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Clinical factors predictive of recurrent febrile neutropenia in adult patients with acute leukemia

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ABSTRACT

Febrile neutropenia (FN) is considered an oncologic emergency in acute leukemia. There were 250 FN events in 124 hospitalized patients with hematologic malignancy. These data imply that two FN events may occur per patient, yet data on the prevalence, risk factors, and outcomes of recurrent FN in adult patients with leukemia are limited. A retrospective cohort study was conducted that enrolled adult patients diagnosed with acute leukemia who developed FN. The eligible patients were categorized as with or without recurrent FN. A stepwise, multivariate logistic regression analysis was performed to identify predictors of recurrent FN. A total of 203 patients met the study criteria; of these, 46 (22.66%) had recurrent FN, and this group had a median of three recurrent FN emergencies. After adjusted, three independent factors remained in the final model including ALL, FN at admission, and treatment with idarubicin (3 days) and cytarabine (7 days). The three factors were positively associated with recurrent FN with adjusted odds ratios of 6.253, 4.068, and 10.757, respectively. No significant differences were found between the two groups in terms of other sources of infection, other pathogens, ICU stay, hospital stay, and mortality. ALL and FN at admission and treatment with idarubicin (3 days) and cytarabine (7 days) were associated with recurrent FN in acute leukemia patients with FN. Clinical outcomes for patients with or without recurrent FN were mostly comparable; however, due to its small sample size, further studies are required to confirm the results of this study.

1. Introduction

Febrile neutropenia (FN) is considered an oncologic emergency[1]. It may occur after chemotherapy in up to 80% of patients with hematologic malignancy[1]. Approximately 12% of acute leukemia patients may develop FN at diagnosis without chemotherapy treatment[2]. The common cause of FN is infection, particularly bacterial[1]. Up to 35% of FN can be documented causes of infection such as *Escherichia coli* or *Staphylococcus*[1]. Fungal infection is another possible infection, particularly in patients with acute leukemia, and has a high mortality rate of 40%[3].

Recurrent FN is one factor associated with antibiotic-resistant bacterial infection such as methicillin-resistant *Staphylococcus aureus* (MRSA) or carbapenemase-producing Enterobacteriaceae (CPE)[4]. It may also indicate a concealed infection such as splenic abscess[5]. A Turkish study identified 250 FN events in 124 hospitalized patients with hematologic malignancy [6]. These data imply that FN occurs twice per patient. However, the data on prevalence, risk factors, and outcomes of recurrent FN in adult patients with leukemia are limited.

2. Materials and methods

This was a retrospective analytical study conducted at Srinagarind Hospital, a teaching hospital associated with Khon Kaen University, and was part of an acute leukemia research project. The subgroup study included adult patients diagnosed with acute leukemia who had developed FN. Eligible patients were divided into two groups: with and without recurrent FN. Recurrent FN was defined as new FN after previous FN. The study period was January 1, 2013 – December 31, 2015. The study protocol was approved by the ethics committee in human research, Khon Kaen University, Khon Kaen, Thailand (HE591013).

Data for the eligible patients were retrieved from admitted medical charts. The studied variables included baseline characteristics, types of leukemia, acute leukemia treatment regimens, leukemic profiles such as

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blasts in the bone marrow, sites of infection, types of pathogens, other treatments, and treatment outcomes including hospital stays and mortality. Sites of infection are defined by clinical findings and/or evidence from cultures, such as lower respiratory tract infection (LRI) defined by the presence of new pulmonary infiltration with or without positive sputum culture. Causative pathogens were defined as positive by culture with clinical confirmation. Prolonged treatment with broad-spectrum antibiotics was administered for more than 10 days.

Statistical analyses: Data were categorized into two groups: with and without recurrent FN. Descriptive statistics were used to compare differences between both groups. Predictors for recurrent FN were calculated using logistic regression analysis. A univariate logistic regression was used to compute unadjusted odds ratio and a p value. Those factors with a p value according to univariate logistic analysis of less than 0.25 or potential factors from previous studies, if available, were included in the subsequent multivariate logistic regression analysis. A stepwise method was used to identify the strongest predictors, and a goodness of fit of the final model was tested using the Hosmer–Lemeshow method. The results were presented as median (range), number (percentage), p values, and unadjusted/adjusted odds ratio with 95% confidence interval (CI). The statistical analyses were performed by STATA software, version 10.1 (College Station, Texas, USA).

3. Results

A total of 203 patients met the study criteria. Of these, 46 (22.66%) had recurrent FN. The recurrent FN group had a median of three recurrent FN emergencies (2–7 times). Among the clinical features, there were four significant factors between those with and without recurrent FN (Table 1) including treatment with idarubicin (3 days) and cytarabine (7 days), FN at admission, neutropenic time, and GCSF. The recurrent FN group had higher proportions of treatment with idarubicin (3 days) and cytarabine (7 days) (47.83% vs 12.90%; p 0.001), FN at admission (50.00% vs 21.85%; p 0.001), and longer neutropenic duration (12 vs 7 days; p 0.002) than the group without recurrent FN. After adjusted, three independent factors remained in the final model including ALL, FN at admission, and treatment with idarubicin (3 days) and cytarabine (7 days). These three factors were positively associated with recurrent FN with adjusted odds ratios of 6.253, 4.068, and 10.757, respectively (Table 2). Note that factors in the stepwise model included age, sex, body mass index, AML, APL, ALL, blasts in the bone marrow, lowest ANC, FN at admission, regimen I3A7, and regimen ALL induction. The Hosmer–Lemeshow chi-squared of the final model was 5.22 (p 0.265).

For treatment outcomes, there were three significant factors between both groups including proportions of septic shock, blood-stream infection, and *E. faecalis* infection (Table 3). The recurrent FN group had a higher proportion of *E. faecalis* infection (8.70% vs 1.27%; p 0.025) than the non-recurrent FN group. However, the proportions of septic shock (4.35% vs 20.38%; p 0.012) and blood-stream infection (10.87% vs 29.94%; p 0.012) were lower in the recurrent FN group than in the non-recurrent FN group. No significant differences were found between the two groups in terms of other sources of infection, other pathogens, ICU stay, hospital stay, or mortality.

Table 1
baseline characteristics and clinical features of acute leukemia patients with febrile neutropenia (FN) categorized by recurrent FN.

Factors	No recurrent FN*n*= 157	Recurrent FN*n*= 46	p value
Age, years	41 (18–71)	37 (18–65)	0.281
Male	76 (48.41)	21 (45.65)	0.867
Body mass index, kg/m^2	21.53 (13.80–41.14)	22.21 (15.73–33.13)	0.640
Body surface area, m^2	1.59 (1.20–2.47)	1.58 (1.28–1.97)	0.617
Types of leukemia			
AML	101 (64.33)	29 (63.04)	0.863
APL	11 (7.01)	1 (2.17)	0.305
ALL	31 (19.75)	11 (23.91)	0.539
Treatment regimen			
I3A7	20 (12.90)	22 (47.83)	0.001
I2A5	5 (3.23)	1 (2.17)	0.999
ALL induction	31 (19.75)	11 (23.91)	0.539
Hypomethylating	35 (22.58)	6 (13.04)	0.211
% Blast in blood smear	53 (0–99)	50 (0–98)	0.572
% abnormal promyelocyte in BM	75 (20–100)	90 (30–99)	0.854
ANC100	141 (89.81)	39 (84.78)	0.426
ANC lowest	5.1 (0–505)	4 (0–521)	0.669
FN at admission	29 (21.85)	21 (50.00)	0.001
Onset of FN	10 (1–20)	10 (1–39)	0.613
Total parenteral nutrition	1 (0.64)	0	0.999
Serum albumin, g/dL	3.8 (2.0–5.0)	3.8 (2.3–5.0)	0.723

Note. Data presented as median (range) for numerical variables and number (percentage) for categorical variables; AML: Acute myeloid leukemia; APL: Acute promyelocytic leukemia;, ALL: Acute lymphoblastic leukemia; BM: bone marrow; I3A7: idarubicin 3 days plus cytarabine 7 days; I2A5: idarubicin 2 days plus cytarabine 5 days; GCSF: Granulocyte-colony-stimulating factor; URI: upper respiratory tract infection; LRI: lower respiratory tract infection; UTI: urinary tract infection;*indicated two most common pathogens in each category; ICU: intensive care unit.

4. Discussion

Almost one-fourth of adult patients with acute leukemia experienced recurrent FN, with a maximum of seven emergencies. The mortality rate for acute leukemia patients with FN in this study was 6.89%, which was lower than the previous report (32%)[3]. The group with FN at admission may have had more blasts in peripheral blood and bone marrow, which may increase the risk of infection[7,8]. We performed an analysis based on this hypothesis. The FN at admission group had non-significant higher percentages of blasts in peripheral blood (51% vs 31%; p 0.255) and bone marrow (80% vs 70%; p 0.399) than those with FN after admission. Even though these differences were not significant, FN at admission increased the risk of recurrent FN by four times after adjusting for other factors. Treatment with idarubicin and cytarabine was also found to have a common febrile neutropenia side effect of 28%[9,10]. Therefore, this regimen showed a positive correlation with recurrent FN by 10 times, the strongest predictor for recurrent FN (Table 2). Note that treatment with idarubicin (3 days) and cytarabine (7 days) in our setting was as follows: idarubicin with a dosage of 12 mg/m^2 and cytarabine with a dosage of 100 mg/m^2. Regarding types of acute leukemia, previous studies showed that AML patients had more severe FN than ALL patients in terms of poorer clinical outcomes and hemodynamic instability[11]. Additionally, infection-related death was low at 1% in ALL patients with FN[12]. These factors may increase survival of ALL patients, which in turn may increase the risk of recurrent FN resulting from further chemotherapy as well. However, definite plausible mechanisms for this correlation should be a goal of further research. Although a previous review found that age, sex, and body mass index were related to FN, the present study did not find these associations[13]. The results may imply that these three factors were stronger than the baseline factors of age, sex, and body mass index. These factors did not remain in the

Table 2
factors associated with recurrent febrile neutropenia in adult patients with acute leukemia.

Factors	Unadjusted odds ratio(95% confidence interval)	Adjusted odds ratio(95% confidence interval)
ALL	1.277 (0.583, 2.795)	6.253 (1.688, 23.164)
FN at admission	3.577 (1.698, 7.533)	4.068 (1.571, 10.535)
I3A7	6.187 (2.937, 13.035)	10.757 (3.382, 34.215)

Note. ALL: Acute lymphoblastic leukemia; I3A7: regimen of Idarubicin 3 days plus Ara-c 7 days.

Table 3
clinical outcomes of adult patients with acute leukemia and febrile neutropenia (FN) categorized by recurrent FN.

Factors	No recurrent FN*n*= 157	Recurrent FN*n*= 46	p value
Neutropenic time	7 (1–47)	12 (1–44)	0.002
GCSF	66 (42.04)	7 (15.22)	0.001
Duration of fever	5 (1–57)	5 (1–26)	0.566
Fever persisted at 4th day	84 (53.50)	29 (63.04)	0.312
Prolong broad antibiotic	97 (61.78)	30 (65.22)	0.731
Current steroid use	4 (2.55)	0	0.576
Septic shock	32 (20.38)	2 (4.35)	0.012
Sites of infection			
Blood	47 (29.94)	5 (10.87)	0.012
Catheter	1 (0.64)	1 (2.17)	0.403
URI	12 (7.64)	5 (10.87)	0.545
LRI	37 (23.57)	12 (26.09)	0.700
Abdominal	5 (3.18)	2 (4.35)	0.658
UTI	6 (3.82)	4 (8.70)	0.239
Skin, soft tissue	22 (14.01)	12 (26.09)	0.071
Anal area	5 (3.18)	2 (4.35)	0.658
Unknown	52 (33.12)	14 (30.43)	0.858
Pathogens*			
Gram positive	18 (11.46)	7 (15.56)	0.449
Gram negative	57 (36.31)	11 (24.44)	0.155
Fungus	20 (12.74)	9 (19.57)	0.240
E. faecalis	2 (1.27)	4 (8.70)	0.025
S. viridians	5 (3.18)	0	0.590
E. coli	18 (11.46)	3 (6.52)	0.419
Klebsiella	10 (6.37)	0	0.115
Aspergillus	14 (8.92)	5 (10.87)	0.774
Candida	6 (3.82)	4 (8.70)	0.239
Galactomannan	0 (0–4)	0 (0–3)	0.713
Galactomannan positive	22 (14.01)	5 (10.87)	0.805
ICU stay, days	7 (1–38)	4 (4–4)	0.446
Hospital stay, days	28 (2–102)	28 (3–66)	0.626
Mortality	11 (7.01)	3 (6.52)	0.999

Note. Data presented as median (range) for numerical variables and number (percentage) for categorical variables; GCSF: Granulocyte-colony-stimulating factor; URI: upper respiratory tract infection; LRI: lower respiratory tract infection; UTI: urinary tract infection;.

* indicated two most common pathogens in each category; ICU: intensive care unit.

final model for recurrent FN using the stepwise method (Table 2).

Regarding clinical outcomes between the recurrent and non-recurrent FN groups in acute leukemia, most of them in this study were comparable except for the proportions of septic shock, bloodstream infection, and *E. faecalis* infection (Table 3). As previously reported, both septic shock and bloodstream infection increased the risk of mortality[2,14,15]. The mortality group had a significantly higher proportion of septic shock than those who survived (86.4% vs 13.6%; $p < 0.001$)[2]. These results may imply that septic shock may increase mortality rate for any organism, while the mortality rate in gram-positive organisms such as *E. faecalis* may be lower than the mortality rate for bloodstream infection or septic shock. Although *E. faecalis* infection was found more in the recurrent FN group, it may not change the overall survival rate. Unlike septic shock or bloodstream infection in the non-recurrent FN, the mortality rate may be non-significantly higher in this group (7.01% vs 6.52%). This non-significant difference could be due to the small sample size. Regarding the causative agents of FN, previous studies have found that there might be different pathogens in FN patients in Thailand from those in other countries. In Thailand, the most common pathogen was gram-negative bacteria, with occurrence ranging from 48.6% to 63.9%[16,17], while a gram-positive bacterium was found to be the highest (ranging from 56.5% to 67.4%) in patients in European countries[18,19]. Clinical epidemiological data regarding causative pathogens in patients with FN are crucial as they might vary among countries.

This present study has several limitations. First, this was a single-site, university-hospital level study that enrolled only those with FN. Data for patients without FN were not included. Second, some data are missing due to the retrospective study design [20–22]. Finally, patients enrolled in this study were those admitted to hospital with FN; those with mild cases were not included. Although we found that treatment with idarubicin (3 days) and cytarabine (7 days) related to recurrent FN was a factor, modifications of this regimen may be optional and would depend on the decision of the attending physician, as the regimens are standard.

In conclusion, ALL, FN at admission, and treatment with idarubicin (3 days) and cytarabine (7 days) were associated with recurrent FN in acute leukemia patients with FN. Clinical outcomes between patients with and without recurrent FN were mostly comparable.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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