

RESEARCH ARTICLE

Composite Adverse Event Outcome in Pediatric Cancer Patients with Prolonged Febrile Neutropenia

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ABSTRACT

Objective: Pediatric cancer patients with prolonged febrile neutropenia have increased risk for severe, recurrent or new bacterial and fungal infection. The aim of this study was to identify the risk factors associated with adverse outcomes in this group.

Methods: We retrospective analyzed the clinical data of 135 hospitalizations of pediatric cancer patients with prolonged febrile neutropenia from a tertiary health care center of Pakistan.

Results: The mean age of the study population was 7.3 ± 4.1 years. There were 98 (72.6%) males and 37 (27.4%) females. Acute leukemia with 88 patients (65.2%) was the most common diagnosis followed by lymphomas 19 patients (14.1%) and solid tumors. Cause of febrile neutropenia was identified in only 58 (43.0%) patients, out of them blood stream infections were found in 22 cases (16.3%), pneumonia in 15 (11.1%), fungal infection in 13 (9.6%), infectious diarrheas in 5 (3.7%) and urinary tract infection (UTI) in 3 (2.2%) of cases. The composite adverse event outcome was observed in 28 (20.7%) of patients, with in-hospital mortality occurring in 7 (5.2%), Pediatric intensive care unit (PICU) admission occurring in 12 (8.9%) and inotropic support was required in 9 (6.7%). On logistic regression analysis AML (Adjusted odds ratio (AOR), 7.6; $P < 0.001$), neutropenia $< 50/mm^3$ (AOR, 10.8; $p < 0.001$), platelets count $< 50,000/mm^3$ (AOR, 5.2; $p < 0.001$), BSI (AOR, 2.3; $p = 0.05$) and fungal infection (AOR, 4.3; $p < 0.001$) were found as independent risk factors for composite adverse event outcome in pediatric cancer patients with prolonged febrile neutropenia.

Conclusions: AML, severe myelosuppression, blood stream infections and fungal infection were identifiable risk factors associated with development of adverse event outcome in pediatric cancer patients with prolonged febrile neutropenia. *J Microbiol Infect Dis 2016;6(2): 69-73*

Key words: Febrile neutropenia, pediatric, oncology, adverse outcome

Uzamış Febril Nötropeni ile Pediatrik Kanser Hastalarında Karma Olumsuz Durum Sonu

ÖZET

Amaç: Uzamış febril nötropeni pediatrik kanserli hastalarında ağır seyirli yeni tanı veya tekrarlayan bakteri ve mantar enfeksiyonu riski artmıştır. Bu çalışmanın amacı, bu grupta olumsuz sonuçlarla ilişkili risk faktörlerini belirlemektir.

Yöntemler: Pakistan'ta bir üçüncü basamak sağlık merkezine uzamış febril nötropeni nedeni ile izlenen pediatrik kanser hastalarının 135 hastane yatış epizodu retrospektif olarak analiz edildi.

Bulgular: Çalışma grubunun yaş ortalaması $7,3 \pm 4,1$ yıl idi. Hastaların 98'i (% 72,6) erkek ve 37'si (% 27,4) kadındı. Akut lösemi 88 hastada (% 65,2) ile birinci sırada, lenfoma 19 hasta (% 14,1) ile ikinci sırada idi ve diğer hastalarda solid organ tümörleri en sık görülen tanı olarak saptandı. Febril nötropenin nedeni sadece 58 (% 43,0) hastada tanımlandı. Bu hastalardan 22 olguda (% 16,3) kan akımı enfeksiyonu (KAE), 15 hastada pnömoni (% 11,1), fungal enfeksiyon 13 (% 9,6) hastada, ve enfeksiyöz diyare 5 hastada (% 3,7) ve üriner sistem enfeksiyonu 3 (% 2,2) hastada saptandı. Karma olumsuz durumlar 28 (% 20,7) hastada görüldü. Hastanede ölüm 7 (% 5,2) hastada, pediatrik yoğun bakıma yatış 12 (% 8,9) hastada ve inotrop ilaç desteğine ihtiyaç 9 (6,7) hastada saptandı. Lojistik regresyon analizi sonucunda akut miyelositer lösemi (Atfedilebilir Risk Oranı (ARO)), 7,6; $p < 0,001$), nötropeni $< 50/mm^3$ (ARO, 10,8; $p < 0,001$), trombosit sayısı $< 50.000/mm^3$ (ARO, 5,2; $p < 0,001$), KAE (ARO, 2,3; $p = 0,05$) ve mantar enfeksiyonu (ARO, 4,3; $p < 0,001$) uzamış febril nötropenili pediatrik kanser hastalarında kompozit advers olay sonuçları için bağımsız risk faktörleri olarak bulundu.

Sonuç: AML, şiddetli miyelosupresyon, kan akımı enfeksiyonları ve mantar enfeksiyonu tanımlanabilir risk faktörleri olan Grubu Derneği'nden-bir- uzamış febril nötropeni olan pediatrik kanser hastalarında advers olay sonucu gelişmesi ile

Anahtar kelimeler: Febril nötropeni, pediatrik onkoloji, olumsuz sonuç

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INTRODUCTION

Despite major advances in the understanding, established guidelines and recommendations for the treatment of febrile neutropenia (FN), prolonged neutropenia continues to be a significant cause of morbidity and mortality in pediatric patients with cancer [1-3].

In recent years, several studies from developed countries have evaluated the risk factors for poor outcomes among pediatric cancer patients (PCP) and helped to establish the current guidelines for the treatment of FN [4-6]. However, no data available from developing countries to identify the risk factors associated with development of adverse outcomes in pediatric patients with prolonged febrile neutropenia (PFN). This study was carried out to describe the composite adverse event outcomes and identify the associated risk factors in PCP with PFN at a tertiary health care center of Pakistan.

METHODS

Study Design and Setting

This is a retrospective study analyzing the clinical data of all children admitted with or who developed prolonged febrile neutropenia in the pediatric oncology unit at the Aga Khan University Hospital (AKUH) in Karachi, Pakistan from January 2011 to December 2012. AKUH is a 600-bed tertiary health care facility. The pediatric oncology unit has 10 beds along with a 5-bed special care unit within the pediatric ward. A total of 11,465 patients were admitted in pediatric oncology unit over the last 7 years with an average of 1638 admissions per year. There is a separate day care facility for chemotherapy administration and transfusion of blood product.

Patient population and definition

Patients from one month to 16 years of age, who were admitted to the pediatric oncology unit from January 2011 to December 2012 with a diagnosis of prolonged febrile neutropenia were included by using the case definition of (1) new episode of fever, documented or by history (2) absolute neutrophil count (ANC) $<0.5 \times 10^9/L$; (3) currently under treatment for cancer at our institution and (4) duration of febrile neutropenia > 5 days. The definitions of fever and neutropenia for this study were adapted as per guidelines of the infectious diseases society of America (IDSA) [7]. Fever is defined as a single oral temperature of $\geq 38.3^\circ C$ or a temperature of $\geq 38.0^\circ$ sustained over a one hour period, or on more than one occasion in a 24-hour period. Neutropenia

is defined as an absolute neutrophil count (ANC) of less than $0.5 \times 10^9/L$. Bloodstream infection (BSI), and pneumonia in immunocompromised patients were defined according to the criteria established by the Centers for Disease Control/National Healthcare Safety Network (CDC/NHSN) Guidelines [8]. For definition of fungal infections revised criteria for invasive fungal disease from the European Organization for Research and Treatment of Cancer/ Infectious Diseases Mycoses Study Group (EORTC/MSG) was accepted in this study [9]. The primary outcomes in this study were defined as Composite Adverse Event Outcome (CAEO) which includes patients who required inotropic support and/or admitted to the pediatric intensive care unit (PICU) within 24 hours of their presentation and/or mortality.

Data collection

All patients who had diagnosis codes for both neoplastic disease [International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM) code 140-239] and febrile neutropenia, and was 16 years of age or younger were identified by using health information management system and included in the analysis. For those patients who had more than one episodes of prolonged febrile neutropenia, each episodes was counted as a separate case. The primary outcomes of this analysis were a) requirement of inotropic support and b) admission to the pediatric intensive care unit (PICU) within 24 hours of presentation. These factors served as markers for severity of illness and mortality in the hospital. Relevant covariate data including demographic features, age, gender, type of malignancy, phase of chemotherapy, clinical features at presentation, duration of symptoms, initial laboratory findings including total white blood cell (WBC) count, absolute neutrophil count (ANC), and platelet count; radiological findings (if applicable) and microbiological results, management and outcomes were also collected. All patients were treated as inpatients following the "International Pediatric Fever and Neutropenia Guideline" [10].

Statistical analysis

For analysis, SPSS version 20.0 (IBM, Chicago, USA) was used. Death is a rare event in pediatric patients with febrile neutropenia, so we created a composite primary adverse event (AE) outcome including in-hospital mortality and/or its antecedents; admission to the pediatric intensive care unit (PICU) within 24 hours of presentation and/or receipt of inotropic support within 24 hours of presentation. Summary statistics were used to describe

the cohort. Frequencies were computed for qualitative variables, and mean and standard deviation were computed for quantitative variables. Independent risk factors associated with development of adverse effect outcomes were identified by comparing patients with and without composite adverse effect outcomes. A p-value at the univariate level of 0.05 was considered significant. For the multivariate model a p-value cut-off of 0.001 along with high crude odds ratio (OR) were taken into account. Finally, a multiple regression model was applied for variables in such a way that the variable with the most significant p-value was entered first in the final model to calculate the adjusted odds ratio and confidence interval.

Ethical approval

The study was approved by the Ethical Review Board (ERB) of Aga Khan University, Karachi.

RESULTS

The total number of admissions in the pediatric oncology unit during the study period was 2,516. A total of 872 febrile neutropenia episodes were identified and out of them 135 episodes had PFN. FN and PFN episodes among all pediatric oncology admissions in our study was 34.7% and 5.3% respectively.

The study cohort included 135 PFN episodes in 68 patients for final analysis. The number of PFN episode per patient ranged from 1 to 5; out of them 32 patients (47.1%) had single episode, 10 (33.8%) patients had 2-3 episodes and 3 (19.1%) patients had 4-5 episodes of PFN. The mean age of the study population was 7.32 (\pm 4.1) years. There were 98 (72.6%) episodes in males and 37 (27.4%) in females with male: female episodes ratio was 2.6. The mean duration of FN was 10.3 \pm 5.2 days (range 1-25 days). Most of the patients had primary diagnosis of acute leukemia (n=88, 65.2%) and lymphoma (n=19, 14.1%), followed by solid tumors (n=28, 20.7%) (Table 1). Pyrexia alone was the most common presenting complaint (85.6%) followed by poor oral intake (50.5%), vomiting (15.1%), respiratory complaints (12.5%), mucositis (11.3%) and diarrhea (10.6%).

The causes of neutropenia were identified in 58 (43%) episodes; BSI in 22 (16.3%), pneumonia 15 (11.1%), fungal infection 13 (9.6%), infectious diarrhea 5 (3.7%) and UTI in 3 (2.2%) episodes. Additionally, the median neutrophil count and platelet count revealed profound myelosuppression (Table 1). More than 50% of the patients had hemoglobin

level less than 10 gm/dl, absolute neutrophil count (ANC) less than 0.05 x 10⁹/L, and platelet counts less than 50 x 10⁹/L.

Table 1. Demographic, Clinical and Laboratory characteristics of the study population

Characteristics	Episodes number (%)
Gender	98 (72.6%)
Male	37 (27.4%)
Female	
Age	
<5 year	96 (71.1%)
>5year	39 (28.9%)
Cancer Type	
ALL	72 (53.3%)
AML	16 (11.9%)
Lymphoma	19 (14.1%)
Sarcomas	13 (9.6%)
Brain tumors	3 (2.2%)
Others	12 (8.9%)
Blood Stream Infection (BSI)	22 (16.3%)
Pneumonia	15 (11.1%)
Fungal Infection	13 (9.6%)
Absolute Neutrophil Count	
0.25-0.5 x 10 ⁹ /L	29 (21.5%)
0.05-0.25 x 10 ⁹ /L	48 (35.6%)
<0.05 x 10 ⁹ /L	58 (42.9%)
Hemoglobin level <10 gm/dl	87 (64.4%)
Platelets count	
<50 x 10 ⁹ /L	66 (55.9%)
<50 x 10 ⁹ /L	52 (44.1%)
Composite AE Outcomes (n=28)	
Inotropic Support	9 (6.7%)
PICU Admission	12 (8.9%)
Died	7 (5.2%)

ALL=Acute Lymphoblastic Leukemia; AML=Acute Myeloid Leukemia; AE, Adverse Event

The composite AE outcome were observed in 28 (20.7%) patients with in-hospital mortality occurring in 7 (5.2%), PICU admission in 12 (8.9%) and inotropic support requirement in 9 (6.7%) (Table 1). On logistic regression analysis (Table 2) cancer type Acute myeloid leukemia (AML) (Adjusted odds ratio, 7.63 [95% confidence interval, 1.12-91.35]; p < 0.001), severe neutropenia ANC < 0.05 x 10⁹/L (AOR, 10.83 [95% CI, 1.37-65.74]; p < 0.001), platelets count < 50 x 10⁹/L (AOR, 5.17 [95% CI, 1.17-23.78]; p < 0.001), BSI (AOR, 2.33 [95% CI, 0.84-15.79]; p 0.05) and fungal infection (AOR, 4.26 [95% CI, 1.34-86.57]; p < 0.001) were found as independent risk factors associated with development of composite AE outcome in pediatric oncology patients with prolonged FN.

Table 2. Risk Factors for Composite Adverse Event Outcome in pediatric cancer patients with Prolonged Febrile Neutropenia

Variables	Without composite AE outcome, n=107 (%)	With composite AE outcome, n=28 (%)	Crude OR† (CI)	p-value	Adjusted OR (CI)
Gender Male††	80 (75)	18 (64)			
Female	27 (25)	10 (36)	1.65 (0.68-3.99)	0.267	--
Age < 5 year††	79 (74)	17 (61)			
> 5 year	28 (26)	11 (39)	1.83 (0.76-4.37)	0.172	--
Cancer Type					
ALL††	58 (54)	14 (50)			
AML	6 (6)	10 (29)	9.24 (2.79-30.6)	<0.001	7.63 (1.12-91.35)
Lymphoma	17 (16)	2 (7)	0.91 (0.23-3.57)	0.598	--
Sarcomas	12 (11)	1 (4)	0.69 (0.14-3.42)	0.491	--
Others	14 (13)	1 (4)	0.61 (0.12-4.42)	0.532	--
Received Chemotherapy within the preceding 2 weeks [§]	89 (83)	19 (68)	0.43 (0.17-1.09)	0.07	--
ANC (< 0.05 x 10 ⁹ /L) [§]	35 (33)	23 (82)	9.46 (3.32-26.99)	<0.001	10.83 (1.37-65.74)
Platelets count (< 50 x 10 ⁹ /L) [§]	29 (27)	23 (82)	12.37 (4.29-35.60)	<0.001	5.17 (1.17-23.78)
Blood stream Infection [§]	14 (13)	8 (29)	2.66 (0.98-7.18)	0.050	2.33 (0.84-15.79)
Pneumonia [§]	11 (10)	6 (21)	2.38 (0.79-7.13)	0.106	--
Fungal Infection [§]	5 (5)	8 (29)	8.16 (2.41-27.52)	<0.001	4.26 (1.34-86.57)

AE=Adverse Event; **OR**=Odd Ratio; **CI**=95% Confidence Interval; **ALL**=Acute Lymphoblastic Leukemia; **AML**=Acute Myeloid Leukemia; **ANC**=Absolute Neutrophil Count; **†**=The odds ratio reflects the risk of composite AE outcome in patients with PFN for each variable; **††**=This is the reference group for the categorical predictor variable; **§**=For each variable of risk factor, not having the specific risk was used as the reference group.

DISCUSSION

A number of studies from developed countries have evaluated the risk factors for bacteremia or poor outcomes in children with febrile neutropenia. There has been increasing interest in stratifying these patients into risk categories to establish guidelines for better management [7,12-14]. The current study uses a single institution database to identify the risk factors for development of adverse outcomes among PCP with PFN.

Although death is the most devastating of all potential complications of FN, most of the studies use bacteremia or other bacterial infections as the main outcomes variables.[11, 15, 16] A recently published study reported 11.1% composite AE outcome in FN patients with in-hospital mortality of (0.7%), PICU admission (4.7%), and fluid resuscitation > 40 ml/kg in (10.1%).[17] In our series, 7 out of 135 episodes (5.2%) of PFN had fatal outcome, 9 (6.7%) required inotropic support and 12 (8.9%) were admitted to PICU for supportive care. Thus over all we found composite AE in 28/135 (20.7 %) episodes. This high mortality was among patients

who had PFN episodes. However, the mortality rate in some other pediatric studies of FN has ranged from 0.7% to 3.9% [16, 18-20].

In many studies, age group emerged as another significant independent risk factor for both longer hospital stay and death. [13] In the current study, the risk of composite AE outcome was higher in children younger than 5 years compared to those who were older (61% vs. 39%; OR 1.83), although the result was not statistically significant (p=0.172).

In comparison to ALL, a diagnosis of AML was associated with eight-fold increased risk of overall adverse outcome and four-fold increased risk of death. A similar study reported three-fold longer length of stay as well as death in AML patients as compared to ALL [13]. A diagnosis of lymphoma and sarcomas was associated with a significant reduction in the risk of composite adverse outcome. This is consistent with studies in adult population [5]. Similarly, pediatric studies have identified de-novo or relapsed leukemia as a high risk factors for bacterial infection [18,20].

Our data also showed that severe myelosuppression was associated with composite AE outcome as patients with more severe neutropenia and thrombocytopenia have a higher risk for AE [13,21]. A diagnosis of sepsis or bacteremia conferred a 2.3-fold increase in the risk (13% vs. 29%; $p=0.05$) of composite AE. Both pneumonia (OR: 2.4) and fungal infection (AOR 4.3, $p<0.001$) were associated with an increased risk of poor outcomes in our study, as compared to eight-fold and five-fold increased risk of death reported [13].

Limitations of this study include a single center study and retrospective design. Additionally, we did not collect physiologic data (heart rate and blood pressure), which may have furthered our understanding of the poor outcome of children. Finally, we did not attempt to account for baseline level of illness, use of growth factors, type of chemotherapy used, existing co-morbidities, and sources of infection other than bacterial and fungal.

CONCLUSION

In conclusion, our study indicates that a diagnosis of AML, severe neutropenia, severe thrombocytopenia, BSI and fungal infection should be considered high risk factors associated with development of composite AE outcome in PCP with PFN. The identification of risk factors for poor outcomes may help in devising FN protocols and update guidelines for providing optimum therapy to reduce the cost of cancer care as well as to improve the overall outcomes in children with cancer. Prospective studies of PFN among children enrolled in large cooperative trials may be beneficial in evaluating these risk factors further.

Declaration of Conflicting Interests: The authors declare that they have no conflict of interest.

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