyte colony-stimulating factor on hospital stay duration, treatment cost, and mortality among children suffering from febrile neutropenia. **Methodology:** This prospective cohort study enrolled 250 children with chemotherapy-induced FN at the Children's Hospital Lahore (CHL) from September 2018 to December 2018. Patients received G-CSF (filgrastim, 10 mcg/kg/day for five days or until ANC >1000 for two consecutive days), primarily in the solid malignancy group. Clinical characteristics, neutrophil counts, hospital stay, treatment costs, and outcomes were recorded. Data were analyzed using SPSS 23. **Results:** G-CSF significantly reduced hospital stay ($p = 0.048$) and was administered more frequently in cases of severe neutropenia (ANC $< 100x10^3/\mu L$ in 82% of cases, $p = 0.000$). Mortality in the G-CSF group was 3%, though not statistically significant ($p = 0.147$). Clinically, G-CSF facilitated better hematological recovery in solid malignancies and proved cost-effective ($p = 0.027$).

Conclusion: G-CSF demonstrated superior clinical efficacy compared to intravenous antibiotics alone by reducing hospital stay and neutropenia severity, without imposing a substantial cost burden. These findings support G-CSF as a desirable FN management strategy, even in low-resource pediatric oncology centers.

INTRODUCTION

Children with cancer are predisposed to infections, usually presented as fever and neutropenia (FN), resulting from chemotherapy-induced immune suppression. FN episodes, being the most common cause for Emergency Department (ED) visits among childhood cancer patients and is the reason most strongly linked with hospital admission[1]. Febrile neutropenia is defined as under the arm (axillary) temperature of 99.9°F (37.7°C) or an under the arm temperature of 99.4°F (37.4°C) or higher that lasts for one hour, and concurrent absolute neutrophil count (ANC) of (ANC) of <500 cells/m [3]. Primary G-CSF prophylaxis is advised for chemotherapy regimens causing FN at rates more than 20% [2]. Prophylactic use of G-CSF markedly reduces both episodes of FN and length of hospital stay. Not only is prophylactic G-CSF recommended for patients on chemotherapy regimens to decrease the risk of developing neutropenia by inducing patients' own production of WBCs, but also effectively resulted in decreased neutropenic side effects of intensive chemotherapy protocols [3].

Neutropenia is the most frequent side effect of chemotherapy medicines, and its most marked complication is febrile neutropenia. It is linked with increased frequency of hospital admissions and increased risk of mortality. Prophylaxis with the use of G-CSF, a powerful therapeutic agent, can reduce the risk of neutropenia and its complications and enhance tolerance to chemotherapy. Timely management of febrile neutropenia is crucial in the treatment of patients with cancer [4]. These FN episodes can result in chemotherapy discontinuations, delays or medicine reductions, that may impact quality of life of patients and subsequent survival outcomes [5].

GCSF accelerates neutrophil recovery, decreases length of hospital stay (LOS), and lower infection-related complications [6, 7]. In several regional guidelines, G-CSF use in patients with chemotherapy-induced FN episodes is recommended for high-risk non-myeloid malignancies, enabling them to receive safely scheduled chemotherapy doses [8,9,10,11]. G-CSFs in the form of filgrastim, pegfilgrastim, and biosimilars, reduce incidence and duration of severe neutropenia and are widely used as primary or secondary prophylaxis, especially with high FN-risk regimens or prior FN. This study seeks to address a critical knowledge gap by evaluating the impact of G-CSF on hospital stay (LOS) and mortality among children suffering from chemotherapy-induced FN episodes admitted to tertiary care pediatric center in Lahore. By systematically assessing these parameters, the study aims to generate evidence that can inform the development of institutional febrile neutropenia (FN) management guidelines tailored to resource-limited environment. Eventually, the results are expected to support optimized, evidence-based care for pediatric patients with solid malignancies, ensuring careful use of G-CSF and ameliorating clinical parameters.

MATERIALS and METHODS:

Study Design: The study was done as a prospective observational cohort design.

Settings: Paediatric Haematology/ Oncology unit, the Children's Hospital Lahore (CHL), Pakistan

Duration: This was done from 1st September 2018 to 31st December 2018

Sampling Technique: The sampling was done by probability method and data collection was done from patient files, admitted in the inpatient ward with the diagnosis of febrile neutropenia during this study period.

Sample Size: A total of 250 pediatric cancer patients having febrile neutropenia and were admitted in the inpatient unit.

Inclusion Criteria:

- Children of ages from 1-18 years old receive first-line chemotherapy for either haematological or
- Solid malignancies, diagnosed with febrile neutropenia and admitted in the inpatients unit and started treatment for FN.

Exclusion Criteria:

- Children with relapses or progressive disease and on palliative care
- Children receiving stem cell transplantation
- Children with benign blood disorders

Data Collection Procedure: Data collection was done after the Institutional Review Board. Performas were filled for patients of hematological and solid malignancies, admitted with FN and completed when they discharged or expired from the event. The data collected for the demographics, clinical and laboratory parameters, number and days of antimicrobial, G-CSF used in a daily dose of 10 mcg/kg/day, cost of therapies and hospital stay (LOS). Data analysis was done by SPSS 23.

AI Use: We acknowledge the use of AI using Microsoft Copilot (https://copilot.microsoft.com/chats/6zdHUjj2irCphNaziBigq) to identify study limitations and strengths and refine my study conclusion which helped me to structure the study interpretations.

RESULTS

Patient Characteristics: A total of 250 children (147 males, 103 females), with mean age in years of 6.27 were included in this study. Seventy-five (30%) were given GCSF during the FN episode, majority of them diagnosed with solid malignancies (n=105) like sarcoma, lymphoma, Wilms tumor and neuroblastoma. Their laboratory parameters showed markedly reduced WBC counts with 61% had WBC $<1 \times 10^3$/ uL; mean WBC was 1.46, median 1.0. Mucositis was commonly present in (81%) patients.

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Neutrophil recovery was marked with significant improvement in ANC with GCSF use (p=0.000). Hospital duration (LOS) was shorter in GCSF group (p=0.048), though overall outcome did not show statistically significant difference in mortality (p=0.147). The cost of treatment analysis showed GCSF use is cost-effective with a p-value of 0.027, and secondly reduced hospital stay may offset expenses incurred in the long term.

Table 1: Laboratory and Clinical Characteristics

Parameter	Category	N	Percentage	
White Blood Cell Count (WBC)	**<1 x 10^3 / uL**	151	61%	Mean WBC: 1.46 Median WBC: 1.00
	1-3 x 10^3 / uL	81	32%	
	>3 x 10^3 / uL	18	7%	
Absolute Neutrophil Count (ANC)	**<100/mm^3**	149	61%	
	100-300/mm^3	101	39%	
Mucositis	**Present**	201	81%	
	Absent	48	19%	
GCSF Use and type of infection	**Respiratory Tract Infection**	26	35%	p-value: 0.008
	Acute gastroenteritis	21	28%	
	Fever alone and others	28	37%	
GCSF	**Given**	75	30%	GCSF use and outcome p-value:**0.147**
	Not given	175	70%	
Type of Malignancies GCSF used	**ALL**	4/145	0.03%	p-value: **0.000**
	Sarcoma	31/41	76%	
	Lymphoma	16/25	64%	
	Wilms tumor	4/12	33%	
	Neuroblastoma	8/13	62%	
	Others	12/14	86%	
	Total Solid tumor	71/105	68%	

Table 2: Benefits of GCSF use in Solid Malignancies cases presenting with FN

Parameter	GCSF given	GCSF not given	Total	p-value
Absolute neutrophil Count (ANC) and GCSF use				

ANC <100	61	88	149	**0.000**
ANC 100-500	14	84	98	
ANC >500	0	3	3	
Total	75	175	175	
Type of malignancies and GCSF use				
ALL patients	**4**	**140**	**145**	**0.000**
Solid Tumors	**71**	**34**	**105**	
Hospital Stay and GCSF use				
1 day	**0**	**5**	**5**	**0.048**
1-3 days	**13**	**19**	**32**	
3-5 days	**16**	**64**	**80**	
>5days	**46**	**87**	**133**	
Total	**75**	**150**	**250**	

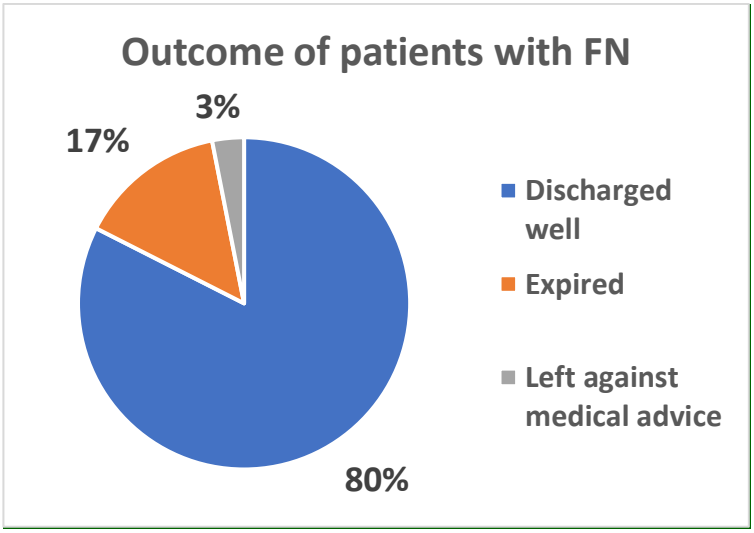

Figure 1: Outcome of FN patients

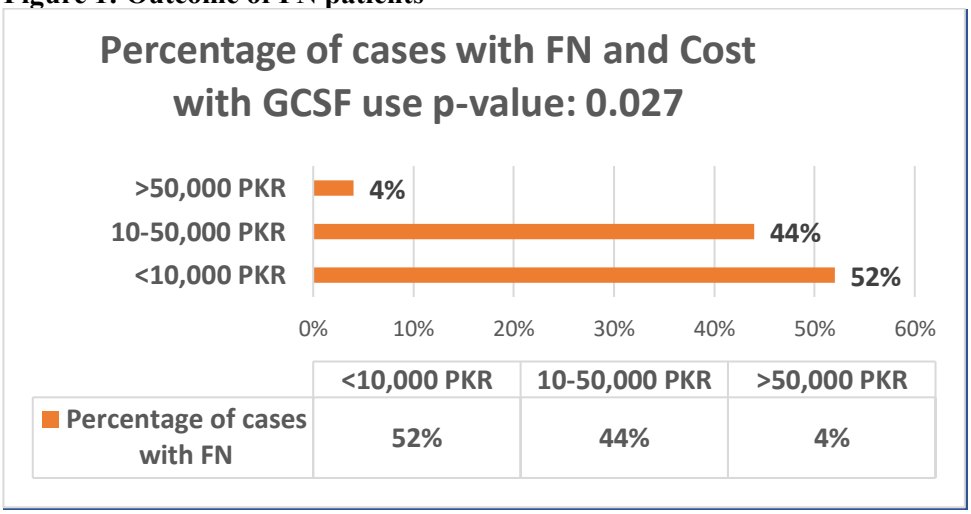

Figure 2: Cost of FN treatment with GCSF Group

DISCUSSION

Febrile Neutropenia remains a life-threatening complication of chemotherapy in children, particularly in LMICs where mortality rates are higher due to limited supportive care compounded by inadequate health literacy, late treatment-seeking behavior and paucity of shared care services [12]. In our study, 61% of patients had WBC <1 × 10^3/uL and 81% had mucositis, emphasizing the vulnerability of pediatric oncology patients. These results are compatible with global reports that FN affects up to 40% of children receiving chemotherapy. There was a significant association between GCSF use and improved neutrophil recovery (p=0.000). Patients receiving GCSF had faster recovery of absolute neutrophil count (ANC), reducing the duration of profound neutropenia (<100x10^3/μL). This finding is compatible with international evidence that filgrastim accelerates marrow recovery and reduces infection-related complications [6]. Only 30% of patients in our study received GCSF, reflecting reduced access in resource-limited settings. Our data show that GCSF use was disproportionately higher in solid tumors (68%) compared to hematological malignancies such as ALL (0.03%). This selective use mirrors clinical practice where GCSF is reserved for regimens with higher myelosuppressive potential[2].

ASCO Guideline for the management of fever and neutropenia in children with cancer recommend GCSF for high-risk FN episodes rather than routine use [11]. The major barrier to widespread GCSF use remains cost. While upfront expenses are high, studies from Pakistan demonstrate that reduced hospitalization and fewer complications may offset costs in the long term [12]. There was a common perception of G-CSF being expensive medicine, preferably to be used for high-risk FN patients having recurrent episodes, but now with availability of cost-effective biosimilar brands, this is being challenged even in high-income countries. Cost-effectiveness analyses suggest that targeted GCSF use in high-risk patients is economically viable even in resource-limited settings [13]. In our study, hospital stays categories showed shorter hospital stay (groups of 1 day, 1–3 days, 3–5 days, >5 days) for GCSF vs. non-GCSF groups, with the significant p-value (0.048). In one of the studies done in Germany, G-CSF prophylaxis costs were argued showing majority of physicians stated that the costs did not play a key role for their decision on starting G-CSF prophylaxis, whereas lesser number declared they did not prescribe G-CSF due to high costs [10].

The overall mortality outcome was not statistically significant in the G-CSF group, but several studies have demonstrated improved survival outcomes with the use of pegfilgrastim along with decreased incidence of FN and hospitalizations in cancer patients [14, 15,] though require larger multicenter studies to explore the pegfilgrastim role in reducing the FN mortality rate [16].

Despite being prospective in design, this study has several limitations that warrant consideration: The study was observational rather than a randomized controlled trial, which may introduce potential biases and limit

causal inference. G-CSF was administered almost exclusively in children with solid malignancies with a few patients with acute lymphoblastic leukemia (ALL) were included, and chemotherapy risk stratification within solid malignancies may have influenced the outcomes. The study was conducted at a single center, with results not fully representative of broader populations or diverse healthcare environments. The modest cohort size reduces the statistical power to find survival benefits and reduces results extrapolation to bigger populations.

The study was conducted prospectively, allowing systematic data collection and reducing recall bias. By evaluating children with chemotherapy-induced febrile neutropenia, the study explores a vulnerable group often underrepresented in clinical research. While conducted in a tertiary care pediatric center in Lahore, the study reflects practical barriers and outcomes in a low-resource environment. The study provides valuable insights into the use of G-CSF in pediatric solid tumors. Study findings contribute directly to the formulation of institutional febrile neutropenia management guidelines, supporting evidence-based decision-making, resulting in better patient care.

CONCLUSION

G-CSF use demonstrated superior clinical efficacy compared to intravenous antibiotics alone. Specifically, G-CSF therapy resulted in a shorter hospital stay and reduced severity of neutropenia, without imposing a significant cost burden. These findings suggest that G-CSF represents a more desirable and pragmatic approach to the management of febrile neutropenia (FN), particularly in low-resource oncology centers, where optimizing both clinical outcomes and healthcare costs is critical.

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