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Original Article

Febrile neutropenia in childhood leukemia: Manado experience 1997 – 2006

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Abstract

Background Febrile neutropenia (FNP) is a common complication of therapy among children with cancer. It is one of the causes of significant morbidity and mortality in children and young adults treated for cancer. With aggressive management of FNP, the outcome of episodes in children has improved dramatically.

Objective To determine factors associated with FNP, to assess how varied the current management, and to evaluate the outcome of FNP in childhood leukemia in Manado over the last 10 years.

Methods Data from medical records was collected retrospectively from January 1997 to December 2006. Variables studied were: age, sex, nutritional status, sosio-economic status, type of leukemia, degree of fever, ANC at fever, phase of chemotherapy, antibiotic used, episodes of FNP and the outcome of patients.

Results Twenty of ninety one patients were studied. The mortality rate was crucial i.e., 11 of 20, it was higher in boys than that in girls. Most children have severe to very severe neutropenia and more than half died (7/13). Seven out of 12 malnourished patients died. Sixteen children are suffered from acute lymphoblastic leukemia (ALL). The outcome of high risk (HR) patients was worse than that of standard risk (SR). FNP occurred along the phase of chemotherapy. None of the factors studied showed significant difference. The choice of antibiotics is varied.

Conclusion The outcome of FNP in our institution is grave. There is a need to evaluate application and compliance to the standard guidelines. **[Paediatr Indones. 2009;49:372-8]**.

Keywords: *leukemia, febrile neutropenia, antibiotic, outcome*

Febrile neutropenia (FNP) is a common complication of therapy among children with cancer. It is one of the causes of significant morbidity and mortality in children and young adults treated for cancer. With aggressive management of FNP, the outcome of episodes in children has improved dramatically. Mortality fell from 30% in the 1970s to 1% in the late 1990s.[1] Intensive care management is required in less than 5% of cases, although a substantial proportion of children have complications which require special care.[2]

During the recent years, several studies have evaluated risk factors for bacteremia or poor outcomes among patients with cancer and helped to establish the current guidelines for the treatment of febrile neutropenia by the Infectious Disease Society of America (IDSA)[3], as well as the recommendations for the use of hematopoietic colony-stimulating factors by the American Society of Clinical Oncology (ASCO)[4]. However, not all guidelines are generalizable to children with cancer because of

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inadequate data in this population. Studies on the pediatric population are rendered difficult by the limited number of pediatric patients with cancer treated in a single institution. This is even true for country like Indonesia with limited resources and dispersed pediatric cancer centers. Despite excellent collaborative approaches to chemotherapy treatment protocols for childhood acute lymphoblastic leukemia (ALL) across many centers in Indonesia (firstly by application of WK-ALL protocol then recently by that of Indonesian 2006 protocol), few large-scale studies of supportive care in children have been performed. The aim of this study was to determine factors associated with FNP, to assess how varied the current management strategies, and to evaluate the outcome of FNP in childhood leukemia patients in our center.

Methods

A retrospective study was conducted on data from medical records with either acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia (AML), chronic myeloblastic leukemia (CML) age 1-18 years who received chemotherapy in Prof.dr. R.D. Kandou General from January 1997 to December 2006.

Factors studied were: age, sex, nutritional status, sosio-economic status, type of leukemia, degree of fever, absolute neutrophile count during fever, phase and dose of chemotherapy, antibiotic used, episodes of FNP and the outcome of patients.

FNP was defined as body temperature higher than 38.5°C on axilla in two consecutive measurements with interval at least two hours and absolute neutrophile count (ANC) less than 1,000/cmm. Sosio-economic status was categorized into poor and common based on the criteria from National Family Planning Coordination Body. Nutritional status was classified into severe, mild to moderate malnutrition, normal and obese based on weight for height (W/H) according to Central for Disease Control (CDC) 2000 scale.

A χ^2 or Fisher's exact test was performed to compare the difference of outcomes from each factor studied. This study was approved by the Ethical Committee for Health Study of Prof Dr. R.D. Kandou General Hospital Manado.

Results

From January 1997 to December 2006, there were 91 children diagnosed as leukemia but only 20 cases were analyzed in this study due to incomplete data. All of the 20 patients suffered from episode(s) of FNP.

Subject characteristics are shown in **Table 1**. The youngest patient was 1.67 years and the oldest was 13.58 years, with mean of age of 5.8 year old. Twelve of 20 patients were malnourished. Most of the children were diagnosed as ALL (16 of 20). During hospitalization, most of the children suffered from once to twice episodes of FNP, with the lowest temperature of 38.5°C and the highest of 40.40°C. The outcome of FNP in our study was still grave with a mortality rate 11 of 20.

The mortality rate was higher in boys that in girls (7/10 vs. 4/10). Seven out of 12 malnourished patients succumbed to the disease. Most of the children had severe to very severe neutropenia and more than half died (7/13). **Table 2** shows distribution of patients according to the outcome, however, none of the factors studied showed significant difference.

In ALL children with FNP, the outcome of HR patients was worse compared to that of SR (mortality

Table 1. Characteristics of patients (n=20)

		Number
Age (years)*		5.8 (SD 3.57)
Sex	Male	10
	Female	10
Nutritional status	Severe malnutrition	1
	Mild-moderate malnutrition	11
	Normal	7
	Obese	1
Sosio-economic status	Poor	7
	Common	13
Type of leukemia	ALL	16
	AML	3
	CML	1
ANC at fever	500-1,000/cmm	7
	200-500/cmm	11
	<200/cmm	2
Degree of fever (oC)*		38.9 (SD 0.61)
Episodes of FNP	1-2 times	18
	3-4 times	2
	>5 times	0
Outcome	Alive	9
	Dead	11

* Mean (SD)

Table 2. Patients distribution according to the outcome (n=20)

		Alive	Dead	P
Sex	Male	3	7	0.185
	Female	6	4	
Nutritional status	Severe malnutrition	1	0	0.425
	Mild-moderate malnutrition	4	7	
	Normal	4	3	
	Obese	0	1	
Sosio-economic status	Poor	5	2	0.102
	Common	4	9	
Type of leukemia	ALL	7	9	
	AML	2	1	
	CML	0	1	
ANC during fever	500-1,000/cmm	3	4	0.983
	200-500/cmm	5	6	
	<200/cmm	1	1	
Episodes of FNP	1-2 times	7	11	0.189
	3-4 times	2	0	
	>5 times	0	0	

rate 7/9 vs. 2/7, respectively). The episodes of FNP occurred along the phase of chemotherapy with demise outcome (**Table 3**).

The choice of antibiotics in our data varied (**Table 4**). Either oral or parenteral antibiotic was given. Treatment by parenteral antibiotics comprised of the combination of broad spectrum antibiotic and aminoglycosides, and third generation cephalosporines either as single agent or in combination with aminoglycosides. The combination of broad spectrum antibiotic (ampicillin) and aminoglycosides was used before the year of 2000; thereafter ampicillin was changed to third generation cephalosporin. Two patients received additional antifungal therapy.

Discussion

There were limitations in our present study. Only few patients enrolled, 20 out of 91. This is due to incomplete data, mainly the value of ANC was not well documented, blood and/or urine cultures and sensitivity test were not routinely performed and recorded, as well as lost to follow up. It might reflect

Table 3. Distribution of ALL patients with FNP according to the outcome (n=16)

		Alive	Dead	
Risk classification	Standard risk (SR)	5	2	P=0.08
	High risk (HR)	2	7	
Phase of chemotherapy	Induction	5	5	
	Consolidation	2	3	
	Maintenance	0	1	

Table 4. Patients distribution according to antibiotic used and outcome (n=20)

Antibiotic used	Outcome		
	Alive	Dead	Total
Cefixime	4	5	9
Ampicillin + Gentamicin	1	1	2
Ceftriaxone	0	2	2
Ceftriaxone followed by Cefixime	1	0	1
Cefotaxime	0	1	1
Ceftriaxone + Amikacin	1	1	2
Cefotaxim + Gentamicin	0	1	1
Fluconazole added	2	0	2

insufficiencies whether the availability of standard clinical practice guideline, compliance to guideline or experience of residents on duty.[5,6]

All of our 20 leukemia children suffered from episode(s) of FNP. In previous studies, the incidence of FNP in childhood cancer in Cipto Mangunkusumo Hospital Jakarta was approximately 34% (21/38 cases)[7] and that in Hasan Sadikin Hospital Bandung was about 48% (87/181 cases)[8].

We could not analyze and deduct the association between factors studied, such as age, sex, nutritional status, sosio-economic status, type of leukemia, phase of chemotherapy, and the risk of FNP due to limited samples. Jain et al[9] reported that complication like febrile neutropenia was more in the malnourished children with malignancy, although the difference was not statistically significant. Sulviani et al[8] suggested several risk factors to develop FNP in children with malignancy who received chemotherapy such as, hematologic malignancy (had 4.6 times higher risk compared to those with solid tumor) induction phase of chemotherapy (OR=8.1, 95% CI 2.2 to 30.5, P=0.002), and ANC $\leq$ 250/cmm (OR=1.005, 95% CI 1.003 to 1.007, P <0.0010. Meanwhile, age, chemotherapy dose, and nutritional status were not risk factors.

The outcome of FNP in this present study was grave (11 out of 20 patients died), but none of the factors studied reach significant difference. Our small group probably lacked sufficient power. Basu et al[10], in a large longitudinal data analysis from 1995-2002 (n=12,446) evaluated risk factors for longer length of stay (LOS) and mortality among hospitalized children with cancer who have febrile neutropenia. They reported a mortality rate of 3%. On multivariate analysis, age group (infant and adolescent), race (other than white), cancer type (acute myeloid leukemia, multiple cancers versus acute lymphoblastic leukemia), and the complication variables (bacteremia/sepsis, hypotension, pneumonia, and fungal infections) were significantly associated with increased risk of longer LOS and death.

The mortality of HR ALL patients in our study was worsened and FNP episodes occurred along the phase of chemotherapy with demise outcome. Bakhshi et al[11] in a retrospective analysis performed on febrile neutropenic episodes in patients with ALL, found 222 febrile neutropenic episodes in 266 ALL patients. Forty four percent had documented focus of infection; the rest were fever without focal infection. Pulmonary infections were the commonest site of infection (27.3%) followed by HEENT (22.9%). Of 69 bacterial isolates, gram-negative bacteria (67%) were twice as common as gram-positive bacteria (33%). Most common site of isolation for gram-negative bacteria was blood (50%) followed by urine (32.6%). Blood (78.3%) was predominant site of isolation of gram-positive bacteria followed by HEENT (8.7%). Escherichia coli (45.7%) were the commonest gram-negative isolate, while Staphylococcus aureus (39%) was the commonest gram-positive bacterial isolate. There were a total of 22 fungal isolates, the majority was from urine (n=12) and HEENT (n=9). The majority of fungal infections were detected during induction chemotherapy. There was 42.8% of febrile neutropenic episodes improved with first-line antibiotic therapy, while modification was required in 57.2% episodes. Antifungal therapy was used in 38.7% episodes. There were a total of 13 deaths, mostly during induction and intensification/consolidation phases, with cause of death were pneumonia, bacteremia, and fungal infection.

Although children with cancer often have fever during chemotherapy-induced neutropenia, only some develop serious infectious complications. The reasons for this are not clear but low concentrations of mannose-binding lectin (MBL) might increase infection susceptibility in these children. MBL is a collagenous lectin of the innate immune system that bounds to sugars on the surface of many microorganisms. Once bound, it activates the lectin pathway of complement activation through a MBL-associated serine protease, MASP-2. The result is direct complement-mediated lysis and opsonization of the micro-organism followed by phagocytic killing. However, the results of studies on the role of MBL in paediatric oncology patients with febrile neutropenia are still contradicting.[12,13]

The distinction of children with FNP at high versus low risk for severe bacterial infection (SBI) based on information accessible at presentation is of paramount important. A better initial predictive approach may allow better therapeutic decisions for these children, with an eventual impact on reducing mortality.

Amman et al[14] outperformed the decision tree

model in predicting serious bacterial infection (SBI) in pediatric cancer patients presenting with FNP based on seven variables: bone marrow involvement, no clinical signs of viral infection, high level of C-reactive protein, high hemoglobin, low leukocyte count, presence of central venous catheter, and diagnosis of pre-B-cell leukemia. These predictors had 96% sensitivity, with the cross validated specificity of 26%, and the negative predictive value of 91%. Paganini et al[15] validated statistically the use of a mortality score for high-risk patients to predict mortality in febrile neutropenic children with cancer. A mortality score was made 3 points for the presence of advanced-stage underlying malignant disease, 2 points for the presence of associated comorbidity, and 1 point for bacteremia. If the patients had score of 4 points then their risk of mortality was 5.8%; if they had score of 5 points, then their risk of mortality was 15.4%; and, if they reached the maximum score of 6 points, then their risk of mortality raised to 40%. For those with scores >3, the scoring system had a sensitivity of 84.2%, a specificity of 83.2%, and a negative predictive value of 99.54% for predicting mortality.

Orudjev et al[1] in their meta-analysis concluded that one-third to one-half of children with FNP are at low-risk of serious infection and they can be safely managed with inpatient or outpatient strategies that maintain close follow-up and reduce the burden of antibiotic therapy. The child with cancer and low-risk febrile neutropenia is clinically well and afebrile within 24-96 hours of antibiotic therapy and has evidence of marrow recovery with a rising phagocyte count. However, adoption of these alternative strategies as the standard of care should proceed with caution guided by written protocols. Boragina et al[16], carried out a cross-sectional mailed survey in 17 tertiary pediatric centers in Canada. Three out of 17 centers carried out exclusively traditional management by hospitalization and application of intravenous antibiotics. The remaining 14 offered modified treatment for low risk children. The majority (n = 10) carried out an early discharge approach. Two thirds of the episodes of febrile neutropenia were treated this way with good results. The rest (n = 4) implemented complete outpatient management. Most specialists agreed on the benefits of short hospitalization for children with cancer. However, more evidence, ideally in the form of multicenter clinical trials, appears to be needed to further safely modify practice.

Santaloya et al[17], evaluated biomarkers obtained within 24 hours of hospitalization as predictors of severe sepsis before it becomes clinically evident in children with cancer and FNP. They suggested the risk factors for severe sepsis i.e., age ≥12 years [OR: 3.85 (95% CI 2.41 to 6.15)], admission CRP ≥ 90 mg/L [OR: 2.03 (95% CI 1.32 to 3.14)], admission IL-8 ≥ 200 pg/mL [OR: 2.39 (95% CI 1.51 to 3.78)], 24-hour CRP ≥ 100 mg/L [OR: 3.06 (95% CI 1.94 to 4.85)], and 24-hour IL-8 ≥ 300 pg/mL [OR: 3.13 (95% CI 1.92 to 5.08)]. El-Maghraby et al[18] identified serum markers within 24 hours of fever that may help to stratify febrile neutropenic pediatric patients treated for hematologic malignancies at the time of first evaluation. Low levels of CRP, MCP-1, and IL-8 could identify patients with unexplainable fever; whereas, high levels of these markers were of help in the diagnosis of infectious episodes. A model combining more than one marker is recommended in the assessment of febrile neutropenia.

Different results were reported by Prat et al[19]. They measured several biomarkers levels in patients with hematological malignancy at diagnosis and at the beginning of neutropenia due to chemotherapy or after hematopoietic stem cell transplantation, daily until six days after the onset of fever. PCT levels were significantly higher in patients with Gram-negative bacteremia at 24-48 hour after the onset of fever. Patients with probable fungal infection presented elevated PCT values when fever persisted for more than 4-5 days. CRP was more sensitive to predict bacteremia (both Gram-positive and Gram-negative) but the specificity was low. Neither neopterin, IL-6 nor IL-8 presented significant differences according to the origin or etiology of fever. They concluded that since PCT showed a high negative predictive value for Gram-negative bacteremia, clinical prediction rules that attempt to predict a high risk of severe infection might be improved by including measurement of PCT.

The variation of antibiotics used in our management strategies for the treatment of FNP were in concordance with international guidelines, although changes were made frequently depend on the availability and affordability of antibiotics. Infectious Diseases Society of America Guidelines recommends initial monotherapy with cefepime, ceftazidime,

imipenem or meropenem, or an aminoglycoside plus antipseudomonal penicillin, cephalosporin or carbapenem [3].

Laoprasopwattana et al[20] found that ceftazidime-aminoglycosides was a reasonable initial treatment of febrile neutropenic children with cancer in their institution. Imipenem is considered in patients who have clinical sepsis and who fail to respond to initial treatment. Corapçioglu and Sarper[21] compared the efficacy, safety, and cost of cefepime and ceftazidime + amikacin as empirical therapy in children with febrile neutropenia. Cefepime monotherapy is as effective as ceftazidime + amikacin combination for febrile neutropenia in pediatric cancer patients and must be preferred due to shorter defervescence of fever, shorter hospitalization, and lower therapy cost. Yildrim et al[22] conducted a prospective, randomized clinical trial to compare the efficacy of piperacillin/tazobactam and amikacin combination with carbapenem monotherapy for the empirical treatment of febrile neutropenic episodes of children with acute lymphoblastic leukemia or acute myeloblastic leukemia. There was no difference between the two regimens from the point of view of durations of fever, neutropenia, and hospitalization ($P>0.05$ for all categories). PTA was as effective as carbapenem monotherapy as an initial empirical regimen for febrile neutropenic episodes in pediatric hematological malignancies. Overall, the microbiologically documented infection rate was 21.9%, with Staphylococcus epidermidis as the most common cause of bacteremia. Sato et al[23] who conducted a randomized study to evaluate the efficacy of cefozopran (100 mg/kg/day) monotherapy and piperacillin-tazobactam(125 mg/kg/day) plus ceftazidime(100 mg/kg/day) (PIPC/TAZ+CAZ) combination therapy in pediatric neutropenic patients, showed that both cefozopran and PIPC/TAZ+CAZ combination therapy are safe and well tolerated. Blood cultures were positive in eight episodes (8.4%), but there were no deaths due to infection. They suggested that cefozopran is a good antibiotic for monotherapy of neutropenic fever. Park et al[24] reported the feasibility (93%) and efficacy (87%) of an outpatient continuation therapy of oral ciprofloxacin (CPR) 25-30 mg/kg/day divided BID and amoxicillin (AMX) 30-50 mg/kg/day divided TID for a selected subgroup with febrile neutropenic episodes defined after initial hospitalization and empiric antibiotic therapy. Duration of neutropenia, lower ANC < 100/cmm at start of oral antibiotic therapy and active malignant disease were associated with failure of oral antibiotic therapy.

We concluded that despite of small number patients studied, the outcome of FNP in our institution is grave. There is a need to evaluate application of and compliance to the standard guidelines, mainly to perform cultures and antimicrobial sensitivity test routinely and to do better registry.

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