

Pattern of Infectious Diseases in Acute Leukemia During Induction Therapy

Sri Rezeki Harun, Debbie Latupeirissa, Taralan Tambunan

(Department of Child Health, Medical School, University of Indonesia, Jakarta)

ABSTRACT An prospective study was conducted to determine risk factors and pattern of infectious diseases in acute leukemia during induction therapy. The study subjects were all new acute leukemia patients of 1 month to 17 years old diagnosed between August 1, 1997 and July 31, 1998 in the Department of Child Health, Cipto Mangunkusumo Hospital, Jakarta. Subjects were categorized into Group with and without infection. Of the 39 subjects studied (23 boys and 16 girls), 22 subjects were infected (10 boys and 12 girls). Most of the subjects were 1-4 year-old age group and 14 subjects of that group were infected. It was found that there were relationships between incidence of infection with leukocyte count below $5000/\mu\text{l}$ ($p=0.02$), neutrophil count below $1 \times 10^9/l$ ($p=0.01$), and evidence of presumptive site of infection ($p=0.0005$). Children under 5 years old, sex, ANLL type, malnutrition, or neutropenia of more than 2 weeks had no relationships with incidence of infection. Besides fever, pattern of infection diseases in acute leukemia patients during induction therapy, were only 36% and 38,% of subjects had clinical manifestations evidence and microbiologically documented, respectively. Most of the laboratory findings were leukopenia or neutropenia, while serum aminotransferase was normal in both groups. Serum CRP serum was elevated in those with infection. All of the isolated bacteriae were Gram-negative; 52.4% of infected subjects had responded to empirical therapy, and 72.7% of the antibiotics used was sefotaxime. [*Paediatr Indones* 1999; 39: 211-220]

Introduction

Acute leukemia is the most common form of malignancy in childhood.^{1,2} At the Department of Child Health, Cipto Mangunkusumo Hospital, acute leukemia represents more than 50% of childhood cancer.³ A child with malignancy may be immunocompromized because of the underlying disease and the antineoplastic therapy, or both.^{4,9}

Neutropenia is more commonly found in acute leukemia than other malignancies and the most important risk factor for infection in acute leukemia.⁴⁻¹¹ Among patients with acute leukemia, the National Cancer Institute files revealed that between 1965-1971 the morbidity rate of infection was 69% and 10% died because of infection.¹⁰ The risk of infection is related to the degree and duration of neutropenia. Increased risk for infection is also associated with malnutrition, immune defect because of the underlying diseases and/or cytostatic therapy; damage to the skin and mucous membranes because of invasive procedures, prolonged antibiotic usage, or hospitalization.⁴⁻⁹

It is always difficult to determine the diagnosis of infection in malignancy because of symptoms and signs indicative of infectious process may be lacking.^{6,11,12,14,15} Fever is often the sole sign of infection in immunocompromized patient with neutropenia.¹⁰⁻¹¹ For approximately 60-80% of febrile neutropenic patients will have an infection.^{13,16} Infection is clinically documented in 30-40% whereas microbiological confirmation is only in 25-30%.^{6,14,17} The objectives of this study were to determine pattern and risk factors of infection diseases in acute leukemia patients to develop an algorithm for the treatment.

Methods

This observational prospective study was conducted at the Department of Child Health, Cipto Mangunkusumo Hospital, Jakarta, from August 1st 1997 to July 31st 1998. All patients with acute leukemia, aged 1 month until 17 years old were enrolled in the study (consecutive sampling). Patients who had received cytostatic therapy were excluded from the study.

Patients identity (age, sex) and initial laboratory findings (hemoglobin, leukocyte and neutrophil count, serum aminotransferase and bone marrow aspiration) were collected on admission. All study subjects were then observed until they have risks factors of infection like presumptive site of infection, malnutrition, LNLA type, neutropenia (below 1000/ μ l) or leukopenia (below 5000/ μ l). Patients with or without presumptive infection were examined for serum aminotransferase, chest X-ray, and microbiological examination. Serum CRP was examined.

We report patients characteristics according the incidence of infection (age and sex), clinical and laboratory findings of patients with infection, response to antibiotic treatment, and relationships between several risk factors with incidence of infection.

Results

1. Patients Characteristics

During the period of August 1, 1997 to July 31, 1998, 39 patients with acute leukemia was admitted to the Department of Child Health, Medical School, University of Indonesia, Jakarta, comprising 23 boys and 16 girls. During observation subjects were divided into group with infection (22 patients) and without infection (17 patients). The age and sex incidence was depicted in Table 1; it shows that most patients of the group with infection were of 1-4 years-old age (35.9%), and no sex preponderance is seen (Table 1).

Table 1. Patient characteristics by occurrence of infection

Patient characteristics	With infection	Without infection	Total
Age (year)			
o 0-	1	0	1
o 1-	14	8	22
o 5-	6	7	13
o 10-	1	2	3
Sex			
o Boys	10	13	23
o Girls	12	4	16

2. Pattern of infection

The source of one-third of infection diseases in acute leukemia were unknown. Most of the patients were diagnosed as sepsis. Skin was the most common site of infection (Table 2 & 3). Leukocyte and neutrophil counts were lower in patients with infection (median : 2650/ μ l and 762/ μ l, respectively). Aminotransferase serum in both groups were normal and all of qualitative CRP serum in infection group were positive. Patients with infection that had indication for chest x-ray were bronchopneumonia and tuberculosis, 1 case each. There were pneumonitis features in 1 patient with sepsis. Only 38.5% subjects had microbiological examination and all pathogens from all specimens were Gram-negative bacteria (*Enterobacter sp*, *E. coli*, and *Pseudomonas aeruginosa*).

Table 2. Diagnosis of infection disease in acute leukemia

Diagnosis	Total
Arachnoiditis	1
Bronchopneumonia	1
Dengue hemorrhagic feve	1
Urinary tract infection	1
Measles	2
Tuberculosis	1
Chronic tonsillitis	1
Pulp gangrene	2
Sepsis	6
Unknown	8
Total	24

Table 3. Presumptive site of infection in acute leukemia patients

Presumptive site of infection	Total
Skin	8
Lung	4
Teeth	2
Perianal skin	1
Tonsil	1
Urinary tract	1
Arachnoid	1
Eyes	1
Unknown	8
Total	27

3. Response to antibiotic treatment

The most choice of empiric antibiotic therapy was cefotaxime which was responded to 72.7% cases. The combination of cefotaxime and aminoglycoside was the second choice. The other choice of cephalosporin were cephadrine, ceftazidime, cefuroxime, and ceftriaxone. Cephalosporin was the first choice of empiric and definitive therapy.

4. The relationships between several risk factors and the incidence of infection

This study revealed neutropenia (less than 1000/ μ l), leukopenia (less than 5000/ μ l) and evidence of presumptive site of infection were associated with the development of infection. On the contrary, relationships were not found between the development of infection with age group, sex, type of leukemia, nutritional status, and duration of neutropenia of more than 2 weeks (Table 4).

Discussion

Patient Characteristics

The most age group of this study according to the incidence of infection was the 1 - 4 years group (14/39). The other study have found the same age group from their studies.^{2,18,19} Abdulsalam, et al reported that the highest age group among ALL patients that been hospitalized in RSCM, Jakarta was 3-5 years.²⁰ Although this study reported that boys were the most sex group, but according to the incidence of infection, girls were more often than boys (12 girls:10 boys). The other study also reported that boys are more prone to acute leukemia.^{2,18,19}

Pattern of infection diseases

According to Willey, the most infection disease that was found in this study was sepsis, too. The presumptive evidence site of infection of five patients with sepsis was skin, initially. Site if infection of one third patients were unknown. Advani, et al reported fever without any clinical signs of infection among 63% acute leukemia patients. Fever in malignant patient without any clinical signs, must be consider as an infection.¹¹

The most frequently judged evidence of presumptive sites of infection were skin and respiratory tract. This finding was similar to other report which have found that oropharynx, lung, perirectal, and skin were the most frequently found site of infection.⁶ Skin as the most common sites of infection is probably related to damage due to diagnostic and therapeutic procedures likes bone marrow aspiration, venipunctures, and catheter insertions.^{4,9}

Table 4. Relation of clinical/laboratory characteristics to the incidence of infection

Variables characteristics	Infection	No infection	Hypothesis testing
Age group			
◦ <5 years	15	8	RR=1.49 (95%CI:0.79; 2.80)
◦ >5 years	7	9	$\chi^2=1.72$; $p=0.1892$
Sex			
◦ Boys	10	13	RR=0.58 (95%CI:0.34; 1.00)
◦ Girls	12	4	$\chi^2=2.64$; $p=0.104$
Nutritional status			
◦ Malnutrition	8	5	RR=1.14 (95%CI:0.65; 2.00)
◦ Good	14	12	$\chi^2=0.20$; $p=0.65$
Leukemic type			
◦ ANLL	5	3	RR=1.14 (95%CI: 0.61; 2.13)
◦ ALL	17	14	$\chi^2=0.15$; $p=1.000$
Site of infection			
◦ known	14	0	RR=3.13 (95%CI:1.76; 5.13)
◦ unknown	8	17	$\chi^2=16.44$; $p=0.00005$
Leukocyte count			
◦ <5000/ μ l	10	2	RR=1.88 (95%CI:1.15; 3.07)
◦ >5000/ μ l	12	15	$\chi^2=4.98$; $p=0.02$
Neutrophil count			
◦ <1000/ μ l	15	5	RR=2.04 (95%CI:1.07; 3.86)
◦ >1000/ μ l	7	12	$\chi^2=5.62$; $p=0.01$
Duration of neutropenia			
◦ ≥ 2 weeks	9	3	RR=1.00 (95%CI:0.60; 1.68)
◦ <2 weeks	6	2	$\chi^2=0.28$; $p=1.00$

Leukopenia and neutropenia were often found in group with infection. There was no difference between aminotransferase serum in both group, but all of infection group had positive CRP serum. Unfortunately, serum CRP was not examined in patients without infection. Arleen Farrow et al reported the increase of serum aminotransferase among patients with hepatitis and herpes simplex infection. CRP could be used to indicate the presence of infection among neutropenia patient.²⁴

Only 38.5% pathogens could be isolated from all of the specimens. All of the pathogens were Gram negative and mostly was *Pseudomonas aeruginosa*. Advani, et al also reported that only 38% patients with acute leukemia showed microbiological evidence of Gram negative pathogens, notably *Escherichia coli*, *Klebsiella sp*, and *Pseudomonas aeruginosa* was the most.^{6,11,12}

Relationship between several risk factors to the incidence of infections

Patients who had neutropenia were more at risk to develop infection than those who did not. Klastersky reported bacteremia in 55% malignant patients with neutropenia and 17% without neutropenia ($p<0.001$).¹⁴ Raje et al⁵ reported, that of the 499 consecutive episodes of fever in 432 patients with acute lymphoblastic leukemia, 92% were neutropenic. There are several degree of neutropenia of malignant patients. Bodey et al²² reported the decline of neutrophil count until 1.5x10⁹/L, 1x10⁹/L, and <0.1x10⁹/L in 5%, 10%, and 28% patients, respectively. This study found 38.5% infection cases in acute leukemia with median of neutrophil count 0.76x10⁹/L. There was a significant association between neutropenia (<1000/ μ l) and the incidence of infection in this study.

Patients who remain neutropenic for more than 2 weeks are more likely to develop severe infection.^{6,11-13,17} This study failed to confirm those report; but the sample size of this risk was not enough to find the relationships. According to the others,^{6,11,17} this study found only 30% infections had clinical evidence site of infection, and there was relation to the incidence of infection. It seems that knowing the presumptive site of infection, the risk of infection is more severe. Advani, et al¹¹ reported the incidence of infection in ANLL, especially during induction therapy, more oftenly. It should be due to the highest dose of corticosteroid in ANLL so that the duration of neutropenia is longer. Of 39 acute leukemia patient in this study, about one half ANLL had been infected. There was no relationships to the incidence of infection.

There was no report about age group and sex, although children under five years related to the critical period of children's life. Malnutrition is the one of risk factor to the incidence of infection among immunocompromized patient, because of this situation can decrease complement serum, depress T cell function, and delayed of migration PMN to inflammatory site.⁶ The most nutritional status in this study was good and only one person who remain severe malnutrition, so that no relationships to the incidence of infection.

4. Response to Antibiotics

This study found 52.4% of leukemic patient with infection were response to first line antibiotic, and among them, 72.7% was sefotaxime. The most choice of the second line was cephalosporin group. The response to the broad spectrum beta-lactam due to Gram negative pathogens finding of this study. Raje et al²⁵ reported the most prominent isolated pathogens among infection in acute leukemia patients were *Pseudomonas aeruginosa*; of the 61.9% which responded to empiric therapy, 65.69% among them responded to seftazidime and amikacin combination. The combination between broad spectrum beta-lactam and aminoglycoside is one of three choices likes combination of two beta-laktam and monotherapy.¹⁰

The conclusion of this study, sepsis was the most prominent infection disease and skin was the evidence of presumptive infection, oftenly. Leukocyte and neutrophil count remain decreased among infection group. Because of the positive finding among all of infected patients, it should be suggest as a supportive examination besides culture. The most oftenly isolated pathogens was Gram negative. Cefotaxime was effective as empiric therapy, besides broad spectrum beta laktam and aminoglycoside combination. Neutropenia, leukopenia and evidence of presumptive site of infection were the risk factors of infection among acute leukemia patients.

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