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Original Article

The risk factors for febrile neutropenia during chemotherapy in children with malignancy

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Abstract

Background Febrile neutropenia is the most common side effect of myelosuppressive chemotherapy. It is important to identify its risk factors to decrease the morbidity and mortality of febrile neutropenia.

Objective To identify whether age, type of malignancy, phase and dose of chemotherapy, nutritional status, and absolute neutrophyl count are risk factors for febrile neutropenia.

Methods A hospital-based case control study was conducted at Hasan Sadikin Hospital from June 2000 to July 2005. Data was collected from medical records. The case group consisted of children with malignancy who received chemotherapy and suffered from febrile neutropenia, while the control group consisted of children without febrile neutropenia. Chi square and logistic regression analysis were performed to analyze data using SPSS for Windows version 13.0.

Results Eighty-seven cases and 94 controls were evaluated. Analysis showed that malignancy type i.e, hematologic malignancy, chemotherapy phase, and absolute neutrophyl count might be the risk factors for febrile neutropenia (OR=4.6, 95% CI 1.3;16.7, P=0.019; OR=8.1, 95% CI 2.2;30.5, P=0.002; and OR=1.0, 95% CI 1.003;1.007, P <0.001, respectively), while age, chemotherapy dose, and nutritional status might not be the risk factors (median 60, range 6-144, P=0.342; OR=1.9, 95% CI 0.8;4.8, P=0.129; and P=0.798, respectively).

Conclusion Hematologic malignancy, induction phase of chemotherapy, and absolute neutrophyl count =250/mm^3 are the risk factors for febrile neutropenia in children with malignancy who received chemotherapy. **[Paediatr Indones 2007;47:83-87]**.

Keywords: *chemotherapy, febrile neutropenia, malignancy in children*

Febrile neutropenia is the most common side effect of myelosuppressive chemotherapy in patients with malignancy.[1-5] Febrile neutropenia can interfere the course of chemotherapy resulting in schedule delays and life threatening complications that may increase morbidity and mortality.[4,5] In 2004, the incidence of febrile neutropenia in childhood cancer at Cipto Mangunkusumo Hospital is approximately 34%.[6] Ten to fourty percent of children with malignancy will have febrile neutropenia during chemotherapy.[7] Death from febrile neutropenia (infection) was 0.4-1% in children versus 4% in adults.[8-10] The ability to identify the risk factors among those children might help to reduce the morbidity due to febrile neutropenia and to increase the likelihood of delivering appropriate dose of chemotherapy on time. In addition, hematopoietic colony stimulating factors could be administered to patients who need them most, allowing an efficient use of medical resources.

Number of studies have shown several clinical characteristics correlated with febrile neutropenia such as hematologic malignancy,[11,12] induction

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therapy,[9,11] age,[5] high dose chemotherapy,[13] malnourishment,[14] and absolute neutrophyl count (ANC)=250/mm.[3,11] Therefore, the purpose of this study was to identify whether age, malignancy type, phase and dose of chemotherapy, nutritional status, and absolute neutrophyl count are risk factors of febrile neutropenia.

Methods

This study was a hospital-based case control study at Hasan Sadikin Hospital from June 2000 to July 2005. Data was collected from medical records. Subjects with malignancy diagnosed by bone marrow puncture or biopsy who received chemotherapy were enrolled. The inclusion criteria were children aged ≤14 years old with complete medical records. The subjects were divided into 2 groups, the case group consisted of cases with febrile neutropenia, and the control group consisted of those without it. Febrile neutropenia is defined as a condition marked by absolute neutrophyl count less than 1000/mm^3 and fever with temperatures more than 38^{o}C.

The type of malignancy was classified into hematologic malignancy and solid tumor. The phase of chemotherapy consisted of induction and post- induction phase. The dose of chemotherapy was divided into high dose and conventional dose. High dose chemotherapy is the treatment of cancer using methotrexate ≥500 mg/m^2, etoposide ≥1200 mg/m^2, cyclophosphamide ≥1.8 g/m^2, ifosfamide ≥3 g/m^2, and cytarabine 3 g/m^2 where as conventional dose was the treatment of cancer using MTX 7.5-30 mg/m^2, etoposide 60-120 mg/m^2, cyclophosphamide 250-1800 mg/m^2, ifosfamide 1600-2400 mg/m^2, and cytarabine 100-200 mg/m^2.

The study was approved by the Ethical Committee for Health Study at Medical School of Padjadjaran University, Hasan Sadikin General Hospital Bandung.

SPSS program version 13.0 for analysis was used. Chi-square test for univariate analysis was used to identify the association of age, malignancy type, phase and dose of chemotherapy, nutritional status, and ANC with febrile neutropenia. Several factors were analysed together using multivariate logistic regression analysis. In analysing the entire sample, P value <0.05 indicated statistical significance.

Results

During 5-year retrospective study period, 722 cases were collected. Of these, only 181 cases were included because the ANC of other cases were not documented. There were 87 cases with febrile neutropenia and 94 cases without it. The prevalence of febrile neutropenia in this study was 12%.

In this study, acute lymphoblastic leukemia (ALL) made up most of childhood malignancy which were 67 (37%) cases followed by acute myeloblastic leukemia (AML) 21 (12.6%), rhabdomyosarcoma 26 (14.4%), retinoblastoma 17 (9.4%), neuroblastoma 13 (7.2%), lymphoma malignum non hodgkin (LMNH) 13 (7.2%), teratoma 9 (5.0%), Wilms tumor 6 (3.3%), nasopharyng carcinoma 6 (3.3%) cases whereas colorectal carcinoma and Hodgkin lymphoma were 1 (0.6%) case each.

Males and malnourished cases were more common in group with febrile neutropenia (**Table 1**). Results of Mann Whitney test showed that age of both groups had no significant difference (P=0.342) while the ANC showed a significant difference (P<0.001).

In this study, nutritional status (P=0.798) was not a risk factor for febrile neutropenia. Hematologic malignancy type (OR=4.5; P<0.001), induction phase of chemotherapy (OR=8.9; P<0.001), and chemotherapy dose (OR=1.9; P=0.129) were risk factors for febrile neutropenia (**Table 2**).

Table 1. Subjects' characteristics

Characteristic	Febrile (+) n=87	Neutropenia (-) n=94	
Sex			
males	54 (62%)	49 (52%)	
females	33 (38%)	45 (48%)	
Age (months)			
mean	66	73	Z_{M-W}=-0.950
median	60	66	P=0.342
SD	39	45	
range	6-144	13-168	
Nutritional status			
wellnourished	39 (45%)	48 (51%)	
mild malnutrition	27 (31%)	26 (28%)	
moderate malnutrition	19 (22%)	19 (20%)	
severe malnutrition	2 (2%)	1 (1%)	
ANC (/mm^3)			
mean	186	3185	Z_{M-W}=-10.595
median	100	2375	P<0.001
SD	204	4871	
Range	18-900	20-44772	

Table 2. Association between several risk factors and febrile neutropenia

Risk factors	Febrile neutropenia (+) n = 87	(-) n = 94	P	OR 95% CI
Malignancy type				
Hematology	65 (75%)	37 (39%)	<0.001	4,5
Solid tumor	22 (25%)	57 (61%)		(2.4-8.5)
Chemotherapy dose				
High	15 (17%)	9 (10%)	0.129	1.9
Conventional	72 (83%)	85 (90%)		(0.8-4.8)
Chemotherapy phase				
Induction	67 (77%)	25 (27%)	<0.001	8.9
Post induction	20 (23%)	69 (73%)		(4.6-17.7)
Nutritional status				
Well nourished	39 (45%)	48 (51%)	0.798	
Mild Malnutrition	27 (31%)	26 (28%)		
Moderate Malnutrition	19 (22%)	19 (20%)		
Severe Malnutrition	2 (2%)	1 (1%)		

Table 3. Association between malignancy type, chemotherapy phase, ANC, and chemotherapy dose

Variable	Coefficient β	SE(β)	P	OR (95%CI)
Malignancy type	1.532	0.655	0.019	4.6 (1.281-16.721)
Chemotherapy phase	2.095	0.676	0.002	8.1 (2.160-30.546)
ANC	0.005	0.001	<0.001	1.005 (1.003-1.007)
Chemotherapy dose	1.220	1.190	0.306	3.4 (0.328-34.898)
Constant	-8.107			

From logistic regression analysis, hematologic malignancy type (OR=4.6; P=0.019), induction phase of chemotherapy (OR=8.1; P=0.002), and ANC (OR=1.005; P<0.001) were risk factors for febrile neutropenia. Chemotherapy dose (OR=3.4; P=0.306) was not a risk factor for febrile neutropenia (**Table 3**).

Discussion

The prevalence of febrile neutropenia in this study was 48% within the range of previous studies which were 10-40%.[6,7] The most common type of malignancy was leukemia (37%) where as the previous data reported leukemia in 25% of cases.[15,16]

Our study revealed that hematologic malignancy was a risk factor for febrile neutropenia. In both groups, patients with hematologic malignancy had 4.5 times higher risk to develop febrile neutropenia compared to those with solid tumor. This is similar with other studies.[8,17] This was due to the involvement of bone marrow and the intensity of chemotherapy regimen used in hematologic malignancy.

This increased risk was also observed in patients with malignancy during induction phase of chemotherapy (8.9 times higher risk) which is also similar with other studies.[9-11] The aim of induction phase is to eliminate as many as possible cancer cells but unfortunately also affect normal cells that may lead to neutropenia and consequently febrile neutropenia.[18]

In this study, we found ANC as a risk factor for febrile neutropenia. In patients receiving chemotherapy, those with ANC ≤250/mm^3 had 1.005 times higher risk to develop febrile neutropenia, concurrent with the others.[19] During neutropenia, the neutrophil cells required to fight bacteria are depleted. Thus, it increases the susceptibility to develop febrile neutropenia.[10]

These findings showed that hematologic malignancy, induction phase of chemotherapy, and ANC ≤250/mm^3 were factors influencing occurrence of febrile neutropenia.

In this study, age was not a risk factor for febrile neutropenia. Unlike other studies where age had an increased risk to develop febrile neutropenia.[5,20] These counter findings might be due to the different method of study, such as sample calculation and data collection. The sample of the study by Basu *et al*[5] was 181 cases, which was 1.5% of 12,446 patients from 1,156 centers in United States. The method used in this study was prospective observational. The large number of patients had been excluded might have decreased the validity of this study.

Our study revealed that nutritional status was not a risk factor for febrile neutropenia (55% vs 48%). Unlike the other, febrile neutropenia was more prevalent in malnourished than that in well-nourished patients.[14] This opposite finding might be due to the difference of research method and nutritional status parameter between this studies and the one performed by Jain *et al*[14] which used a prospective cohort method and anthropometry, hematology, and biochemical parameter as nutritional status measurement.

Multivariable analysis of our study concluded that chemotherapy dose did not pose an increased risk for febrile neutropenia. This result differed from other study which reported a higher proportion of febrile neutropenia in patients receiving high dose chemotherapy compared to conventional dose.[21] This might be due to the limitation of the cases obtained in our study. Since most of the data in the medical records were not complete, many of the cases were excluded in this study.

In this study, hematologic malignancy, induction phase of chemotherapy, and absolute neutrophyl count $\leq 250/mm^3$ are risk factors for febrile neutropenia in children with malignancy who received chemotherapy, thus anticipation could be made.

Hematopoietic growth factors can be safely administered as an adjunct to induction therapy of ALL and is clinically beneficial by ameliorating neutropenia and reducing infectious complications.[22,23]

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