Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.58, No.6(2018). p. 298-304; doi: http://dx.doi.org/10.14238/pi58.6.2018.298-304

Original Article

Impact of malnutrition on febrile neutropenia in children with acute lymphoblastic leukemia during induction phase chemotherapy

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Abstract

Background Acute lymphoblastic leukemia (ALL) is the most common malignancy in children and adolescents. Febrile Neutropenia (FN) is a medical emergency on ALL that often leads to death. Nutrition status assessment on ALL patient is important because malnutrition can reduce the tolerance of chemotherapy, increase incidence of infection and decrease survival rate.

Objectives To assess malnutrition as a risk factor for FN in children with ALL.

Methods This case-control study was performed at Sardjito Hospital, Yogyakarta on patients aged 1 month to 18 years diagnosed with ALL and undergoing induction phase chemotherapy between January 2013 and December 2015. The case and control subjects were children with and without FN, respectively. Febrile neutropenia was confirmed by patients temperature above 38 ° C at one measurement and a peripheral neutrophil count of less than 1,000/mm3. Malnutrition was defined as body weight-for-height was between -2 and <-3 standard deviation. Subjects were included using simple random sampling.

Results Bivariate analysis showed a significant correlation between malnutrition and FN (OR 2.62; 95%CI 1.07 to 6.45; P=0.03). However, there was no inverse correlation between socioeconomic status and FN (OR 1.1; 95%CI 0.42 to 2.41; P=0.83). There was no correlation between nutritional status and duration of FN (P= 0.48).

Conclusion Malnutrition is a risk factor for FN in children with acute lymphoblastic leukemia. **[Paediatr Indones. 2018;58:298-304; doi: http://dx.doi.org/10.14238/pi58.6.2018.298-304**].

Keywords: *febrile neutropenia; childhood acute lymphoblastic leukemia; nutritional status*

The annual incidence rates of malignancy was reported 186.6 per 1 million children aged birth to 19 years. Acute leukemia is a common malignancy in children.[1] Incidence rate of ALL during 2003-2007 ranged from 1.08-2.12 cases per 100,000 children. Incidence was generally higher in America and Oceania, and the lower incidence in Asia and Eastern countries. In the most countries, the incidence rate of childhood ALL was approximately four times that in adults.[2] The estimated average annual incidence rate of childhood ALL was 20.8 cases per 1,000,000 in Yogyakarta.[3]

Febrile neutropenia is a frequent emergency complication, requiring rapid identification and intervention to save and improve quality of life.[4] In India, the incidence of FN during induction phase chemotherapy was 89.2% of all acute leukemia cases,[5] compared to 47% incidence in Thailand.[6] Kandou Hospital in Manado reported an FN incidence of 22% from all leukemia cases.[7]

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Asturias *et al.* showed that hypotension, C-reactive protein, thrombocytopenia, chemotherapy, nutritional status, and leukemia morphology were not risk factors for FN.[8] Tamam *et al.* showed that poor socioeconomic status was a risk factor for FN (OR 4.59; 95%CI 1.078 to 15.08; P=0,032), while nutritional status was not (P=0.382).[9] Also, a study by Alexandre et al. noted that nutritional and inflammatory status (NIS) were significantly associated with the occurrence of FN.[10] In other studies, FN events were significantly influenced by nutritional status,[11] and malnutrition was a risk factor for FN (RR 24.57; P=0.000).[12]

Assessment of nutritional status in patients with malignancy is important because malnutrition can reduce chemotherapy tolerance, increase the incidence of infection, and decrease survival rate.[13] Malnutrition may be associated with immune response disorders such as impaired phagocyte function, cytokine production, antibody secretion and complement system defects.[14] A critical review of the prognostic value of the nutritional status in children with ALL noted that the mortality rate for children with malnutrition was 1.8 times greater than in ALL children with good nutrition (95%CI 1.72 to 1.88; P <0.001).[15] However, in Yogyakarta to date, there is still no published data on the relationship between nutritional status and FN in children with ALL. The aim of the study was to assess malnutrition as a risk factor for FN in children with ALL, and the results may be used by clinicians or researchers as a reference to improve remission rates and overall survival in children with ALL.

Methods

This case-control study was conducted using medical records data from Sardjito General Hospital. Subjects were children (aged 1 month-18 years) with ALL who underwent induction phase chemotherapy from January 2013 to December 2015. The diagnosis of ALL was based on bone marrow examination, those with FN during induction phase were included in the case group. The control group were patients confirmed ALL and had not FN during induction phase. We excluded patients diagnosed with ALL who previously had been treated with chemotherapy or steroids, as well as patients with clinical finding of Down syndrome, heart failure, or patients with incomplete medical record data (weight, height and socioeconomic status).

Nutritional status assessment was based on the 2006 WHO child growth Z-score for weight-for-height (age <5 years) or body mass index for age (≥5 years). Severe malnutrition was defined as Z-score ≤-3 standard deviation (SD), malnutrition as -2<Z<-3 SD and good nutrition as -2<Z<+2 SD.[16,17] Subject selection was done using simple random sampling to reduce bias. We classified parent education as: primary education (graduated from elementary or junior high school), middle (graduated from senior high school), high (graduated from diploma, bachelor or magister). Socioeconomic status was considered as low if total income of parents is ≤ Rp. 1.300.00,00 per month. Based on prognostic factor, patients were grouped into high risk and standar risk. High risk patients were defined as: age <1 year or >10 years, white blood count was more than 50,000/uL, immunophenotyping was T-cell leukemia, had a mediastinal mass at diagnosis and blast number at peripheral blood >1,000/uL after one week of steroid and 1 dose of intrathecal methotrexate. The remaining patients were classified into standard risk group.[18]

Bivariate analysis results with P values of <0.05 were considered to be statistically significant. Multivariate analysis was done, if needed, by stepwise logistic regression. The results were reported as odds ratio (OR) with 95% confidence interval (CI). This study was approved by the Medical and Health Research Ethics Committee (MHREC), Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital.

Results

A total of 228 patients were diagnosed with ALL and received induction phase chemotherapy at Sardjito General Hospital from January 2013 to December 2015. Eighty-three patients were excluded. Of the 145 patients who met the inclusion criteria, 75 patients were treated as cases (FN) and 70 patients as the controls (no FN). Based on minimal sampling calculation and to reduced bias, we took 50 patients as cases and 50 patients as controls. We numbered a

queationnaire at the top right, made a small paper, gave a number (75 cases and 70 controls), folded, mixed and with the closed eyes we took 50 time (each for cases and controls). The subjects' characteristics are presented in **Table 1**.

Of 50 subjects with FN, 44 (88%) developed 1 episode of FN during 7 weeks of induction chemotherapy, 5 (10%) subjects developed 2 episodes of recurrence FN and 1 (2%) subject developed 3 episodes of recurrent FN. Two of 50 (4%) subjects died due to FN (**Table 2**).

Table 1. Characteristics of subjects

Characteristics	FN (n=50)	Without FN (n=50)
Median (range) age at ALL diagnosis, months	56 (14-191)	73 (12-208)
Sex, n (%)		
Male	30 (60)	28 (56)
Female	20 (40)	22 (44)
Paternal education, n (%)		
Primary education	23 (46)	28 (56)
Middle education	18 (36)	12 (24)
High education	9 (18)	10 (20)
Maternal education, n (%)		
Primary education	25 (50)	29 (58)
Middle education	18 (36)	9 (18)
High education	7 (14)	12 (24)
Maternal occupational status, n (%)	38 (76)	20 (40)
Working	12 (24)	30 (60)
Not working		
Risk of therapy group, n (%)		
High risk	32 (64)	25 (50)
Standard risk	18 (36)	25 (50)
Nutritional status, n (%)		
Severe malnutrition	3 (6)	6 (12)
Malnutrition	21 (42)	11 (22)
Over nutrition	2 (4)	0 (0)
Good nutrition	24 (48)	33 (66)
Albumin level, n(%)		
Albumin < 3,5 g/dL	16 (32)	8 (16)
Albumin ≥ 3,5 g/dL	34 (68)	42 (84)
Socioeconomic status, n (%)		
Low	21 (42)	20 (40)
High	29 (58)	30 (60)
Median ANC (range), cells/uL	265 (0-1000)	-

Table 2. Frequency of FN and outcome of FN subjects

Parameters	(N=50)
Frequency FN during induction phase, n (%)	
1 time	44 (88)
2 times	5 (10)
≥ 3 times	1 (2)
Outcome, n (%)	
Died	2 (4)
Alived	48 (96)

Bivariate logistic regression analysis on nutritional status was done using good nutrition as standard compared to severe malnutrition, malnutrition, and over malnutrition. Malnutrition was significantly higher in the FN case group than in the control group (P=0.03). However, severe malnutrition showed no significant differences between good nutrition. We could not analyze between patients with over malnutrition and good nutrition because only two patients had FN and no patient without FN. Bivariate analysis revealed that malnutrition had significant relationship with FN occurrence (OR 2.62, 95%CI 1.07 to 6.45; P=0,03) (**Table 3**).

Further bivariate analysis was conducted to identify confounding factors suspected to affect the occurrence of FN. Socioeconomic status was categorized as low or high, but we found no significant differences between the case and control groups (OR 1.1, 95% CI 0.49 to 2.41, P=0.83). We did not proceed to multivariate analysis because only malnutrition had P values <0.25 (**Table 4**).

We also assessed for a relationship between duration of FN and nutritional status. Gamma correlation test revealed no significant relationship between duration of FN with nutritional status (P=0.48) (**Table 5**).

Table 3. Analysis of nutritional status as a risk factor for FN

Nutritional status	FN (n=50)	Without FN (n=50)	OR	95%CI	P value
Severe malnutrition, n(%)	3 (6)	6 (12)	0.68	0.15 to 3.02	0.,62
Malnutrition, n(%)	21 (42)	11 (22)	2.62	1.07 to 6.45	0.03
Over nutrition, n(%)*	2 (4)	0 (0)	-	-	-
Good nutrition, n(%)**	24 (48)	33 (66)	-	-	-

* Over nutrition vs. good nutrition OR, CI and p value could not be calculated

** Good nutrition as the standard reference

Discussion

The main purpose of this study was to determine if poor nutritional status (malnutrition or severe malnutrition) is a risk factor for febrile neutropenia in children with ALL. A previous study showed that malnutrition increased the risk of infection 2-3 times, as well as lengthened hospital stay and duration of induction phase chemotherapy.[20] Another study reported that malnutrition was correlated with FN in children with ALL underwent induction phase chemotherapy.[12] However, a previous study in our center showed no statistically significant relationship between nutritional status and incidence of FN during induction phase chemotherapy.[21] A Guatemala study also showed no association between nutritional status and FN.[8]

Because of the inconsistent results of previous studies, we aimed to further assess malnutrition as a risk factor for the occurrence of FN in children with ALL who underwent induction phase chemotherapy. A differences of our study, compared to Kholisa study,[21] was the division of nutritional status into 4 categories based on the 2006 WHO chart: severe malnutrition, malnutrition, good nutrition and over nutrition.[16] We noted that few newly diagnosed ALL patients had over nutrition or obesity. The body's response to cancer is to produce TNF, IL-1, and IL-6. The TNF suppresses lipoprotein kinase activity that reduces fat reserves.[22,23] The IL-1 and IL-6 break down protein and decrease albumin synthesis.23 Taken together, these conditions lead to malnutrition in children with ALL. Malnutrition impairs immune function, leading to increased incidence of infection, chemotherapy toxicity, poor quality of life, as well as death.[24,25]

We found that malnutrition was a risk factor for FN in children with ALL during induction phase chemotherapy (OR 2.62; 95%CI 1.07 to 6.45; P=0.03) (**Table 3**). However, severe malnutrition was not a significant risk factor for FN because few of our subject were diagnosed with severe malnutrition. The ALL patients with severe malnutrition undergo severe malnutrition management with oral antibiotics of cotrimoxazole (if no sign of infection) for 5 days or empirical, intravenous antibiotics, in case of infections, consisting of ceftazidime and gentamicin. Cotrimoxazole is a combination antibiotic consisting of sulfamethoxazole (bacteriostatic) and trimethoprim (bactericidal). The spectrum of cotrimoxazole can kill the Gram-positive bacteria (Staphylococcus sp. and Streptococcus), Gram-negative bacteria (Enterobacter sp. and Klebsiella sp), anaerobes, and protozoa. Cotrimoxazole mechanism of action inhibits DNA, RNA and protein formation by blocking the folate pathway.[26] Standard risk group of ALL patients who had FN needed prophylactic antibiotic (Level of Evidence 1B).[27] Prophylactic cotrimoxazole was reportedly effective in preventing pneumocystis pneumonia (PCP) in ALL (Level of Evidence 1A)[28] and was associated with decreased mortality caused by PCP.[29,30]

Table 4. Risk factors for FN in children's ALL (logistic regression)

Risk factors	FN (n=50)	Without FN (n=50)	Bivariate analysis		
			OR	95%CI	P value
Malnutrition, n(%)*	21 (42)	11 (22)	2.62	1.07 to 6.45	0.03
Low socioeconomic status, n(%)*	21 (42)	20 (40)	1.1	0.42 to 2.41	0.83

Note: * no multivariate analysis was performed

Table 5. Analysis of duration of FN and nutritional status

Nutritional status, n(%)	FN ≥ 7 days (n=30)	FN < 7 days (n=20)	Correlation coefficient (r)	P value
Severe malnutrition	3 (10)	0 (0)		
Malnutrition	11 (36)	10 (50)		
Over nutrition	1 (4)	1 (5)	0.17	0.48
Good nutrition	15 (50)	9 (45)		

Notes: Cut off point 7 days was used based on length of care FN.[19] Duration of FN was calculated when the patient had first episode of FN

In addition to antibiotics, severe malnutrition management includes supplements such as zinc and other micronutrients. Zinc has a direct immunomodulatory effect and an indirect effect of protecting the epithelium. Zinc supplementation in long-term malnutrition enhances cellular immunity.[31] Zinc also decreases the duration and severity of FN.[32]

Tamam *et al*. found that poor socioeconomic status was a risk factor for FN (OR 4.59; 95%CI 1.078 to 15.08; P=0.032), while we did not.[9] This difference may be due to most of our patients were covered by the National Health Insurance System to finance either hospitalization or polyclinic treatment. However, using monthly parental income data obtained from medical records as an economic indicator, we found no such association. In this study, low economic status was not connected with FN (OR 1.1; 95%CI 0.42 to 2.41; P=0.83). Overall survival was reported elsewhere as higher in children with ALL those with high than with low socioeconomic status.[33,34]

Other results of our study were similar to previous findings: FN was common in the first and second weeks of chemotherapy administration in induction phase and improved within 14-26 days. This event is due to the timing of ALL diagnosis, in which bone marrow was already in a state of FN, and chemotherapy then made conditions worse.[35] None researchers studied between influence nutritional status with first occurrence of FN.

The number of FN occurrence in our subjects who underwent induction phase chemotherapy for 7 weeks were 44 subjects (88%) with one occurrence, 5 subjects with two occurrence and 1 subject with three occurrence. A previous study showed that FN occurred 2-4 times during 6 months of chemotherapy36 and patients with malnutrition experienced 3 times higher incidence of FN.[14]

The risk of death, comorbidities, bacteremia or infectious complications associated with FN were relatively high in ALL patients.[32,37] In our study, 4% of children with FN died during induction phase, which was less than the 11% who died in a pevious study.[38] Asim *et al.* showed that infection was the dominant cause of death (85%).[37]

We also aimed to determine if duration of FN was influenced by nutritional status (**Table 5**). Gamma correlation test revealed no such association (P=0.48). In contrast, Corner *et al.* found that malnutrition had 1.5 times higher risk of longer hospitalization than good nutrition (95%CI 1.0 to 2.3).[39] This difference may have been due to practice guidelines for treating FN patients regardless of their nutritional status. Those with FN were immediately put in isolation, with restrictions on the number of attendants, guards and medical teams, using strict hand-washing and masks procedures before touching the patient, as well as empirical antibiotics (ceftazidime and gentamicin) in accordance with the most common up-to-date research and types of pathogens.[4,40] In Addition, Avilés-Robles et al. found that patients with sepsis had a long FN duration than those without sepsis (95%CI 1.6 to 2.6).[41]

The shortcoming of this study was the retrospective design, which relied heavily on the accuracy of medical records for socioeconomic status data. Further research is needed to analyze the role of antioxidants (selenium and tocopherol) on the occurrence of FN and improvement of nutritional status. Early nutritional status screening and FN management in children with ALL may be to reduce mortality, shorten treatment length and increase survival rate. Despite the initial nutritional status at the time of ALL diagnosis, malignancy patients need high-caloric content than the normal dietary allowance and can be given in smaller portion,[42,43] also weight checks throughout therapy,43 as chemotherapy side effects can lead to weight loss.[42,43] Prevention of FN requires awareness and education of patient's parents and the medical team.

Conflict of Interest

None declared.

Funding Acknowledgment

The authors received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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