Selamawit Assefa, Tinsae Alemayehu, Workeabeba Abebe, *Ethiop Med J, 2017, Vol. 55, No. 1*

ORIGINAL ARTICLE

FACTORS ASSOCIATED WITH TREATMENT OUTCOME OF PEDIATRIC CANCER PATIENTS ADMITTED WITH FEBRILE NEUTROPENIA IN TIKUR ANBESSA SPECIALIZED TEACHING HOSPITAL, ADDIS ABABA, ETHIOPIA

Selamawit Assefa MD[2], Tinsae Alemayehu MD,[1]Workeabeba Abebe MD, MPH[1*]

ABSTRACT

Background: *Cancer treatment is associated with variable degrees of myelosupression. Infection is often a life-threatening complication of chemotherapy-induced neutropenia, and it is also considered an oncologic emergency. Febrile neutropenia is a common, costly and potentially fatal complication in oncology.*
Objective: *To assess factors affecting treatment outcome of cancer patients with chemotherapy induced febrile neutropenia.*
Method: *We conducted a review of records of pediatric patients hospitalized and treated for chemotherapy-induced febrile neutropenia from January 1, 2013 to December 31, 2013 and met the selection criteria.*
Result: *A total of 60 patients (36 males and 24 females) fulfilled the selection criteria. Twelve of them died while in hospital. The mean (SD) age of patients who died was 4.78 (±2.48) years and the mean (SD) hospital stay before death was 20.2 (±5.26) days. Ten children had hematologic malignancy and two had a solid tumor. Ten of the 12 patients had an absolute neutrophil count of less than 100/mm^3 (p=0.008, OR=20.3) and a platelet count of less than 50,000/mm^3. Six of the 10 children (10%) had sepsis. Patients with profound neutropenia, platelet count of less than 50,000 and sepsis were more likely to die (P=0.048, OR=7).*
Conclusion: *The result of this study showed that absolute neutrophil count of less than 100/mm^3, platelet count of less than 50,000/mm^3 and a diagnosis of sepsis were factors affecting outcome patients with febrile neutropenia. Careful evaluation of these factors and assessing severity of patients' clinical condition at time of admission can be useful for triaging children with febrile neutropenia.*
Keywords*: fever, neutropenia, cancer, absolute neutrophil count , febrile neutropenia, oncologic emergency.*

INTRODUCTION

Fever with neutropenia is one of the most common sequelae among pediatric oncology patients and fever is often the first and only sign of infection (1). Fever in a neutropenic patient is defined as a single oral temperature of greater than 38.3°C (101°F) or a temperature of 38°C (100.4°F) sustained over 1 hour. Axillary temperatures are discouraged and rectal temperatures are contraindicated in children with chemotherapy induced febrile neutropenia (FN). Neutropenia is defined as an absolute neutrophil count (ANC) of less than 500 cells/mm^3 or an ANC of less than 1000 cells/mm^3, which is expected to decrease to less than 500 cells/mm^3 in the next 48 hours. Profound neutropenia is defined as an ANC of less than 100 cells/mm^{3}and prolonged neutropenia is one lasting greater than 7 days (2,3). Fever during neutropenia has always been considered a medical emergency and should always be considered due to infection, unless otherwise proven (4).

Clinically or microbiologically proven infections account for 10-40% of children with fever and therapy-induced neutropenia. Bacteremia dominates among proven infections with majority of cases in febrile neutropenic patients being due to gram-positive organisms. Potential reasons for the unobserved dominance of gram-positive bacteria include the use of indwelling catheters, local environmental conditions, and the administration of prophylactic antibiotic agents. The mainstay of treating FN is an empirical parenteral broad-spectrum antibiotic.(5-7). Fungi, typically Candida, occasionally may be a primary pathogen. Empirical antifungal drugs are rec-

[1] Department of Pediatric and Child Health, Assistant Professor of Pediatrics
[2] Department of Pediatric and Child Health
* Corresponding author: *workeabebasol@yahoo.com, workeabeba.abebe@aau.edu.et*

ommended for children with persistent neutropenic fever after 4–7 days of empirical antibiotics (5,8). The most significant viral etiologies are respiratory viruses, herpes simplex and varicella-zoster virus. (9).

Various studies have attempted to identify factors contributing to morbidity and mortality in febrile neutropenia among pediatric oncologic patients. Duration of neutropenia, medical co-morbidities, cancer type and stage, proven infection at time of presentation, the presence or absence of bone marrow recovery, identified pathogens, the severity of vital sign derangements, lab abnormalities at presentation like elevated blood urinary nitrogen (BUN) and serum lactic dehydrogenase (LDH) and age of child have all been related to outcome of febrile neutropenia episodes (10,11).

Even though the data is lacking, FN is one of the common causes of emergency admission of pediatric cancer patients in our setup. FN frequently leads to chemotherapy dose reductions and treatment delays that may compromise long-term clinical outcomes in responsive and potentially curable malignancies. Therefore, the present study primarily intended to assess factors affecting treatment outcome of pediatric cancer patients with chemotherapy-induced FN in Tikur Anbessa Specialized Teaching hospital (TASTH). The knowledge will help for risk stratification and better management in the future.

PATIENTS AND METHODS

In this retrospective study, we reviewed pediatric oncologic patients with chemotherapy induced febrileneutropenia (ages 0-15 years) admitted to TASTH in Addis Ababa from January 2013 to December 2013. The pediatric hematology oncology unit is the only center of its kind in the country and has isolated ward with 26 beds in it. All records of pediatric cancer patients fulfilling the study selection criteria included. It has ANC of less than or equal to 500/mm^3 and fever record of more than or equal to 38^0C over one hour or a single measurement of 38.3°C were included. Charts with incomplete information were excluded. Records of patients with chemotherapy induced febrile neutropenia were retrieved from the record office and the charts were reviewed using a structured questionnaire/checklist. Treatment outcome was the dependent variable and independent variables included age, gender, type of malignancy, degree of neutropenia, degree of fever, co-morbid conditions and duration of neutropenia.

Data was analyzed using SPSS version 20. Chi-squared test was used when comparing categorical variables and 95% confidence intervals (CI) were calculated to measure precision of point estimates. A P value of less than 0.05 was considered statistically significant. Ethical clearance was obtained from Addis Ababa University, Department of Pediatrics Research and Publication Committee (DRPC). All information collected from patients records were kept strictly confidential and names of children were not included in the abstracted data.

RESULTS

A total of 60 patients (36 males and 24 females) were included in the study. Forty-six (76.7%) of the patients were between 1 and 10years of age, 10 (16.7%) were between 10 and 12 years of age and 4 (6.7%) were below 1 year of age with the mean (SD) age of patients being 5.9 (±3.62) years.

The topographic distribution of tumors according to the primary site was hematological malignancies in 47children (78.4%) and solid tumors in 13 children (21.6%). Further stratification of hematological malignancies revealed 34 cases of acute lymphoblastic leukemia (ALL), 2 cases of acute myelogenous leukemia (AML), 10 cases of non-hodgkin's lymphoma (NHL) and a single case of Hodgkin's lymphoma. The distribution of solid tumors was 6 children with wilm's tumor, 4 with rhabdomyosarcoma, and 3 with neuroblastoma. Overall, thirty five (58.3%) patients had co-morbid conditions including mucositisi n 25 (41.7%), gastroenteritis 14(23.3%), urinary tract infections in 8(13.3%), and sepsis in 6(10%). More than one co-morbid condition were diagnosed in 13 children (21.7%) (Table 1).

The mean (SD) of ANC was 155.3/mm^3(±124). Profound neutropenia was observed in 26 (43.3%) of the patients. Twenty (33.3%) of the patients had a platelet count of less than 50,000/mm^3 with a mean (SD) platelet count of 75,550/mm^3(±40767). The temperature at diagnosis was more than 39^oC in 16(26.7%) of the patients with a mean (SD) temperature record of 38.8^oC (±0.5)(Table 2).Seven children (11.7%) had a positive blood culture result. The pathogens isolated were 3 Klebsiella species, 3 Acinetobacter species, 1 Escherichia. coli, and 1 coagulase-negative Staphylococcus.

Twelve (20%) of the patients died and their mean age of patients who died was 4.78 years and 7 were males. Death occurred at a mean (SD) duration of 20.2 (± 5.26) days after admission. Their mean ANC and platelet counts were 78.6/mm^3 and 32,000/mm^3. Ten of the mortalities had a hematologic malignancy: 8 ALL, and 2 lymphoma. The remaining 2 had a solid tumor.

Ten of the twelve patients who died had a profound neutropenia (p=0.008, OR=20.3) and platelet of less than 50,000/mm^3 (p=0.012, OR=8.6). Profound neutropenia, a platelet count of less than 50,000/mm^3 and sepsis (P=0.048, OR=7) were significantly associated with mortality (Tables 1 & 2). Two of the 12 patients had a positive blood culture with Klebsiella species.

Table 1: Demographic and Clinical factors of the total Children and those who Died during the Febrile Neutropenia episode

Variable	Children	
	Total n = 60	Died n = 12
Mean age (year)	5.89	4.87
Gender		
Male (%)	36(60)	7(58.3)
Female (%)	24(40)	5(42.7)
Type of malignancy (%)		
Hematologic malignancies	47(78.3)	10(83.3)
Solid tumors	13(21.7)	2(16.7)
Co morbidity (%)	35(58.3)	7(58.3)
Mucositis(%)	25(41.7)	
Gastroenteritis(%)	14(23.3)	
Urinary tract infections(%)	8(13.3)	
Sepsis(%)	6(10)	

Table 2: Laboratory Findings during Febrile Neutropenia Episodes

Variables	Children		P-value	OR [95% CI]
	Total n = 60	Died n = 12		
Mean absolute neutrophil count (ANC)	155	78.58	< 0.001	20.365 [2.172-190.99]
ANC less than 100/mm^3	26(43.3%)	11(44%)		
Mean absolute monocyte count (AMC)	1024.5	1309	0.05	
Platelets less than 50,000/mm^3	20(33.3)	9(47.4%)	0.001	8.590 [1.607-45.915]
Positive culture (%)	7(18.4)	2	0.473	
Mean duration of neutropenia (days)	8.32	11.7	0.098	

DISCUSSION

Despite the widespread approach of treating all febrile neutropenic patients with empiric broad-spectrum antibiotics for potential bacteremia, febrile neutropenia in the child with cancer remains associated with a significant mortality rate.

In our study, a death rate of 20% was noted. This outnumbers observations from a multi-center study from Chile (3.8%), the US (3%), Iran (7.5%), and Norway (1%) (11-14).This might be due to poor supportive care, inadequate use of antimicrobials or a smaller sample size (60) in the study as compared to 373 (Chile), 12,446 (US), 120 (Iran) and 95 (Norway). Infants and adolescents were found to be at a greater risk of death in the US, which contrasts to the mean age of patients who died in our study (12). Overall, 58.3% of the children enrolled in our study had co-morbid conditions. Mucositis and gastroenteritis accounted for nearly two-thirds of co-morbid diagnoses in our patients. Patients with sepsis accounted for 10% of all children; which is lower than that the 21.3% observed by Basu et al. in the USA (12).

The most common malignancy identified among children with febrile neutropenia episodes in our series was ALL accounting for 56.7% of the cases. This concurs with reports by Badiei et al (Iran), Stabell et al. (Norway) and Timothy et al. and Trinidad & Tobago where ALL was documented in 53.3%, 51.6% and 43.7% of childhood febrile neutropenic episodes, respectively (13,14,16). Only 7 (11.7%) of the patients had documented bacterial infection as compared to a German and a Swiss studies (21.5%) and a Norwegian report which showed bacterial infection of 16.5% (14,15).The lower proportion of cases with positive culture result our series can be attributed to the smaller study sample size and a poor culture yield due to prior antibiotic use or laboratory quality.

As opposed to the global shift toward a preponderance of gram-positive organisms, this study showed predominance of gram-negative sepsis. Our finding contrasts to the results reported by Agyeman et al., which showed preponderance of gram-positive sepsis (15). All of our patients were on prophylactic co-trimoxazole, not ciprofloxacin, and non-use of indwelling venous catheter might be the reasons for gram-negative preponderance in our set up.

Profound neutropenia was observed in 43.3% of our patients whereas one-third had a platelet count of less than 50,000/mm^3. The mean ANC was 155.3/mm^3,which is in agreement with a mean ANC of 160/mm^3 reported from Trinidad & Tobago (16).

Our study revealed that profound neutropenia, thrombocytopenia of less than 50,000/mm^3 and sepsis were high risks factors associated with death. This differs from what was detected in Missouri, USA, where AMC less than 30/mm^3 rather than ANC or platelet count was a significant risk for death (17). AMC of less than 100/mm^3 was found to be the only factor associated with patient outcome in Ottawa, Canada (18).

A unique high risk factor identified in the United Kingdom associated with morbidity among febrile neutropenia in pediatric ALL cases was the presence of Down syndrome (19). On the other hand, as in our series, thrombocytopenia of less than 20,000/mm^3 and ANC of less than 100/mm^3 were identified as risks for life threatening infections in Iran and New York, United States. Additional associated factors were fever of more than 39^oC, mucositis, and an abnormal chest x-ray (12,20). Further similarities were seen in the Chilean study where a diagnosis of sepsis contributed to poor patient outcome (11).

Limitations: We were not able to locate some of patient charts and it is likely that the missed charts could be those of patients who died. This might have resulted in underestimation the number patients who died. Incomplete recording of information in the patient charts could also be a reason for not being able to fully assess some of the study variables.

Conclusion: In summary, profound neutropenia, thrombocytopenia less than 50,000/$mm^3$and sepsis were found to have significant associations with poor clinical outcome in the children in our series. Further analysis of data from a larger series of patients preferably with prospective data collection is required in order to devise risk stratification and treatment protocols for febrile neutropenia episodes among our pediatric oncology patients.

ACKNOWLEDGEMENT

We would like to extend our gratitude to the Department of Pediatrics and Child Health of the College of Health Sciences, Addis Ababa University for the support we received.

REFERENCES

1. Hakim H, Flynn P, Srivastava DK, Knapp K, Li C, Okuma J et al. (2009); Risk prediction in pediatric cancer patients with fever and neutropenia. Pediatr Infect Dis J 2010;29: 53–9
2. Debra LP. The use of antimicrobial agents in children with fever during chemotherapy-induced neutropenia. Pediatr Infect Dis J 2011;30: 887–90
3. Sung L, Johnston D . Approach to febrile neutropenia in the general pediatric setting. Paediatr Child Health 2007; 12(1): 19-21
4. Mandell GL, Bennett JE, Doolin R, 6theds (2005). Principles and practice of infectious diseases. Philadelphia: Churchill Livingstone, 2005:3442–62.
5. Castagnola E, Fontana V, Caviglia I, Caruso S, Faraci M, Fioredda F et al.. A prospective study on the epidemiology of febrile episodes during chemotherapy-induced neutropenia in children with cancer or after hemopoietic stem cell transplantation. Clin Infect Dis 2007; 45(10):1296-304
6. Ramphal R. Changes in the etiology of bacteremia in febrile neutropenic patients and the susceptibilities of the currently isolated pathogens. Clin Infect Dis 2004; 39:25–31
7. Hakim H, Flynn PM, Knapp KM. Etiology and clinical course of febrile neutropenia in children with cancer. J Pediatr Hematol Oncol 2009;31(9):623.
8. Gedik H, Yildirmak MT, Simsek F, Aydin D, Demirel N, Yokus O et al. Fungal pathogens and primary antifungal prophylaxis in patients with hematologic malignancies. African Health Sciences 2012; 12(3): 390-4
9. Licciardello M, Pegoraro A, Cesaro S. Prophylaxis and therapy of viral infections in pediatric patients treated for malignancy. Pediatric Reports 2011; volume 3:e5
10. Koh AY. Prolonged febrile neutropenia in the pediatric patient with cancer. In American Society of Clinical Oncology educational book/ASCO. American Society of Clinical Oncology. Meeting 2011 Dec (pp. 565-9).
11. Santolaya M, Alvarez A, Aviles C, Becker A, Mosso C, O'Ryan M et al. Admission clinical and laboratory factors associated with death in children with cancer during a febrile neutropenic episode. Pediatr Infect Dis J 2007;26:794-8
12. Basu SK, Fernandez ID, Fisher S, Asselin B, Lyman G. Length of stay and mortality associated with febrile neutropenia among children with cancer. J ClinOncol 2005; 23:7958-66.
13. Badiei Z, Khalesi M, Alami MH, Kianifar HR, Banihashem A, Farhangi H et al, Risk factors associated with life-threatening infections in children with febrile neutropenia. J Pediatr Hematol Oncol 2011; 33(1):e9-12.
14. Stabell N, Nordal E, Stensvold E, Gammelsrud KW, Lund B, Taxt A et al. Febrile neutropenia in children with cancer: a retrospective Norwegian multicentre study of clinical and microbiological outcome. Scand J Infect Dis 2008;40(4):301-7
15. Agyeman P, Kontny U, Nadal D, Leibundgut K, Niggli F, Simon A. A prospective multi-center study of microbiologically defined infections in pediatric cancer patients with fever and neutropenia. Pediatr Infect Dis J 2014;33:e219–e225
16. Timothy M, Bodkyn C. The outcome of febrile neutropenic episodes in pediatric oncology at the Wendy Fitzwilliam pediatric hospital. West Indian Med J 2011; 60 (2): 153
17. Baorto EP, Aquino VM, Mullen CA, Buchanan GR, De Baun MR. Clinical parameters associated with low bacteremia risk in 1100 pediatric oncology patients with fever and neutropenia. Cancer 2001; 92(4):909-13.
18. Klaasen RJ, Goodman TR, Pham B, Doyle JJ. "Low risk" prediction rule for pediatric oncology patients presenting with fever and neutropenia. J Clinical Oncol 2000; 18(5):1012-9.
19. O'Connor D, Bate J, Wade R, clack R, Dhir S, Hough R et al. Infection-related mortality in children with acute lymphoblastic leukemia: an analysis of infectious deaths. Blood 2014; 124(7): 1056-61
20. Lucas K, Brown A, Armstrong D, Chapman D, Heller G. The identification of febrile, neutropenic children with neoplastic disease at lower risk for bacteremia and complications of sepsis. Cancer 1996;77:791-8