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Granulocyte Colony-Stimulating Factor (Filgrastim) for the Prevention and Management of Chemotherapy-Induced Febrile Neutropenia in Children

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ABSTRACT

Background: Febrile neutropenia (FN) is a serious complication of cytotoxic chemotherapy, marked by fever and critically low absolute neutrophil counts, leading to heightened infection risks, morbidity, and treatment interruptions. FN affects up to 40% of patients on standard chemotherapy and is particularly common in regimens for hematologic cancers and solid tumor. Granulocyte colony-stimulating factors (G-CSFs), such as filgrastim, help restore neutrophil counts by stimulating bone marrow activity. Filgrastim reduces the duration and severity of neutropenia, improving treatment continuity. Despite newer agents like pegfilgrastim, filgrastim remains widely used, especially in low-resource settings, though its dosing and side effects require careful management.

Aim of the study: This study aims to evaluate the clinical utility of filgrastim in managing chemotherapy-induced FN, focusing on its effectiveness in neutrophil recovery, reduction of hospitalization duration, and overall patient outcomes.

Methods: This prospective observational study was conducted at the Pediatric Hematology and Oncology Department of BSMMU in Dhaka, Bangladesh, enrolling 135 children with chemotherapy-induced febrile neutropenia (FN) during 1.5 years, from January 2023 to July 2024. Inclusion required confirmed malignancy, recent chemotherapy, and FN diagnosis, while exclusions included prophylactic G-CSF use and bone marrow failure. Data were collected using a structured form covering demographics, clinical details, chemotherapy regimen, FN onset, and Filgrastim administration (5 µg/kg/day subcutaneously). Outcomes included ANC recovery, fever resolution, hospital stay, ICU need, mortality, and FN recurrence. Data were analyzed using SPSS v26.0 with descriptive statistics.

Results: Among 135 patients with chemotherapy-induced febrile neutropenia, the mean age was 16.2

years, with 76 males. ALL (Acute Lymphoblastic Leukemia) 48.14%, AML (Acute Myeloid Leukemia)14.81%, NHL (Non-Hodgkin Lymphoma)14.07%, Ewing's Sarcoma (3.70%), Rhabdomyosarcoma (2.96%), Hodgkin Lymphoma (8.14%), Hepatoblastoma (4.44%), Others (3.70%). FN occurred mainly during the 2nd or 3rd chemotherapy cycle, predominantly with platinum-based regimens. Filgrastim was initiated within 1.2 days of FN onset and continued for 5.6 days. The average ANC recovery time was 4.8 days, and the fever resolved in 2.9 days. Bone pain occurred in 16% of patients. Hospital stay averaged 6.2 days, with a 96% recovery rate, 8% ICU admission, 4% mortality, and 16% FN recurrence in later cycles.

Conclusion: Filgrastim effectively reduced the duration of neutropenia, fever, and hospitalization in children with chemotherapy-induced febrile neutropenia. It was well-tolerated with minimal side effects and high recovery rates. These results support its use as a safe and beneficial adjunct in pediatric oncology for managing febrile neutropenia in resource-limited settings.

Keywords: Febrile Neutropenia, Chemotherapy Complications, Filgrastim and Granulocyte Colony-Stimulating Factor (G-CSF).

INTRODUCTION

Febrile neutropenia (FN) is a life-threatening complication frequently observed in patients undergoing cytotoxic chemotherapy. It is characterized by a significant decrease in the absolute neutrophil count (ANC) coupled with fever, typically defined as an oral temperature ≥38.3°C once or ≥38.0°C sustained over an hour, and an ANC of <500 cells/mm³ or an expected decline to this level within 48 hours [1]. FN is considered a medical emergency due to the increased risk of severe infections, morbidity, prolonged hospitalizations, and treatment delays or dose reductions that may compromise cancer outcomes [2,3]. The pathogenesis of FN stems from myelosuppression caused by cytotoxic agents, particularly in regimens used to treat hematologic malignancies and lymphoma and Solid Tumor This suppression leads to a compromised immune system, allowing endogenous or opportunistic infections to flourish [4]. As the intensity and efficacy of chemotherapeutic regimens increase, so too does the risk of FN. Clinical trials have shown that FN can occur in up to 25–40% of patients receiving standard-dose chemotherapy, and even higher rates have been reported in high-risk populations [5]. To mitigate this risk, granulocyte colony-stimulating factors (G-CSFs) such as filgrastim have been developed to stimulate the production, maturation, and activation of neutrophils in the bone marrow. Filgrastim is a recombinant human G-CSF that has been extensively studied and widely adopted in clinical practice. It binds to specific cell surface receptors on hematopoietic progenitor cells, leading to increased proliferation and differentiation into neutrophils, thereby reducing the duration and severity of neutropenia [6,7]. Prophylactic or therapeutic administration of filgrastim has demonstrated significant benefits in reducing the incidence of FN, lowering the risk of infection-related mortality, and enabling patients to maintain the planned dose intensity of chemotherapy [8]. Guidelines from the American Society of Clinical Oncology (ASCO), the European Organisation for Research and Treatment of Cancer (EORTC), and the National Comprehensive Cancer Network (NCCN) recommend the use of G-CSFs in patients receiving chemotherapy regimens associated with a ≥20% risk of FN, or in selected patients with intermediate risk based on age, comorbidities, and disease burden [9–11]. Despite its widespread use, the optimal timing, duration, and dosing of filgrastim remain subjects of ongoing research. While daily filgrastim is effective, long-acting alternatives such as pegfilgrastim offer the convenience of a single dose per chemotherapy cycle, leading to better patient compliance and possibly improved outcomes [12]. However, cost considerations and accessibility in low- and middle-income countries often make filgrastim the more feasible option. Moreover, side effects such as bone pain, splenomegaly, and rare but severe events like acute respiratory distress syndrome and leukocytosis necessitate cautious and judicious use [13]. This study aims to evaluate the clinical utility of filgrastim in managing chemotherapy-induced FN, focusing on its effectiveness in neutrophil recovery, reduction

of hospitalization duration, and overall patient outcomes.

METHODOLOGY & MATERIALS

This prospective observational study was conducted over a period of 1.5 years, from January 2023 to July 2024, in the Department of Pediatric Hematology and Oncology at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. The study aimed to evaluate the clinical profile, therapeutic outcome, and safety of Filgrastim in pediatric patients who developed febrile neutropenia (FN) following chemotherapy. A total of 135 children, aged under 18 years, who developed chemotherapy-induced febrile neutropenia were enrolled consecutively based on predefined inclusion and exclusion criteria. All participants were undergoing chemotherapy for solid tumors or hematological malignancies.

Inclusion Criteria:

- Children aged 1 to 18 years.
- Diagnosed with a solid or hematologic malignancy and receiving chemotherapy.
- Developed febrile neutropenia, defined as:
    - Oral temperature >38.3°C once or >38.0°C sustained for over 1 hour, and
    - Absolute neutrophil count (ANC) <500 cells/µL or an anticipated decline to <500 cells/µL within 48 hours.
- Received Filgrastim therapy after onset of FN.

Exclusion Criteria:

- Received prophylactic G-CSF before the FN episode.
- Known hypersensitivity to Filgrastim or related compounds.
- Diagnosed with bone marrow failure syndromes or primary hematologic diseases not receiving chemotherapy.

A structured and pretested data collection sheet was employed to gather relevant clinical and demographic information for each participant systematically. Sociodemographic variables included age and sex. Clinical data encompassed the type and stage of malignancy, Eastern Cooperative Oncology Group (ECOG) performance status, details of the chemotherapy regimen (including drug type and number of cycles completed), and the presence of comorbidities such as diabetes, hypertension, or chronic infections. Febrile neutropenia-specific parameters included the time of onset relative to chemotherapy, duration of fever, highest recorded body temperature, absolute neutrophil count (ANC) at presentation, results of microbiological cultures (blood, urine, sputum), and clinically or radiologically identified sites of infection. Data on Filgrastim therapy covered the total daily dose administered (5µg/kg/day), the number of days of treatment, the time from FN onset to G-CSF initiation, and any observed adverse drug reactions (e.g., bone pain, hypersensitivity). Treatment outcomes were meticulously recorded, including time to ANC recovery (defined as >1500 cells/µL for two consecutive days), resolution of fever, total duration of hospital stay, need for intensive care unit (ICU) admission, in-hospital mortality, and recurrence of febrile neutropenia during subsequent chemotherapy cycles. This comprehensive data collection enabled a robust analysis of the efficacy and safety profile of Filgrastim in real-world clinical practice. All patients received subcutaneous Filgrastim (5 µg/kg/day) starting within 1–2 days of FN onset, continued until ANC recovery (>1500/µL for two consecutive days). Antibiotics and supportive care were administered according to institutional FN management protocols.

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using SPSS version 26.0. Descriptive statistics were used to summarize sociodemographic data and clinical characteristics. Categorical variables were expressed as frequencies and percentages, while continuous variables were expressed as mean±standard deviation (SD). No inferential statistics were used due to the study's small sample size and observational nature.

RESULTS

The study evaluated 135 Bangladeshi children under 18 years undergoing chemotherapy and receiving Filgrastim for febrile neutropenia (FN). The average age was 10.6±3.5 years, with a slight male predominance (53.3%) (Table 1). ALL (Acute Lymphoblastic Leukemia) 48.14%, AML (Acute Myeloid Leukemia) 14.81%, NHL (Non-Hodgkin Lymphoma) 14.07 %, Ewing's Sarcoma (3.70%), Rhabdomyosarcoma (2.96%) Hodgkin Lymphoma (8.14%), Hepatoblastoma (4.44%), Others (3.70%), while most patients presented with advanced cancer stages Stage III (41.9%) and Stage IV (33.3%). A significant proportion (59.0%) had good performance status (ECOG 0–1), and 22.9% had comorbidities. Regarding treatment and FN events (Table 2), platinum-based regimens were most frequently used (40.0%), and FN occurred on average during the third cycle of chemotherapy (2.7±1.3). Over one-third (35.2%) had a prior history of FN. The mean temperature at FN onset was 38.8°C, and the average ANC was critically low (0.39 × 10⁹/L). Blood cultures were positive in 39.0% of cases, with respiratory tract infections being the most common documented site (19.0%). Filgrastim was typically initiated within 1.2±0.6 days of FN onset (Table 3), at an average dose of 5.3 µg/kg/day. Most patients received it subcutaneously (79.0%), with a treatment duration averaging 5.8 days. Dose adjustments were needed in 10.5% of patients. Notably, adverse effects were rare; only 8.6% experienced bone pain. Clinical outcomes were favorable (Table 4), with ANC recovery achieved in 4.6±1.1 days and fever resolution in under 3 days. The average hospital stay was 6.7 days. ICU admission was necessary for 7.6% of patients, and the mortality rate was low at 2.9%. Overall recovery was high (97.1%), though FN recurred in 16.2% during subsequent cycles.

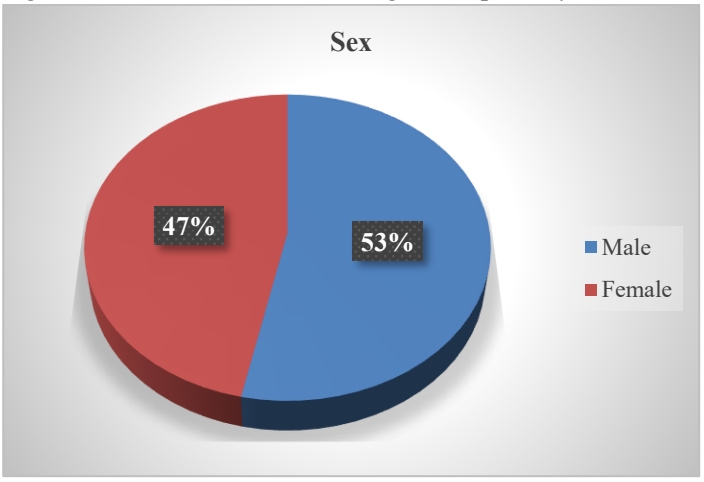

Fig-1: Sex distribution of the study patients.

Table 1: Baseline Characteristics of the Study Population (n =135)

Variable	Frequency (n)	Percentage (%)
Age (mean ± SD)	10.6 ± 3.5 years	
Sex		
Male	76	56.29
Female	59	43.70
Cancer Type		
(ALL) Acute Lymphoblastic Leukemia	65	48.14

AML (Acute Myeloid Leukemia)	20	14.81
NHL (Non-Hodgkin Lymphoma)	19	14.07
Ewing's Sarcoma	05	3.70
Rhabdomyosarcoma	04	2.96
Hodgkin Lymphoma	11	8.14
Hepatoblastoma	06	4.44
Others	05	3.70
Solid Tumor		
Stage II	26	24.76
Stage III	44	41.90
Stage IV	35	33.33
ECOG Performance Status		
0–1	62	59.05
2	30	28.57
3	13	12.38
Comorbidities Present	24	22.86

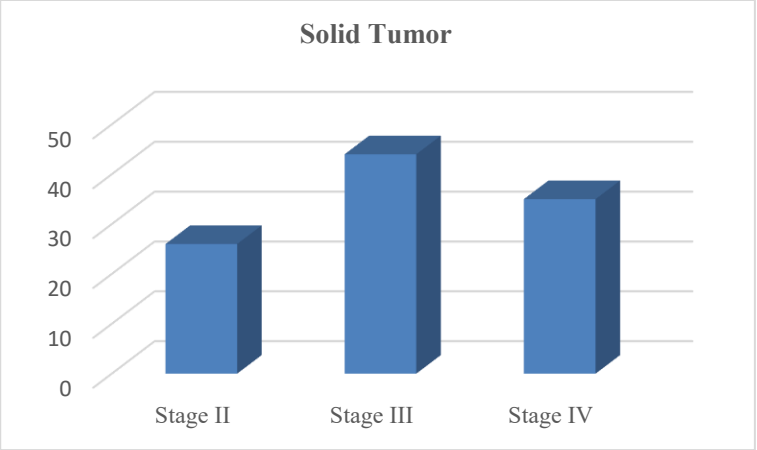

Fig-2: Cancer Stage of the study patients

Table 2: Febrile Neutropenia and Chemotherapy Details of the Study Population

Parameter	Frequency (n)	Percentage (%)
	Mean ± SD	
Chemotherapy Regimen Type		
Platinum-based	42	40.00
Anthracycline-based	38	36.19
Others	25	23.81
Cycle of Chemotherapy when FN occurred	2.7 ± 1.3	
Prior FN History	37	35.24
Temperature at FN Onset (°C)	38.8 ± 0.5	
ANC at Onset (×10⁹/L)	0.39 ± 0.14	
Blood Culture Positive	41	39.05
Documented Infection Site		
Respiratory tract	20	14.81
Urinary tract	9	6.66

Skin or soft tissue	6	4.44
Unknown	70	51.85
Antibiotic	30	22.22

Table 3: Filgrastim Administration Details of the Study Population

Parameter	Frequency (n)	Percentage (%)
	Mean ± SD	
Time from FN onset to Filgrastim Start (days)	1.2 ± 0.6	
Dose of Filgrastim (µg/kg/day)	5.3 ± 0.8	
Route of Administration		
Subcutaneous (SC)	83	79.05
Intravenous (IV)	22	20.95
Duration of G-CSF Treatment (days)	5.8 ± 1.2	
Dose Adjustments Required	11	10.48
Adverse Effects Due to Filgrastim		
Bone pain	9	6.66
No adverse effects	96	71.11
Antibiotic	30	22.22

Table 4: Clinical and Hematological Outcomes of the Study Population

Outcome Parameter	Frequency (n)	Percentage (%)
	Mean ± SD	
Time to ANC Recovery (days)	4.6 ± 1.1	
Duration of Fever (days)	2.9 ± 1.0	
Hospital Stay Duration (days)	6.7 ± 2.3	
ICU Admission Required	8	7.62
Mortality	3	2.86
Overall Recovery	102	97.14
Recurrence of FN in Next Cycle	17	16.19

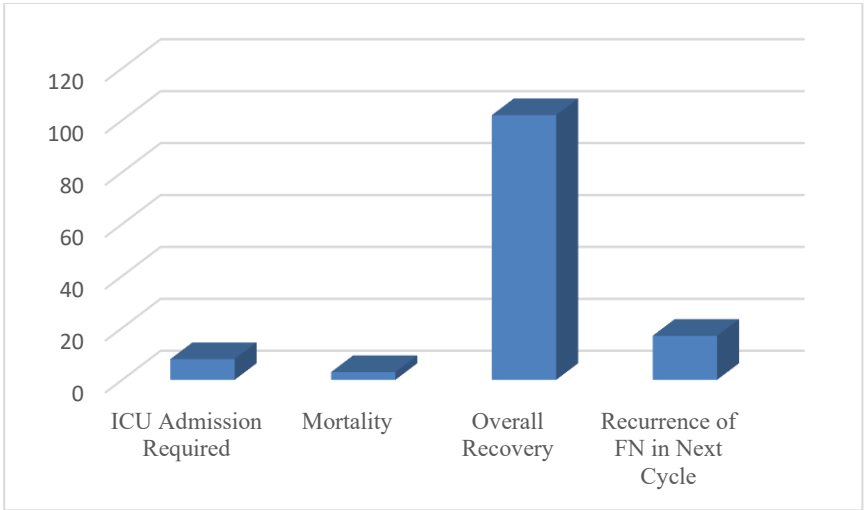

Fig-3: Hematological Outcomes of the Study Population

DISCUSSION

Febrile neutropenia (FN) remains a significant complication in pediatric oncology, often leading to dose delays, treatment modifications, prolonged hospitalization, and increased mortality risk. The findings of this study, involving 135 children in Bangladesh receiving chemotherapy for various malignancies, reaffirm the critical role of granulocyte colony-stimulating factor (G-CSF), specifically Filgrastim, in mitigating these risks and promoting clinical recovery. The study population reflected a realistic cross-section of pediatric oncology cases, with (ALL) Acute Lymphoblastic Leukemia, AML (Acute Myeloid Leukemia) NHL (Non-Hodgkin Lymphoma), Ewing's Sarcoma, Rhabdomyosarcoma, Hodgkin Lymphoma, Hepatoblastoma and Others being the most common diagnoses, consistent with regional data on childhood cancer prevalence [14]. The majority of patients (75.2%) presented with advanced-stage disease (Stages III and IV), which is known to correlate with a higher risk of chemotherapy-induced neutropenia due to aggressive treatment protocols [15]. The mean age (10.6±3.5 years) and the slightly higher male-to-female ratio (53.3% vs. 46.7%) also align with global pediatric cancer demographics [16]. Febrile neutropenia occurred most frequently around the third cycle of chemotherapy (mean 2.7±1.3), with prior FN episodes reported in over one-third of patients. This recurrence underlines the need for sustained vigilance and perhaps even prophylactic G-CSF in high-risk cases, as suggested by previous study [17], where the importance of individualized FN risk assessment in pediatric cancer care was emphasized. The mean temperature at onset (38.8°C) and profound neutropenia (ANC 0.39 × 10⁹/L) highlight the urgency and severity of FN episodes in this cohort. Infections were documented in approximately one-third of cases, with respiratory tract infections being the most prevalent (19.0%). This is consistent with prior research by Das [18], which noted respiratory infections as the predominant source in pediatric FN cases. Notably, the high percentage of "unknown" infection sites (66.7%) is common in FN studies, as microbiological cultures often yield negative results despite clinical signs of infection [19]. The study supports the efficacy of Filgrastim, which was administered within an average of 1.2 days following FN onset. Early initiation is associated with faster neutrophil recovery and reduced infection-related complications [20]. The standard Filgrastim dose used (5.3 µg/kg/day) aligns with international guidelines and was generally well-tolerated. The majority of patients received it via subcutaneous injection (79.0%), the preferred route due to ease of administration and comparable efficacy to intravenous delivery [21]. Adverse effects were minimal, with only 8.6% reporting bone pain, a known but manageable side effect. This safety profile is encouraging and supports findings from Lyman [22], who noted that Filgrastim's adverse event rate in pediatric patients is significantly lower than in adults, likely due to fewer pre-existing comorbidities and organ impairments. Importantly, the clinical outcomes observed in this study were favorable. Neutrophil recovery occurred within an average of 4.6 days, fever subsided within three days, and the average hospital stay was under seven days. These findings indicate the role of Filgrastim in reducing FN duration and associated healthcare burden. Additionally, the overall recovery rate was 97.1%, and mortality was limited to just 2.9%, echoing previous studies showing that prompt G-CSF use in FN management significantly improves survival outcomes [23]. However, 16.2% of patients experienced FN recurrence in subsequent cycles, suggesting that while Filgrastim is effective for treatment, its prophylactic use may be warranted in select cases. According to the American Society of Clinical Oncology (ASCO) and the Infectious Diseases Society of America (IDSA), primary prophylaxis with G-CSF should be considered in patients with a ≥20% risk of FN [24]. Given that a notable portion of this cohort had advanced-stage disease and prior FN history, extending G-CSF use prophylactically could further reduce recurrence rates. The study's implications are especially relevant in resource-limited settings such as Bangladesh, where timely management of FN can be hampered by logistical and economic challenges. The use of Filgrastim in this setting demonstrates that high-quality supportive care is feasible and beneficial, even in low- and middle-income countries (LMICs). Moreover, reducing the length of hospital stay through accelerated ANC recovery can decrease overall

treatment costs and free up critical care resources a significant consideration in overburdened healthcare systems [25].

Limitations of the study: The retrospective design increases the risk of information bias and limits the ability to establish causal relationships. The small sample size may not capture all potential adverse events or rare outcomes. Additionally, the cause of infection remained unidentified in many cases, limiting insights into microbiological trends. Lack of long-term follow-up also prevents assessment of recurrence and late complications.

CONCLUSION AND RECOMMENDATIONS

This study demonstrates that Granulocyte Colony-Stimulating Factor (Filgrastim) is effective and well-tolerated in managing chemotherapy-induced febrile neutropenia (FN) among Bangladeshi children with cancer. Filgrastim use was associated with faster absolute neutrophil count (ANC) recovery, shorter fever duration, reduced hospital stays, and a high overall recovery rate. Adverse effects were minimal and manageable, with bone pain being the most common. Early administration, predominantly via subcutaneous route, proved beneficial. These findings support the role of Filgrastim as a valuable adjunct in pediatric oncology care. Broader studies are encouraged to further validate its efficacy and guide optimal dosing and timing strategies.

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