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

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ARTICLE INFO
Keywords:
Acute leukemia
Predictive factors
Recurrent febrile neutropenia

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...
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 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.

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/m² and cytarabine with a dosage of 100 mg/m². 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 final model.

### Table 1

| 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/m²         | 21.53                   | 22.21               | 0.640   |
| Body surface area, m²          | (13.80–41.14)           | (15.73–33.13)       | 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                     | 71 (–)                  | 40 (–)              | 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 (2.9-5.0)           | 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.

### Table 2

| 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 | Recurrent FN | 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                 | 37 (23.61)      | 11 (24.44)   | 0.455   |
| Fungus                        | 20 (12.74)      | 9 (19.57)    | 0.240   |
| E. faecalis                   | 2 (1.27)        | 0 (0)        | 0.025   |
| E. stieltii                   | 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)        | 3 (6.52)     | 0.239   |
| Galactomannan                 | 0 (0)           | 0 (0)        | 0.713   |
| Galactomannan positive        | 22 (14.01)      | 5 (10.87)    | 0.805   |
| ICU stay, days                | 7 (1–38)        | 4 (4–44)     | 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.

The authors declare that they have no competing interests.

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