Efficacy of Granulocyte Colony-Stimulating Factor in Established Neutropenia in Pediatric Solid Tumors

Sayed HA[1], Amir Y[1], Osman AM[1]

[1] Pediatric Oncology Department, South Egypt Cancer Institute, Assiut University, Egypt

Correspondence should be addressed to Youstina Amir at Pediatric Oncology Department, South Egypt Cancer Institute, Assiut University, Egypt, yous.amir23@yahoo.com

Abstract

Background: Intensive chemotherapy is required to achieve cure in pediatric oncology patients who are at increased risk for serious infections while neutropenic. Administration of Granulocyte Colony-Stimulating factor (G-CSF) may reduce the severity of neutropenia. This study assessed the efficacy of adjunctive G-CSF in the treatment of established neutropenia by evaluating clinical outcomes.

Methods: Prospective study conducted at the Pediatric Oncology Department, South Egypt Cancer Institute (SECI), Assiut University. Pediatric patients with solid tumors who developed neutropenia after receiving myelo-suppressive chemotherapy between February 2018 and February 2020 were included in the analysis. The clinical efficacy of adjunctive G-CSF was evaluated by assessing the duration of neutropenia, duration to absolute neutrophilic count (ANC) recovery, duration of fever, the duration of hospital stay and infection related mortality.

Results: Thirty seven patient experienced 50 episodes of neutropenia with de novo solid tumors were analyzed. The median age was 6 years with 60% of episodes occurred in males. Neuroblastoma was the most common underlying malignancy (44%). The majority of episodes had low risk criteria (64%). The mean durations of neutropenia, absolute neutrophil count (ANC) recovery, fever resolution and hospitalization after receiving G-CSF were (6.79±3.80, 15.47±2.85, 4.21±1.73, 7.82± 3.82 days) respectively. Recovery from neutropenia reported in 98% while infection related mortality was 2%. All factors were significantly affecting the pattern of recovery expect gender and disease status.

Conclusion: This study suggested that the use of adjunctive G-CSF in established febrile neutropenia may confer clinical benefits among pediatric patients with solid tumors.

Key words: Solid tumors; chemotherapy; febrile neutropenia; granulocyte colony-stimulating factor (G-CSF); pediatric

Introduction:

Fever and neutropenia (FN) remains a life-threatening medical condition; despite the wide availability of effective antibiotics **[1]**.The frequency and severity of infections in these patients are directly related to the severity and duration of neutropenia **[2].** It is important to underline the fact that completion of all planned chemotherapy cycles is essential in order to provide patients with the maximum chance of treatment success; however FN may cause dose reduction and treatment delay limiting the efficacy of therapy. The administration of colony stimulating factors (CSFs) decreases the incidence of FN and allows the maintenance of a correct dose density and intensity **[1].**

Granulocyte Colony-Stimulating factor (G-CSF) are secreted glycoproteins that expand circulating pools of neutrophils by binding to receptor proteins on the surfaces of myeloid progenitor cells, thereby activating intracellular signaling pathways that can cause the cells to proliferate and differentiate **[3].**

Here, we conducted a prospective study to assess the efficacy of G-CSF in children with solid tumors who developed neutropenia after receiving myelo-suppressive chemotherapy by investigating the duration to absolute neutrophil count (ANC) recovery, duration of neutropenia, duration to fever resolution, the duration of hospitalization, length of chemotherapy delay and infection related mortality.

Patients and Methods:

This prospective study was carried out at the Pediatric Oncology Department, South Egypt Cancer Institute (SECI), Assiut University between February 2018 to February 2020 after ethical committee approval and informed consent from patient's family.

During study period thirty seven patients with solid tumors with age ranged between 1-18 years who experienced 50 episodes of established neutropenia after receiving myelosuppressive chemotherapy were enrolled in this study. Relapsed cases, patients who undergone bone marrow transplantation (BMT) and those who developed neutropenia due to radiotherapy were excluded from

the study.

For each patient demographic data collected included age, gender, diagnosis, disease status and treatment phase. Detailed history about chemotherapy include first and last day, presence of fever and any complaint ,complete physical examination and routine laboratory investigations including complete blood counts (CBC) with determination of absolute neutrophil counts (ANC) were mandatory, liver and kidney function tests, CRP, serum electrolytes and blood cultures at presentation and during treatment course.

Neutropenia was defined as an ANC of <500 cells/µL or ANC is expected to decrease to <500 cells/µL within a 48-hour period. ***Fever*** was defined as a one-time oral temperature of ≥38.3°C or a sustained temperature of ≥38°C over 1 hour period **[4]**. Then risk assessment of FN for the patients was done according to Infectious Diseases Society of America (IDSA) guidelines **[5]**.

Analysis of the neutropenic episodes concerning the onset, amplitude, duration and grade of neutropenia (mild neutropenia when the ANC is 1000-1500 cells/µl, moderate neutropenia when the ANC of 500-1000 cells/µl, severe neutropenia refers to an ANC <500/µl, profound neutropenia refers to an ANC <100 cells/µl) **[6]** and time to recovery from it were done. Also we assessed presence of associated fever and its duration and days of hospitalization

G-CSF was given at time of diagnosis of neutropenia with a dosage of 5µg/kg/day subcutaneously, intravenous G-CSF was allowed in patients with severe thrombocytopenia. G-CSF was discontinued when ANC >500 cells/µl.

The outcome of each episode was assessed regarding recovery or infection related mortality and prognostic factors affecting their outcome.

Statistical analysis:

Data entry and data analysis were done using SPSS version 24 (Statistical Package for Social Science). Data were presented as number, percentage, mean, standard deviation. P value <0.05 considered significant.

Results:

Thirty seven patients with solid tumors treated with myelo-suppressive chemotherapy who experienced 50 episodes of established neutropenia were included in the study. Demographic data and patients' characteristics are summarized in **Table 1**. Thirty episodes out of the fifty occurred in males (60%). The median age was 6 years with the majority of episodes (62%) noticed in age group (<10 years). Neuroblastoma was the most common underlying malignancy in our patients, accounting for 44% of episodes. Twenty six episodes (52%) were reported during consolidation phase. The episodes mainly recorded in patients with localized disease (52%) versus 48% of episodes recorded in patients with advanced disease, the majority of episodes stratified as low risk 64%.

Table (1): Patients characteristics among the study group

Variable (Frequency)	No. of episodes= 50
Age "years"	
• Mean ±SD	7.35±1.85
• Median	6.0
• Age groups:	
▪ <10 (n=22)	31 (62%)
▪ ≥10 (n=15)	19 (38%)
Sex:	
• Male (n=21)	30 (60%)
• Female (n=16)	20 (40%)
• Male: female ratio	1.5:1
Diagnosis:	
• Neuroblastoma (n=15)	22(44%)
• Brain tumors (n=5)	6(12%)
• Ewing sarcoma (n=5)	5(10%)
• Osteosarcoma (n=2)	4(8%)
• Rhabdomyosarcoma (n=2)	4(8%)
• Wilm's tumor(n=2)	2(4%)
• Germ cell tumors (n=2)	2(4%)
• Hepatoblastoma (n=2)	2(4%)
• Non-Rhabdomyosarcoma (n=1)	2(4%)
• Retinoblastoma (n=1)	1(2%)
Disease Status	
• Localized (n=20)	26(52%)
• Advanced(n=17)	24(48%)
Treatment phases:	
• Induction (n=7)	10(20%)
• Consolidation (n=19)	26(52%)
• Continuation(n=11)	14 (28%)

SD Standard deviation, **No.** Number

As shown in **Table 2** the duration of neutropenia had a mean of 6.79± 3.8 days with recovery from neutropenia achieved within a mean of 15.47±2.85 days. Most of episodes (40%) stratified as moderate neutropenia followed by mild neutropenia in 24% of episodes while severe and profound neutropenia reported in only 22% and 14% of episodes respectively. Fever associated with neutropenic episodes recorded in 17 episodes (34%) and persisted fora mean of 4.21±1.73 days. Forty six percent of episodes needed admission in hospital between 5 to 10 days with a mean of hospital stay of 7.82±3.82 days.

Among the study group, recovery from neutropenia reported in 49 (98%) episodes while infection related mortality reported only in one episode (2%);the patient was male had Ewing sarcoma with advanced disease during consolidation phase of treatment suffered from profound neutropenia associated with fever.

Age group and treatment phase were significantly affect the outcome of the studied group of patients (p=0.044, 0.025 respectively), with better outcome reported among age group ≥ 10 years and in both induction and continuation phases of treatment.

Also, the grade of neutropenia, its stratification

and presence of associated fever were significantly affecting the outcome of our patients (p=0.042, 0.005, 0.001 respectively). **Table (3)** shows prognostic factors affecting the outcome of the neutropenic episodes.

Table (2): Analysis of neutropenic episodes among the study group

Variable	No. = 50
Onset (mean± SD)	9.16±1.99*
Amplitude (mean± SD)	10.09±1.78*
Duration (mean± SD)	6.79±3.80*
Recovery from neutropenia (mean± SD)	15.47±2.85*
Grades :	
✓ Mild	12(24%)
✓ Moderate	20(40%)
✓ Severe	11(22%)
✓ Profound	7 (14%)
Associated Fever	17 (34%)
Duration (mean± SD)	4.21±1.73*
Duration of hospital stay	7.82±3.82*
✓ <5days	20(40%)
✓ 5-10days	23(46%)
✓ >10days	7(14%)

***Days** **No.** Number**, SD** Standard deviation

Discussion:

Intensive chemotherapy is required to achieve cure in pediatric oncology patients who are at increased risk for serious infections while neutropenic **[2]**. Administration of G-CSF may reduce the severity of neutropenia and allows the maintenance of a correct dose density and intensity **[1].**

Male predominance were reported (60%) with a median age of 6 years among our patients. This is nearly similar to that reported in the study done by Mack et al. who reported male predominance (66%) with a median age 6.2 years among their patients **[7]**.

Patients with neuroblastoma represent the main group who suffered neutropenia among the study group presented in 22 episodes (44%) followed by brain tumors 6 episodes (12%) and Ewing sarcoma 5 episodes (10%).Mack et al. recorded that patients with neuroblastoma and Ewing sarcoma were equally affected and were the main group among their patients (22.6%) followed by patients with brain tumors (16.1%) **[7]**.

Although slightly less aggressive therapy is planned for patients with localized disease compared to advanced disease, the episodes in our study mainly recorded in patients with localized disease (52%). This matches with Nordvig et al. that recorded 56% of their patients presented with localized disease **[8]**.

Table (3): Prognostic factors affecting the outcome of the neutropenic episodes

Item	Recovery No. = 49	Death No. = 1	P Value
Age groups:			
• <10yrs (n=31)	30 (96.8%)	1(3.2%)	**0.044**
• ≥10yrs (n=19)	19 (100%)	0	
Sex:			
• Male (n=30)	29 (96.7 %)	1 (3.3%)	0.105
• Female (n=20)	20 (100%)	0	
Disease status:			
• Localized (n=26)	26 (100%)	0	0.681
• Advanced (n=24)	23 (96.2%)	1(3.8%)	
Treatment phase:			
• Induction (n=10)	10 (100%)	0	
• Consolidation (n=26)	25 (96.2%)	1(3.8%)	**0.025**
• Continuation(n=14)	14 (100%)	0	
Grade of neutropenia:			
• Mild (n=12)	12 (100%)	0	
• Moderate (n=20)	20 (100%)	0	**0.042**
• Severe (n=11)	11 (100%)	0	
• Profound (n=7)	6 (85.7%)	1 (14.3%)	
Risk Stratification:			
• Low risk (n=32)	32 (100%)	0	
• High risk(n=18)	17 (94.4%)	1 (5.6%)	**0.005**
Associated fever:			
• Yes (n=17)	16 (94.1%)	1 (5.9%)	
• No (n=33)	33 (100%)	0	**0.001**

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According to risk stratification, the majority of episodes (64%) stratified as low risk while low risk patients in Chan et al. study were 81% **[9]**.

The median time of onset of neutropenia reported after 9 days from the start of previous cycle of treatment and persisted for 6 days with recovery from neutropenia recorded within a median of 15 days. Comparable results reported by Mitchell et al. that the onset of neutropenia recorded after a median of 10 days and persist for a duration ranged from 1 to 5 days. O¨zkaynak et al. reported recovery of neutropenia among their patients within a median of 13 days **[10, 11]**.

Regarding grade of neutropenia, most of our episodes (40%) stratified as moderate grade, while severe and profound neutropenia were recorded in 22% and 14% respectively. This is unlike what reported by Osmani et al. where 43.5%, 26% and 31% of their patients presented by profound, severe and moderate neutropenia respectively. This difference may attributed to high percent of hematological malignancies among their patients which known by their aggressive chemotherapy and more bone marrow suppression more than solid tumors **[12]**.

Fever associated with neutropenia in 34% of episodes, this is higher than Mack et al. who reported association of fever with neutropenia in 25% but less than Wittman et al. who reported FN occurred in 59% **[7, 13]**.

Forty six percent of episodes developed by patients needed hospitalization between 5-10 days with mean duration was 7.82± 3.82 days, this is near to results

Mitchell et al. who reported that duration of hospitalization ranged from 4 to 8 days **[10]**.

Recovery from neutropenia reported in 98% of episodes while infection related mortality was 2%.Chan et al. reported 2.4% neutropenia-related mortality among those who have received G-CSF **[9]**.

The outcome of our patients was affected by degree of neutropenia during the episodes. Patients with mild and moderate neutropenia had better outcome with no deaths reported among them compared to profound neutropenia. This is in agreement with Osmaniet al. who recorded that patients with profound neutropenia were more likely to die than patients with severe and moderate neutropenia**[12]**.

Indeed, patients with high risk criteria of neutropenic episodes had worse outcome as they are vulnerable to developed serious infection and complications related mortality than low risk group. This is similar to Ahn et al. who found that high risk patients developed serious infection related mortality with unfavorable outcome **[14]**.

Also, the infection related mortality episode had fever associated with neutropenia. This is in agreement with Nordvig et al. study that reported among their patients who develop associated fever with neutropenia had increased risk of infection related mortality **[8]**.

Conclusion:

Although relatively small number of patients were included in our study, we can conclude that the adjunctive use of G-CSF associated with clinical improvement of the outcome among children with solid tumors with established neutropenia after receiving myelosuppressive chemotherapy. Larger study with inclusion of more number of patients and disease specification is recommended.

List of Abbreviations:

ANC	Absolute neutrophilic count
BMT	Bone marrow transplantation
CBC	Complete blood count
CSFs	Colony stimulating factors
FN	Fever neutropenia
G-CSFs	Granulocyte colony stimulating factors
IDSA	Infectious Diseases Society of America
SECI	South Egypt Cancer Institute
SPSS	Statistical Package for Social Sciences

Competing Interests:

There are no competing interests

Authors' Contributions:

Youstina Amir had carried out the acquisition of data, analysis and interpretation of data and drafted the manuscript.

Amira M. Osman had contributed to designing the work.

Heba A.Sayed had contributed by supervising and revising the work.

All authors read and approved the final manuscript

Authors' Information:

Heba A. Sayed: Professor at Pediatric Oncology department of South Egypt Cancer Institute, Assiut University

Amira M. Osman: Lecturer at Pediatric Oncology department of South Egypt Cancer Institute, Assiut University

Youstina Amir: Demonstrator at Pediatric Oncology department of South Egypt Cancer Institute, Assiut University

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References:

1. **Innocenti R, Rigacci L, Restelli U, Scappini B, Gianfaldoni G, Fanci R, Mannelli F, Scolari F, Croce D, Bonizzoni E, Perrone T, Bosi A:** Lenograstim and filgrastim in the febrile neutropenia prophylaxis of hospitalized patients: efficacy and cost of the prophylaxis in a retrospective survey. Journal of Blood Medicine 2018,10 : 21-27
2. **Ammann RA, Tissing WJE, Philips B:** Rationalizing the approach to children with fever in neutropenia. Curr Opin Infect Dis 2012, 25: 258-265
3. **Thomas J, Liu F, Link DC:** Mechanisms of mobilization of hematopoietic progenitors with granulocyte colony-stimulating factor. Current Opinion in Hematology 2002 , 9 : 183–189
4. **Zimmer AJ, Freifeld AG:** Optimal Management of Neutropenic Fever in Patients with Cancer. J Oncol Pract 2019, 15: 19-24.
5. **Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito JI, Mullen CA, Raad II, Rolston KV, Young JH, Wingard JR :** Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clinical Infectious Diseases 2011, 52: 427–431
6. **Llamas RMH, Acosta MEH, Silva JD:** Management of febrile neutropenia in pediatric cancer patients. J Pediatr Neonatal Care 2019, 9:22–26.
7. **Mack JM, Spray BJ, Mack D , Mason K, Becton D , Bielamowicz K:**Pegfilgrastim Administration Timing and its Effect on Febrile Neutropenia in Pediatric Cancer Patients.Int J Cancer Oncol 2019, 6 :37-41
8. **Nordvig J, Aagaard T, Daugaard G, Brown P, Sengeløv H, Lundgren J, Helleberg M:** Febrile Neutropenia and Long-term Risk of Infection Among Patients Treated With Chemotherapy for Malignant Diseases. Open Forum Infect Dis 2018, 5: 255.
9. **Chan A, Wong QX, Ali MK, Wong M, Hsu LY:** Clinical efficacy of adjunctive G-CSF on solid tumor and lymphoma patients with established febrile neutropenia. Supportive Care in Cancer 2014,22:1105–1112

10. **Mitchell PLR, Morland BJ, Stevens MCG, Dick G, Easlea D, Meyer LC, Pinkerton CR:** Granulocyte colony-stimulating factor in established febrile neutropenia: A randomized study of pediatric patients. J Clin Oncol 1998, 15:1163–1170.
11. **O¨ zkaynak MF, Krailo M, Chen Z, Feusner J:** Randomized Comparison of Antibiotics With and Without Granulocyte Colony-Stimulating Factor in Children With Chemotherapy-Induced Febrile Neutropenia: A Report From the Children's Oncology Group. Pediatr Blood Cancer 2005, 45:274–28.
12. **Osmani AH, Ansari TZ, Masood N, Ahmed B:** Outcome of febrile neutropenic patients on granulocyte colony stimulating factor in a tertiary care hospital. Asian Pacific Journal of Cancer Prevention 2012, 13:2523-2526
13. **Wittman B, Horan J , Lyman GH:** Prophylactic Colony – stimulating factors in children receiving myelosuppressive chemotherapy : A meta-analysis of randomized controlled trials. General and Supportive care 2006, 32: 289-303.
14. **Ahn S, Lee YS , Chun YH , Kwon IH, Kim W, Lim KS, Kim TW, Lee KH :** Predictive factors of poor prognosis in cancer patients with chemotherapy-induced febrile neutropenia. Support Care Cancer 2011,19: 1151–1158.